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Ecology of Human Medical Enterprises: From Disease Ecology of Zoonoses, Cancer Ecology Through to Medical Ecology of Human Microbiomes

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In nature, the interaction between pathogens and their hosts is only one of a handful of interaction relationships between species, including parasitism, predation, competition, symbiosis, commensalism, and among others. From a non-anthropocentric view, parasitism has relatively fewer essential differences from the other relationships; but from an anthropocentric view, parasitism and predation against humans and their well-beings and belongings are frequently related to heinous diseases. Specifically, treating (managing) diseases of humans, crops and forests, pets, livestock, and wildlife constitute the so-termed medical enterprises (sciences and technologies) humans endeavor in biomedicine and clinical medicine, veterinary, plant protection, and wildlife conservation. In recent years, the significance of ecological science to medicines has received rising attentions, and the emergence and pandemic of COVID-19 appear accelerating the trend. The facts that diseases are simply one of the fundamental ecological relationships in nature, and the study of the relationships between species and their environment is a core mission of ecology highlight the critical importance of ecological science. Nevertheless, current studies on the ecology of medical enterprises are highly fragmented. Here, we (*i*) conceptually overview the fields of disease ecology of wildlife, cancer ecology and evolution, medical ecology of human microbiome-associated diseases and infectious diseases, and integrated pest management of crops and forests, across major medical enterprises. (*ii*) Explore the necessity and feasibility for a unified medical ecology that spans biomedicine, clinical medicine, veterinary, crop (forest and wildlife) protection, and biodiversity conservation. (*iii*) Suggest that a unified medical ecology of human diseases is both necessary and feasible, but laissez-faire terminologies in other human medical enterprises may be preferred. (*iv*) Suggest that the evo-eco paradigm for cancer research can play a similar role of evo-devo in evolutionary developmental biology. (*v*) Summarized 40 key ecological principles/theories in current

disease-, cancer-, and medical-ecology literatures. (*vi*) Identified key cross-disciplinary discovery fields for medical/disease ecology in coming decade including bioinformatics and computational ecology, single cell ecology, theoretical ecology, complexity science, and the integrated studies of ecology and evolution. Finally, deep understanding of medical ecology is of obvious importance for the safety of human beings and perhaps for all living things on the planet.

Keywords: medical ecology, disease ecology, cancer ecology, integrated pest management (IPM), theoretical ecology, cell ecology, computational biology and bioinformatics, genomics and metagenomics

INTRODUCTION

Where we came from, who we are, and where we are going have been explored since the existence of recorded history. Although most of us ignore various doomsday predictions about our planet and species, plus nature mother is often benign, it is an undisputed fact that nature can be a horrific enemy occasionally (McGuire, 2002). Humans have been fighting somewhat recurring battles against the results of its capriciousness—severe floods and storms, devastating earthquakes, cataclysmic volcanic eruptions (McGuire, 2002), and disease pandemics such as Justinian plague in year 541, which was estimated to have killed then half of world population (Morens and Fauci, 2020). The extinction of dinosaurs and 2/3 extant species at the Cretaceous period 65 million years ago reminds us that human race may exist and thrive only by geological accident and may be within a hair's breadth of extinction, if the hypothesis of asteroid struck turns out to be true (McGuire, 2002). A recent report by Hyndman et al. (2018) suggests the protection obtained through the integration of bornaviruses into the genomes of Cretaceous-era mammals may have given them an advantage over reptiles as the predominant terrestrial vertebrates after dinosaurs went extinct. The integrated bornavirus genes, known as "endogenous bornaviral-like elements" (EBLs), which was lacking in birds and reptiles, granted mammals a level of protection against bornaviruses. As a side note, this advantage granted by EBLs is somewhat similar to the work principle of mRNA vaccine (against the COVID-19 infections). Of course, there is a fundamental difference between mRNA vaccine and EBLs. In the case of mRNA vaccine, the mRNA is not inserted into the human genome and is not inheritable. Enard and Petrov (2020), through reanalysis of the 1,000-genomes project data, detected approximately 4,500 host loci that may have preserved the footprints left by ancient viral epidemics in the past 50,000 years. Their findings suggest that RNA viruses have exerted significantly stronger selective pressures than DNA viruses across diverse human populations, also highlighting the more important zoonotic potential of RNA viruses.

SARS-CoV-2 is the gravest microbial threats to humans in the 21st century to date. The COVID-19 pandemic is obviously a stunning wakeup call that forces us to adapt, react, and reconsider the nature of our relationship with the natural world, and emerging and re-emerging infectious diseases such as COVID-19 are epiphenomena of human existence and our interactions with each other, and with natural world (Morens and Fauci, 2020). In the Anthropocene epoch, human activities have been frequently aggressive, damaging, and unbalanced interactions with nature, which creates an endless variety of opportunities for genetically unstable infectious agents (such as corona-viruses that are extremely easy to mutate) to spillover to the "unfilled" ecologic niches such as those created by biodiversity loss and climate changes (Cardinale et al., 2012; Faust et al., 2018; Johnson et al., 2020; Morens and Fauci, 2020). Without enacting essential adaptations, humans may increasingly trigger new disease emergences and remain at risk for the foreseeable future (Morens and Fauci, 2020).

Bernardo-Cravo et al. (2020) presented a pyramid model (diagram) for illustrating the manifold interactions among host, host microbiome, pathogens and the environment, which has one more component, human microbiome, than Morens and Fauci (2020) model. **Figure 1** exhibited a slightly revised version of Fauci-Morens-Bernardo-Cravo model (termed FMB model hereafter) that highlights the key threads of medicine, ecology and environment. Bernardo-Cravo et al. (2020) argued that the tendency of host-disease risk or susceptibility is generally determined by his or her resistance and tolerance to pathogens, pathogen permeability of the host microbiome, pathogenicity (as determined by pathogen infectivity and virulence), as well as by environment (**Figure 1**). The severity of a disease may range from asymptomatic to fatality. The far-reaching influences of environmental factors, including various anthropogenic impacts such as pollution, climate change, and land use (i.e., deforestation, urbanization, and agricultural intensification) on our health and diseases have been receiving public attentions increasingly (Patz et al., 2005; Schmeller et al., 2020). We argue that most of the environmental factors, especially those caused by human activities, can lead to biodiversity loss that in turn may have significant influences on the risks of emerging diseases, particularly the spillover of zoonoses to humans, and on our susceptibility to diseases. In other words, pandemic disease emergence is likely determined by dynamic equilibriums of complex globally distributed ecosystems consisting of animals, pathogens, humans, and the environment (Cardinale et al., 2012; Newbold et al., 2015, 2018; Plowright et al., 2017; Rohr et al., 2020). Biodiversity conservation, which can be defined as "preserving functioning ecosystems with predominantly native species" (Rohr et al., 2020), is therefore of critical importance for us to fight against the emerging pandemics such as ongoing COVID-19.

Broadly speaking, medical enterprises humans involve are not limited to the diseases of humans and animals that are briefly touched previously. One obvious missing block is the

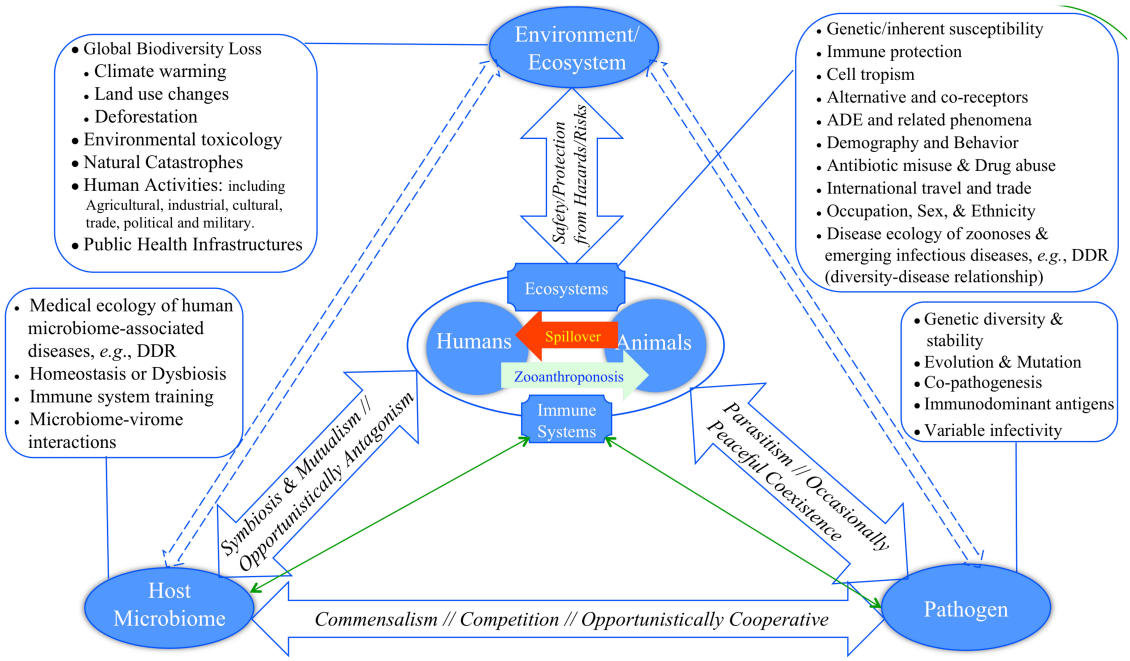

FIGURE 1 | Revised FMB (Fauci-Morens-Bernardo-Cravo) pyramid model of human diseases for describing the four-way interactions between host, host microbiome, pathogen, and environment (Fauci and Morens, 2012; Bernardo-Cravo et al., 2020; Morens and Fauci, 2020): (*i*) The relationship between host and his or her microbiome may not be monotonically competitive; for example, host microbiome can be refuge camps for opportunistic pathogens, and the microbiome may lose suppressive effects to opportunistic pathogen when itself enters alternative dysbiosis states. (*ii*) Similarly, the relationship between host and host microbiome can be complicated, could even be frenemy relationship; for example, diseases such as BV (bacterial vaginosis) may be caused by the dysbiosis of vaginal microbiome, and there may not be a formally identified BV pathogen. On the other hand, host physiology and immunology can significant impact the ecology and physiology of microbiomes, and therefore their relationship are bidirectional. In fact, the triangle relationship in the floor of the pyramid should by cyclic, and perhaps the cyclic nature is a norm in all facets of the pyramid.

diseases of plants, particularly of crops and forests, from which humans get food and major ecosystem services such as timbers, habitats for wildlife, conservation of soil erosion, prevention of desertification and watershed preservation and stable rainfall and climate. **Figure 2** summarizes the major components of medical enterprises we discuss in this article, from disease and/or insect pests of plants (crops and forests), animals (livestock and wildlife), and humans. Obviously, the medical enterprises span many facets of science, technology, socioeconomics, and humanity (e.g., Dobson et al., 2020). In the present article, our focus is exclusively on ecological facet, the justifications of which are briefly explained below.

The ecological perspective of "One Health" is a strategy for tackling diseases, which takes into accounts all components and factors that may cause or raise risk of disease, and in which properties of human, environmental, and animal health are assessed in a unified manner to detect, understand, and solve public health problems (Ellwanger et al., 2020). Those components/factors may include environmental and ecological/wildlife, as well as domestic animal and human. The human factors also cover behavioral and medical issues, such as cultural, political and other socio-economic drivers that can influence disease spread and epidemics (Lloyd-Smith et al., 2005, 2009; Luis et al., 2015, 2018; Cunningham et al., 2017; Ellwanger et al., 2020). The devastating impacts of zoonoses on human health and wellbeing have been vividly demonstrating by the current COVID-19 pandemic, which is currently classified as emerging infectious disease (EID) with probable animal origin. Identifying the possible zoonotic emergence and the exact mechanisms responsible for its initial transmission can play a critical role in designing and implementing suitable preventive barriers against the further transmission of SARS-CoV-2. In consideration of the strong interrelatedness among animals, humans, and environment, prioritized research focus on one-health approach is likely to identify critical intervention steps in the transmission of zoonotic viruses (Gibb et al., 2020a,b; Latinne et al., 2020; Rahman et al., 2020; Tiwari et al., 2020).

The "One Health" strategy has been playing a critical role in investigating and dealing with emerging and reemerging infectious diseases, and it is undoubtedly one of the most successful ecological frameworks for dealing with emerging and reemerging infectious diseases. Since there are already many excellent reviews on "One Health" strategy, we are not going to further discuss it in this article. Different from the One Health strategy, in this article, we further broaden the scope of our discussion to virtually all major medical enterprises aimed to protect human well-beings from diseases of plants, livestock, wildlife, and ourselves. Furthermore, we focus on theoretical ecology foundations for diseases and supporting

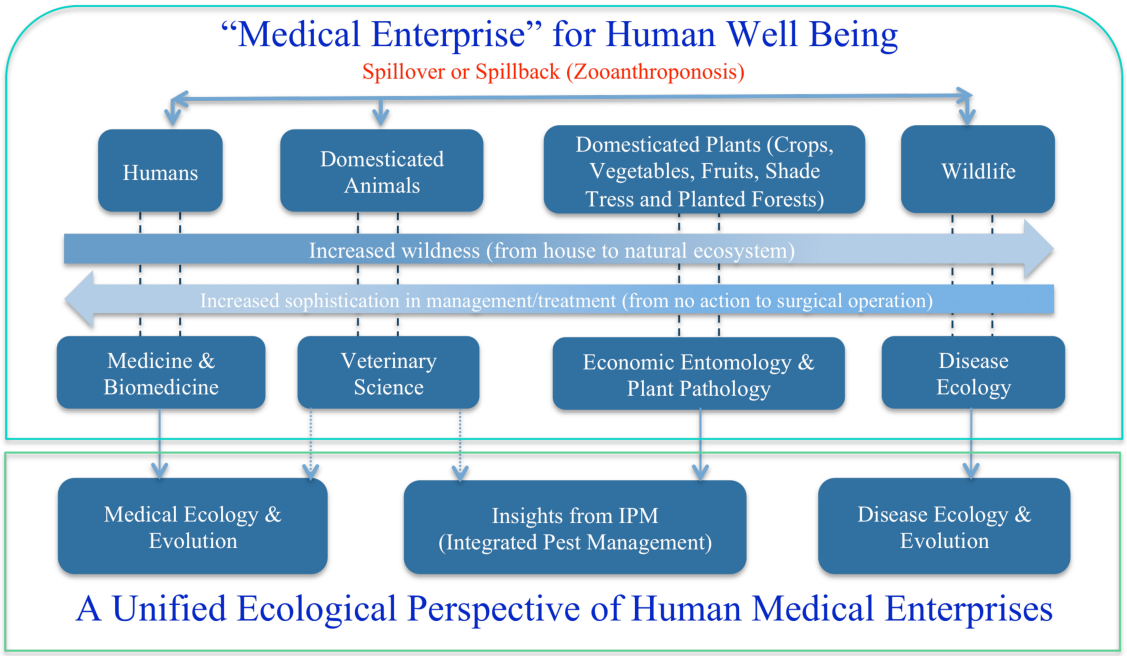

FIGURE 2 | A unified ecological perspective of the human medical enterprises (sciences and technologies): three fields or subjects—medical ecology for human diseases, integrated pest management (IPM) for diseases and insect pests of crops and forests, and disease ecology of wildlife.

fields such as genomics, metagenomics, bioinformatics, and computational biology.

Ecology is not only relevant but also critical to virtually all major aspects of medical enterprises (sciences and technologies) illustrated in **Figure 2**. This is because pathogen, the causing agent of disease, is not an isolated entity; instead, pathogen interacts with its host and constitutes an ecosystem, not to mention that both pathogen and host are influenced by their environment. Ecosystem and environment are the very entities that ecology investigates. In fact, pathogen and host, and possible vector organism that introduces pathogen to host, frequently constitute the core of the host-pathogen ecosystem. As shown in **Figure 2**, at least three ecological subjects: disease ecology, IPM and medical ecology, are associated with medical enterprises of human well beings. The remainder of this reviewer is organized as four sections: (*i*) disease ecology of plants; (*ii*) disease ecology of animals; (*iii*) cancer ecology; (*iv*) ecology of human microbiome associated diseases; and (*v*) proposal toward a unified medical ecology of human diseases.

DISEASE ECOLOGY OF PLANTS—THE INTEGRATED PEST MANAGEMENT

Before discussing the emerging/reemerging infectious diseases of animals and humans, we first discuss the diseases of plants. A simplified view of diseases is the diseased states of hosts caused by pathogens, which are usually microbes (bacteria, fungal, viruses, etc.) but insect pests, nematodes, mites as "pathogen" for plants (crops and forests) are obviously the largest exception. Here, we first discuss the disease ecology of plants, i.e., the integrated pest management (IPM).

The disease ecology can be defined as "the ecological study of host-pathogen interactions within the context of their environment and evolution" (Kilpatrick and Altizer, 2010). Broadly speaking, the origin of disease ecology can be traced back to the 1930s when entomologists studied the insect-parasitoid dynamics, known as Nicholson–Bailey model, which can be considered as difference equation version of the classic Lotka–Volterra differential equations for modeling species interactions (predator-prey, competition, etc.). The latter was proposed by mathematician and physicist Alfred Lotka and Vito Volterra during 1910s–1920s and their work set the foundation for theoretical (mathematical) ecology (Kingsland, 1995). Therefore, it can be seen that from the very beginning, theoretical (mathematical) ecology has been closely associated with the study of disease pathogen, although initially it was about the disease of animals and plants. The field took off in the 1950s and 1960s when population ecologists, entomologists, and plant pathologists were engaged in hot debates on the mechanisms of population regulation in nature. Theoretically, the debates helped to expand the breadth of theoretical ecology, and somewhat "ironically" shifted the focus of ecology away from population ecology, because the debates pushed ecologists and mathematicians to recognize that the mechanisms of population regulation and closely related themes such as population (ecosystem) stability, species extinctions could hardly be understood without looking into beyond species interactions. Those debates culminated at annual Cold Spring Harbor symposiums on population ecology in the 1960s but, as many ecologists believe, generated little

consensus until today, other than shifting the focus of ecology from population ecology to community ecology, and directly catalyzed the emergence of ecosystem ecology from 1960s to 1980s. Although population ecology has never regained its glory since then, the methodology of using mathematical models pioneered by population ecologists has been firmly established as a tradition in whole ecological sciences, including landscape ecology and global change ecology (or planetary ecology). Practically, those debates had far reaching impacts on the strategies for humans to fight against diseases and insect pests of crop and forest plants.

By the 1960s, a consensus has been written into the textbook, and the consensus was that it is generally neither wise nor feasible to eradicate insect pests and/or plant diseases (Kogan and Jepson, 2007). The so-termed IPM is both the strategy and philosophy for humans to deal with the pest (insect pest and plant diseases) problem (**Figure 3**). Philosophically, we human usually have to coexist with pests, and indeed, we should tolerate their damages as long as the damages are below the so-termed economic tolerance level (ETL) (Kogan and Jepson, 2007). The reason we have to tolerate pests is certainly not because we do not wish to eradicate them, simply because we usually cannot destroy them or the eradication is too costly to bear. In fact, during the approximately two decades after World War II, the wide availability and usage of the pesticide DDT, once convinced people that the insect pest problem was solved forever. DDT was first developed in 1939 and was first used during World War II to clear South Pacific islands of malaria-causing insects for United States troops while being used as an effective delousing powder in Europe. It was believed to be the most powerful pesticide human had ever invented given it could virtually kill all kinds of insects tested from lice, mosquitoes, to caterpillars, and the inventor was awarded Nobel chemical prize.

When DDT was first introduced for civilian use in 1945, few expressed doubts. One was nature writer Edwin Way Teale (The Pulitzer Prize Winner of 1966), who warned, "A spray as indiscriminate as DDT can upset the economy of nature as much as a revolution upsets social economy. Ninety percent of all insects are good, and if they are killed, things go out of kilter right away." Another was Rachel Carlson, the author of "Silent Spring" (1962) (NRDC, 2015), which spawned the environment movement since 1960s and the establishment of EPA (Environmental Protection Agency) in the United States. It was already known that in the 1960s, DDT was found in the ocean's deepest and most inaccessible reaches such as fishes, mollusks and seabirds, and in penguin of the South Arctic. When the pesticides such as DDT was banned from usages due its potential healthy implications, entomologists and plant pathologists began to adopt a more ecological and environmental friendly approach, that is, the IPM (e.g., Kogan and Jepson, 2007). With the IPM philosophy, besides backing off from the eradication to tolerating (co-existence) strategy, and an *integrated* approach (rather than relying on a single tactic in particular pesticide, which should be minimized or avoided as much as possible) with multiple tactics such as quarantine, biological control with natural enemies, crop rotation, mixed plantation, biodiversity augmentation, etc. should be adopted. With the IPM, complex system analysis and mathematical modeling of pest-crop (forest) ecosystem should be used to quantify the ETL and economic threshold (ET), to predict the pest population dynamics, and to devise decision-making rules. By the 1990s, decision support systems (DSSs) using expert system and AI

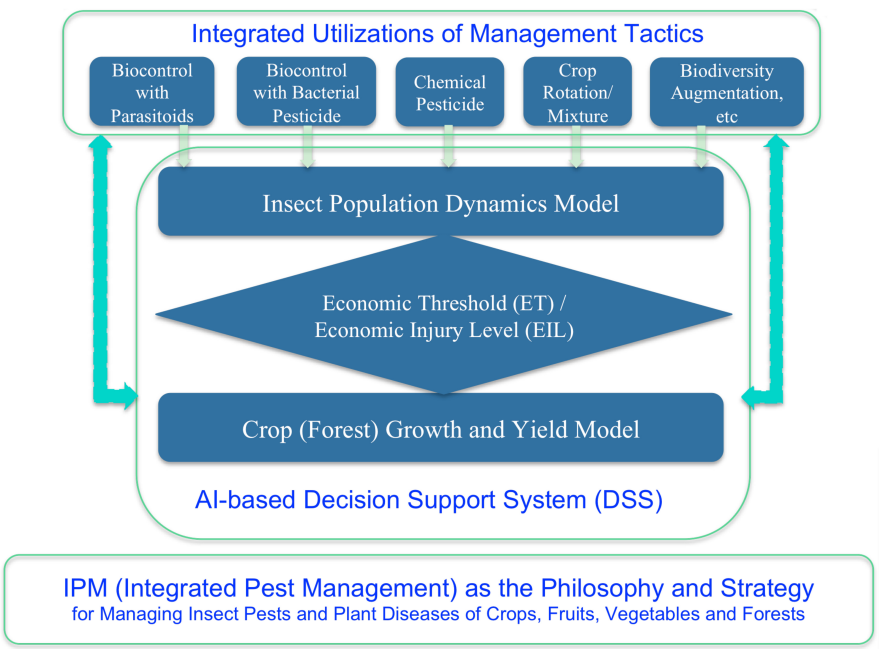

FIGURE 3 | Strategy, tactics, and decision-making in the integrated pest management (IPM).

technologies had already been advocated to implement and guide the practice of IPM (Ma et al., 1992; Kogan and Jepson, 2007). Of course, constrained by then state-of-the-art in AI, the application of AI in IPM was rather primitive in today's standards. Nevertheless, the ideas to use mathematical modeling and AI technology still certainly make sense not only in today's IPM, but also in biomedicine of humans, especially as future trends (He et al., 2019; Zeng et al., 2021).

In retrospect of the history of IPM and in perspective of bio- and clinical medicines, we may draw the following four analogical principles:

(i) First, the tolerance vs. eradication philosophy: with IPM (**Figure 3**), the tolerance or coexistence is the predominant strategy, although the so-termed TPM (total pest management) for a handful of insect pests were attempted with mixed results, similarly attempted in veterinary medicine of livestock. In bio-/clinical- medicine of most human diseases, humans are forced to coexist with pathogens from population perspective, although a handful of human pathogens appear to have disappeared (e.g., SARS) or have been eradicated by humans (e.g., Smallpox). We argue that even though the eradication of human pathogens seems infeasible as in the IPM, the determination and efforts are often the top priority because the tolerance thresholds for human diseases are much smaller and frequently approach to zero.

(ii) Second, integrated applications of multiple control tactics are appropriate in both IPM and biomedicine. *Quarantines* to prevent the spread of invasion insect pests and plant diseases are standard practices in the international trade and a basic law enforcement function of customs on *global* scale. In fact, quarantines are often the only effective measures to control invasion pests. Similarly, to control COVID-19 like pathogens, apparently, quarantines are equally important, if not more. *Lockdown* can be considered as "*local*- or *population* level-quarantines," and *social distancing* and *masking* may be considered as quarantine measures at the scale of *individuals*. Even if we do not believe integrated treatments or measures are necessary or desirable for treating human diseases, the alarm from superbugs (antibiotic resistant bacteria) is a proof for the severe side effects of chemical drugs. Although it is obvious that chemical drugs are and will still be predominant treatment measures for human diseases, the importance of alternative medicines has received increasing recognition. We argue that the recognition of human microbiome in human health and diseases can be considered as the counterpart of recognizing the importance of natural enemies in IPM—the biological control. In fact, biological control or bio-control is well recognized as the most desirable control tactics thanks to its ecological safety because it usually only kills pest and produces no harms to humans and environment. Without biological control, the only way to produce truly organic food may be to supply the humans with the "leftover" of insect pests or plant diseases, which may also partially explain the high cost (low yield) of organic foods, not to mention the aesthetic devaluation of the vegetables and fruits bitten by bugs. Therefore, we believe that the importance of human microbiome (especially human virome) in prevention, containment and treatment of human diseases cannot be overly emphasized because there must be natural opponents of pathogens among thousands (if not millions) species of fellow microbes and because competition or struggling for living is part of life as predicted by Darwin's evolutionary theory.

(iii) In the era of IPM, mathematical modeling (including system analysis and primitive AI in the 1990s) plays significant role for predicting pest dynamics and decision-making (when and what integrated management measures should be taken promptly). In bio-/clinical medicine, besides traditional mathematical modeling and renovated AI technologies, bioinformatics and computational biology become indispensible. Without them, we cannot even "see" the existence of "natural opponents" of pathogens in human microbiomes. One example of showing the emergence of bioinformatics in biomedicine is the transformation of the previously mentioned Cold Spring Harbor, which is famous for its bioinformatics today, while it was well known for its symposiums on *population ecology*, as mentioned previously.

(iv) Where are the first principles that motivated the IPM philosophy and also the underlying mechanisms that support the IPM strategy and most of its tactics? The answer is *ecological science* (**Figure 3**). In fact, virtually the whole insect ecology and significant part of crop (forest) ecology are devoted to the IPM. Similarly, microbiome research is first an ecological problem because understanding species interactions (among microbes and between microbes and their hosts) is a typical topic of ecological science. Somewhat unique to microbiome research is that the ecological studies of human microbiome depend on bioinformatics and computational biology. In fact, the subject of molecular ecology also depends on bioinformatics. This is because in the IPM era, human naked eyes augmented by optical microscopes (occasionally electronic microscopes) are sufficient for the identifications and counting of pathogens/pests; however, for microbiome research, DNA sequencing technology and consequent bioinformatics analyses are indispensable for the very first step of microbiome research—identify microbial species and estimating their abundances. For this reason, medical ecology of human microbiome can be defined as cross-disciplinary studies of human microbiomes for the objectives to understand their implications to human health and diseases from the ecological perspective, which are supported by bioinformatics and computational biology, theoretical ecology, clinical medicine and medical microbiology.

DISEASE ECOLOGY OF ANIMALS WITH A FOCUS ON ZOONOSES

The disease ecology, of course, is not limited to the ecology for plant diseases as briefly introduced previously, where the

IPM has been established as the philosophy and strategy for managing insect pests and diseases of plants (crop, vegetables, fruits, and forests), and the biological control (bio-control with natural enemies) is well regarded as the most appropriate measure because of its ecological and environmental friendly nature. In addition, biodiversity augmentation such as mixed plantation of tree plants (mixed forests) has been demonstrated to be effective in managing forest diseases and insect pests. Nevertheless, the role of biodiversity augmentation in control plant diseases and pests is limited, perhaps because manipulating plant diversity is often economically unworthy or infeasible. Of course, increasing natural enemies may also be considered as increasing biodiversity, but it is usually categorized as bio-control. As it is briefly discussed below, in the disease ecology of wildlife, biodiversity or the so-termed diversity–disease relationship (DDR) has been a focus from early days of zoonotic research. Indeed, the importance of DDR of wildlife zoonoses cannot be overly emphasized because it is highly relevant to the spillover risk of zoonoses to humans!

Strictly speaking, the previous discussed IPM is traditionally not investigated in the context of disease ecology; instead it belongs to the domain of applied entomology (agricultural entomology, forest entomology, and horticulture entomology) and plant pathology. The reason we put the IPM into the context of disease ecology is to draw the common and essential principles underlying the diseases of plants, animals, and humans as shown later. The strict usage of disease ecology is usually limited to the diseases of the wildlife. Obviously, pathogens of wildlife are not only a common and integral part of natural ecosystems, but they are also linked to dynamics of wildlife populations. Their actions may drive their hosts to the extinctions occasionally; consequently pose deadly challenges to conservation efforts of endangered species. In the long run, they are also drivers of evolution and play pervasive ecological and evolutionary roles in the ecology and evolution of wildlife. At the foundational level, the mission of disease ecology includes the efforts to deepen our understanding on the pathogen transmission and spreading over space and time as well as their impact on host populations. These efforts also set foundation for epidemiology, which aims to identify risk factors for infectious and non-infectious diseases. **Box 1** summarized some key concepts and aspects of disease ecology.

In our opinion, the field of zoonoses and EID are severely fragmented, possibly due to its highly cross-disciplinary nature. The fragmentation is highly undesirable because an inadvertent knowledge gap may leave the door open for an unwelcome black swan to enter. Therefore, sufficient coverage from cross-disciplinary perspectives is crucial for the healthy development of the field. The field traditionally involves epidemiology, public health, clinical medicine, veterinary medicine, medical microbiology and virology, immunology, ecology and evolution, environmental science, etc. In the 21st century, some emerging novel sciences and technologies joined in, notably molecular biology, bioinformatics, disease ecology, medical ecology, AI, and big data science and technology. The focus of this article is disease- and medical-ecology perspectives.

Arguably the most important mission in studying disease ecology of wildlife or zoonoses is to do with the emerging/reemerging infectious diseases (EID), which are frequently caused by pathogens originating from animal hosts, especially wildlife animals (Guégan et al., 2020). EID events are dominated by zoonoses (60.3% of EIDs): the majority of which (71.8%) originate in wildlife (e.g., SARS and Ebola virus), and are increasing significantly over time (Jones et al., 2008). Zoonoses are infectious diseases that are naturally transmittable from vertebrate animals to humans. Zoonotic viruses are not only the most frequently (constituting over 65% of pathogens discovered since 1980) newly emerging human pathogens, but also include some of the most heinous infectious diseases such as Ebola and Marburg virus, HIV-1 and HIV-2, Sin Nombre virus, Nipah, Hendra and Menangle virus, West Nile virus, Borrelia burgdorferi, and more recently (after 2000), SARS, Middle East respiratory syndrome (MERS) and several subtypes of avian influenza, as well as most recently and likely COVID-19. Some zoonoses requires intermediate vectors (also known as vector-borne pathogens: VBPs), including important human diseases such as malaria and dengue, as well as zoonotic diseases for which people are dead-end hosts, such as Lyme disease and West Nile virus (Taylor et al., 2001; Woolhouse et al., 2001; Woolhouse, 2002; Woolhouse and Gowtage-Sequeria, 2005; Kilpatrick, 2011; Kilpatrick and Randolph, 2012; Johnson et al., 2015a). Johnson et al. (2015a) survey suggested that wild animals were the major source (91% or 86 out of 95) transmission of zoonotic viruses, while only 34% (32 out of 95) transmitted by domestic animals, and 25% by both wild and domestic animals. For example, the Nipah virus (NIV) was introduced into pigs from wild animals, time after time, such as bats, leading to persistent enzootic infection in pigs. Eventually, spillover of NIV to livestock workers occurred (Walsh, 2015).

It was found that the majority (94%) (N = 162) of zoonotic viruses discovered before 2015 were RNA viruses, far more than the number of zoonotic DNA viruses. RNA viruses, such as influenza viruses, flaviviruses, enteroviruses, and coronaviruses, have inherently deficient or absent polymerase error-correction mechanisms and are transmitted as quasi-species or swarms of many, often hundreds or thousands of, genetic variants. Their genetic instability is particularly high, which allows for rapid microbial evolution in an extremely diverse population under natural selection (Morens and Fauci, 2020).

Wild rodents were identified as a spillover source of some zoonotic viruses, such as zoonotic arenaviruses and zoonotic bunyaviruses (Han et al., 2015). Bats belong to oldest mammals and contribute about 20% to mammalian diversity (Zhang et al., 1992; Johnson et al., 2020). Their vast diversity and long co-evolutionary relationships with pathogens maximize the opportunity for cross-species mixing and maintenance of quasi-species pools of viruses that may infect a range of hosts (Menachery et al., 2017). Bats appear to be the most active transmitters given they were more implicated for zoonotic paramyxoviruses and most zoonotic rhabdoviruses (Brook and Dobson, 2015), while primates were implicated as a transmission source of zoonotic retroviruses (Johnson et al., 2015a). Bats are also among the most abundant source for novel viral sequences

BOX 1 | Eight selected key concepts and topics in the *disease ecology* of zoonoses, mainly summarized from Kilpatrick and Altizer (2010) and others.

No.	Key concepts/aspects	Interpretations
1	Pathogen classifications: macroparasites vs. microparasites	In disease ecology, terms such as pathogens, parasite, and infectious diseases are frequently used interchangeably, but strictly speaking, what are transmitted are parasites or pathogens, and diseases are simply a host state of pathogenic conditions. (1) The *microparasites* (including viruses, bacteria, fungi, and most protozoa including malaria) reproduce inside their hosts on rapid time scales that are much shorter than their hosts' lifetimes. The microparasite usually causes short-term infections that may result in host death or the development of immunity. (2) The *macroparasites* (including most parasitic worms termed helminthes and parasitic insects and other arthropods), which are usually larger, long-lived and rarely complete their whole life cycles within a single host. Vector (hosts) may be necessary to complete the transmission life cycles of macroparasites. For macroparasites, the host immune response may be lost—often short-lived or incomplete—leading to persistent infections and continuous re-infections (Kilpatrick and Altizer, 2010).
2	Population-level (scale) parameters: basic and effective reproductive ratios (R_0 and R_e)	Compared with clinical medicine, disease ecology of wildlife heavily depends on mathematical modeling. For example, the basis transmission models (either *density-dependent* or *frequency-dependent* transmissions), *basic reproductive ratios* (R_0) of pathogens, *equilibriums* of infections (transmissions) are commonly used and majority of them are derived from population ecology. For example, the basic R_0, which specifies the initial growth of pathogen in a previously unexposed host population (such as the initial invasion of human population by SARS-CoV-2), can be a rough measure for predicting whether the pathogen can invade and spread (e.g., if $R_0 > 1$). A more general metric is the effective reproductive ratio (R_e) in a population, in which some individuals may not be susceptible due to previous exposure (immunity), vaccination, or inherited maternal anti-bodies. A rough estimation of R_e could be R_0 discounted by the fraction of resistant individuals (Kilpatrick and Altizer, 2010).
3	Population-level (scale) relationships: density-dependence and critical threshold density; frequency-dependent transmission; continuum of density- and frequency-dependence	Besides R_0 (R_e), a key aspect of pathogen transmission is whether and how it depends on host population density, which could be density-dependent, inversely density-dependent or density-independent. Consequently, there can be a *threshold density*, below which transmission is inefficient and the pathogen would not persistent in the host population. Alternatively, when the transmission is density-independent, it can be frequency-dependent. In the frequency-dependent transmission paradigm, the force of infection—the per capita rate at which a susceptive individual becomes infected—rises with the fraction of the host population that is infectious but does not rise with the overall host density. Different from density-dependent transmission, there may not be a threshold associated with frequency-dependent transmission. Theoretically, the frequency-dependent pathogens may exist at very low host densities. In practice, most pathogens may fall in the continuum of the both extremes. The mode of transmission can play an important role in whether transmission is density or frequency-dependent. For example, transmission *via* aerosol and water often increases with host density; transmission *via* sex and some vector-borne diseases is often frequency-dependent (Kilpatrick and Altizer, 2010).
4	Community-level (scale) paradigm: diversity–disease relationships (DDR)	As mentioned previously, the impacts of pathogens on individual hosts are usually either death or induced immunity. The impacts of pathogens should also be observed and analyzed at population and community levels. At population level, the impacts depend on pathogen virulence, the reduction in host fitness (survival or reproduction) caused by the pathogen. Generally for pathogens that reduce host survival, those with intermediate virulence appear to have the largest negative impacts on host populations. Pathogens can also impact host species interactions in other ways that increase host community diversity, including preventing competitive exclusion and altering predation pressure. The DDR (diversity–disease relationship) of zoonoses has been an active research field since the 1960s. Biodiversity changes can lead to alternations of infections in many zoonoses, but the underlying mechanisms are diverse. The richness and abundance of alternate hosts, infection "decoys," intermediate vectors, predators, and even other symbionts may have enormous potential to either inhibit or facilitate the transmission of pathogens. It is the net effects of these mechanisms that may lead to either an overall increase or decrease in disease risk with the decline of biodiversity. When the disease risk decreases with the biodiversity increase, it is termed *dilution effect.* The opposite pattern—the increased risk associated with biodiversity increase—is termed *amplification effect* (Keesing et al., 2006, 2010). If dilution effects are prevalent, it is expected that biodiversity loss should lead to "*loss of dilution effects*" to pathogen infections, namely the "*release*" of pathogens. Note that dilution and amplification effects may be present concurrently in the same host–pathogen system: for example, there may be a component of amplification effect (increase in transmission rate), but overall a net dilution effect is observed if the effect of diversity on reservoir host population density is stronger (Luis et al., 2018). For further information on DDR, readers are referred to Keesing et al. (2006, 2010), Cardinale et al. (2012), Randolph and Dobson (2012), Salkeld et al. (2013), Wood et al. (2014), Civitello et al. (2015), Johnson et al. (2015b), Luis et al. (2015, 2018), Newbold et al. (2015, 2018), Shah et al. (2019), Merrill and Johnson (2020), Rohr et al. (2020), and Schmeller et al. (2020).
5	Community-level (scale) paradigm: heterogeneity–disease relationship (HDR)	Host heterogeneity is a critical aspect of disease ecology. Heterogeneity is different from diversity, but distinguishing it from diversity is not trivial, given that heterogeneity and evenness (one aspect of diversity) is frequently considered as both sides of the same coin. Shavit et al. (2016) cited from Robert Frost (1916) "The Road Not Taken," the following sentence "*Two roads diverged in a wood, and I took the one less traveled by, and that has made all the difference*." According to Shavit et al. (2016) "heterogeneity implies a collective entity that interactively integrates different entities, whereas diversity implies divergence, not integration." Therefore, diversity emphasizes divergence and partition and is usually measured with system entropy, while heterogeneity stresses integration and interactions, and consensus for measuring it is still weak. In disease ecology, the heterogeneity concept usually refers to variability of individuals in susceptibility and other characteristics (such as contact rates, infectiousness as well as spatio-temporal variability in host characteristics or the environment) (Bloomfield et al., 2020). We call this "inter-individual variability" usage of heterogeneity in disease ecology as traditional heterogeneity concept, but we emphasize the previously mentioned "interaction" focused heterogeneity concept may open meaningful new research frontiers in disease ecology and certainly worthy of explorations in future.

(Continued)

BOX 1 | (Continued)

No.	Key concepts/aspects	Interpretations
		The heterogeneity can have critical impacts on pathogen transmission, and consequently on efforts to control disease. The so-termed 80/20-rule seems widely applicable in disease transmission, which refers to phenomenon that 20% of the host individuals may be responsible for at least 80% of subsequent transmission. In the extreme, the super-spreaders may cause disproportionally huge secondary transmissions, sometimes, as much as 95th or 99th percentile of a Poisson distribution with mean R_e). This kind of phenomenon is somewhat ubiquitous in disease ecology under various guises such as 80/20 rule, power-law distribution, and scale free networks, which often exhibit so-termed phase transitions with certain critical thresholds. For examples, if their thresholds can be predicted in advance, we may be able to prevent the transitions from local endemic to regional epidemic, from the epidemic to ultimately global pandemic. For these arguments, power law, especially Taylor's variance-mean power law can play a critical role in measure heterogeneity (Taylor, 1961, 2019; Ma, 2020b; Ma and Taylor, 2020). Another cross-scale metric that can be used to measure heterogeneity is Ma and Ellison (2019) dominance concept (metrics). In our opinion, the heterogeneity–disease relationship (HDR) in disease ecology has not been systematically investigated, and the first challenge should be to develop proper heterogeneity metrics.
6	Heterogeneity-host-switching (spillover) probability	An important type of heterogeneity in disease ecology is to do with the *multi-host pathogens* that can be transmitted between several different host species, which include one particularly important group—the zoonoses that can be transmitted between humans and non-human animals including HIV, influenza, SARS and possibly COVID-19. For these multi-host pathogens, some hosts are amplifiers (their existence raise pathogen transmission) while others may be diluters or dampeners (their existence decreases transmission). The identities and abundances of different host species (which are measured in *diversity metrics* in ecology) are shown to have a significant impact on the transmission of plant diseases as well as animal diseases. There are two important hypotheses in disease ecology regarding multi-host pathogen systems: the dilution (amplification) effect hypothesis postulates that disease risk will decrease (increase) as the host species diversity increases. More advanced research topics regarding host heterogeneity in disease ecology include the studies on how spatial structures (especially in the context of meta-population), dispersal patterns, and landscape-level heterogeneity can influence the spatial spread of pathogens.
7	Host-pathogen co-evolution	Host-pathogen *evolution* is obviously a key field of disease ecology given that ecology and evolution studies are hardly separable. Parasites and hosts, together with their changing environments, can act as selection force to each other. The first fundamental question in the field is: Why do parasites harm their hosts at all, given they depend on their hosts for their own living and transmission? The core of the first question is actually the virulence of pathogens, which is a key question of disease ecology and evolution. Conventional wisdoms would predict that parasites should evolve to become benign and consequently prolong the lives of the hosts they infect. For example, it is believed that many symbionts are evolved from parasites that had lost virulence ultimately. However most extant parasites cause substantial harm, partially because replications unavoidably damage host tissue and consume host resources. The *trade-off theory for virulence* posits that parasites with extremely high virulence tend to kill hosts too quickly before they can transmit, and with extremely low virulence tend to produce insufficient replications for transmission. Therefore, intermediate levels of within-host replication (hence virulence) are favored by natural selection. Alternative theories to the trade-off theory exist for explaining the observed virulence in parasite-host systems (Kilpatrick and Altizer, 2010). Host strategies to fight infection can be classified into two types: host tolerance and host resistance. The former refers to the capacity for a host to tolerate infection with a pathogen by minimizing the damage done by the parasite but without preventing replication or transmission of the pathogen. In contrast, the latter refers to the capacity for a host to reduce the probability of being infected, reduce the pathogen replication within the host, and/or increase the speed of pathogen clearance (recovery). This brings about the second fundamental question in disease evolution: Why are not hosts more resistant to pathogens, given that hosts would benefit most from resisting infection? Potential explanations include a *trade-off* between resistance traits and other fitness-related traits, or the counter-back selection pressure from pathogen evolution to evade or counter host resistance traits, etc. The last explanation is related to a broad topic in evolutionary biology—the Red Queen hypothesis for co-evolution. The host-parasite interactions can lead to co-evolutionary dynamics that may increase the genetic diversity of both hosts and pathogens through co-speciation events and genetic arms races (Becker et al., 2018). The Red Queen hypothesis predict that high infection rates can ultimately favor host sexual reproduction as a strategy for generating host genotypes that may resist infection by common parasite clones. It is postulated that host microbiomes may also be involved in the Red Queen hypothesis, especially in sexual selection (Ma and Taylor, 2020).
8	Insights for disease prevention and control	Understanding above key aspects of disease ecology is essential for devising disease prevention and control strategies. In humans (clinical medicine) and domesticated plants (agricultural and forest entomology and plant pathology) and animals (veterinary medicine), enormous efforts have been made to lower pathogen transmission and/or eradication. Three main strategies are *culling* (prescribed killing for animals, plants and disease vectors), *behavioral modifications* (such as quarantines and social distancing), and *vaccination*. Culling can be adopted when the transmission is believed to be density-dependent with an objective to reduce host densities below the threshold density. Quarantines and social distancing are efforts to lower contact rates between infectious and susceptible individuals when the transmission is believed to be frequency-dependent (Bloomfield et al., 2020). The third major strategy—vaccination—is aimed to raise herd immunity, i.e., the percentage of the population that is immune to infection, either through prior exposure or vaccination. The goal of vaccination is often set to prevent invasion by locally eradicating the pathogen. For homogenous population, the critical threshold for achieving such a herd immunity level is $(1 - 1/R_0)$, because it reduces $R_e = R_0$ (S/N) under *1* (Kilpatrick and Altizer, 2010).

(Anthony et al., 2013), which have been identified mainly from enteric samples (i.e., bat guano). The huge pools of viruses in bat guano may play a critical role in the bat microbiome to prime their immunity (Menachery et al., 2017).

Despite harboring exceptionally diverse kinds of viruses, surveyed bats rarely display signs of disease, a phenomenon similarly discovered in humans with herpes viruses (Barton et al., 2007). Understanding why bats seem to possess exceptional immunity against viruses is of obvious importance. One important reason may be that virus tropism differences between species and tissues may contribute to limiting disease in bats. Enteric infection can be a significantly different tissue than the respiratory tract in terms of disease and adaptive immunity. The enteric location may generate a dampened adaptive response that permits viral maintenance, while elements of adaptive immunity in bat species keep functional, similar to the members of the microbiome in human guts (Menachery et al., 2017).

The unique host environment of bats is also responsible for the broad diversity in corona-virus (CoV) quasi-species pools. During flight, bats can accumulate reactive oxygen species (ROS) for short periods of time, which may have mutagenic effects, possibly overwhelming CoV proofreading repair and/or altering viral polymerase fidelity and increasing species diversity. The mutagenic effects may also be critical for cross-species or spillover transmission (Seronello et al., 2011). Similarly, Zhou et al. (2016) found that the constitutive expression of type-I IFN (interferon or IFN-α) in bat hosts may select for advantageous viral mutations that enhance resistance to innate immune antiviral defense pathways and provide a replication advantage, especially after cross species transmission. That is, constitutively expressed IFN-α may result in the induction of a subset of IFN-stimulated genes associated with antiviral activity and resistance to DNA damage, suggesting a unique IFN system of bats that promotes their capacity to coexist with viruses (Zhou et al., 2016).

It should be noted that, in spite of previous discussed multiple suspicions bats are implicated, those animals should not be automatically labeled as "bad guys" in spillover events. It is a fact that bats harbor more viruses than many animals, and several studies already pointed important features of bat immune system as involved in both resistance to disease and viruses maintenance in bat populations (Zhou et al., 2016). In other words, bats may possess special mechanisms to "neutralize" disease risks from viruses they host. Actually, few data is available concerning other wildlife species eventually similarly or even more "spillover prone" than bats.

Phylogenetic analyses based on sequence similarity have been playing an important role in studies of the origin and cross-species transmission (spillover) of coronaviruses (e.g., Latinne et al., 2020). Munnink et al. (2020) conducted an in-depth investigation of SARS-CoV-2 infections in animals and humans working or living in 16 mink farms in the Netherlands. SARS-CoV-2 infections were detected in 68% (66 out of 97) of the owners, workers, and their close contacts. Their study provided evidence of SARS-CoV-2 spillover back and forth between animals and humans within mink farms given some people were infected with viral strains with an animal sequence signature. Theoretically, an animal species of sufficiently high population density to allow natural selection and a competent ACE2 protein for SARS-CoV-2 to "hook," such as mink, would be a possible host of the direct progenitor of SARS-CoV-2 (Zhou and Shi, 2021). However, whether bats or pangolins, which carry coronaviruses with genomes that are ∼90 to 96% similar to human SARS-CoV-2, were the animal source of the first human outbreak, are still in hot debates because there is not certain evidence other than the previously mentioned genome similarity (Hu et al., 2020). Phylogenetic analyses of viral genomes from bats and pangolins revealed that further adaptations, either in animal hosts or in humans, must have occurred before the virus caused the COVID-19 pandemic, if SARS-CoV-2 was indeed spillover from bats or pangolins. SARS-CoV-2 antibodies were detected in human serum samples taken outside of China before the COVID-19 outbreak was detected, which indicates that SARS-CoV-2 had existed for some time before the first cases were described in Wuhan (Andersen et al., 2020). Therefore, it is possible that spillover of SARS-CoV-2 had occurred long before humans discovered its infections.

The zooanthroponosis of SARS-CoV-2 (COVID-19) has been confirmed by its successful detections in animals including domesticated cats, dogs, and ferrets, as well as captive-managed mink, lions, tigers, deer, and mice. Other than circumstantial evidence of zoonotic cases in mink farms in the Netherlands (Zhou and Shi, 2021), no cases of natural transmission from wild or domesticated animals to humans have been confirmed; therefore the zoonotic status of COVID-19 is still a conjecture (e.g., Dhama et al., 2020). Currently nearly 1/4 billion human COVID-19 infections documented seem to be exclusively *via* human–human transmissions. That is, SARS-CoV-2 virus and COVID-19 do not seems to satisfy the WHO (World Health Organization) definition for zoonoses. For this reason, Haider et al. (2020) suggested to classify SARS-CoV-2 (COVID-19) as an EID of probable animal origin. Compared with other emerging viruses, such as Ebola, avian H7N9, SARS-CoV, and MERS-CoV, SARS-CoV-2 is of relatively low pathogenicity and moderate transmissibility.

ECOLOGY AND EVOLUTION OF CANCERS

Arguably, few other human diseases have been investigated more extensively from ecological and evolutionary perspectives than cancers. Perhaps, the only exceptional category has been the epidemiological studies of infectious diseases, and more recently the microbiome-associated diseases. Ecological concepts and principles have been extensively applied to study cancer and so does the evolutionary theory. **Box 2** summarized 20 such concepts, principles, and theories that originated from ecological and evolutionary sciences and found applications in cancer research. Two particular points are worthy of special mentions here, as explained below:

One is that ecology and evolution are innately interwoven for cancer studies: using Hutchinson (1965) classic monograph titled "*The Ecological Theatre and Evolutionary Play*," cancer evolution is played out in the ecological setting (the "theater")

BOX 2 | Twenty selected key concepts and theories in the cancer ecology and evolution.

No.	Key concepts/hypotheses in cancer ecology	Evo-eco-oncology interpretations	References
1	Tumor vs. ecosystem: tumor represents ecosystem of cancer cells and their environment that may include other host cells, host microbiomes, and their shared environment.	Cancer is an evolving ecosystem. Within a patient, the cancer cells display ecological dynamics of meta-population—consisting of different cancer cell lineages (local- or sub- populations). Cancer cells can evolve adaptive resistance to virtually all treatments due to their access to vast information of human genome. The eco-evolutionary dynamics is exceptionally robust against therapeutic disturbances (perturbations) for three reasons: (1) the cellular diversity (spatial heterogeneity) in the genotypic and phenotypic properties of tumor cells; (2) variations in the tumor environment, dominantly governed by variations in blood flow; (3) response and resistance of cancer cells are shaped by their complex interactions with adjacent host cells, including immune and microbiome cells.	Horning, 2017; Gatenby and Brown, 2018; Reynolds et al., 2020
2	Cancer (cells) vs. X-species | metastasis is similar to *speciation* in evolution, to *migration* and *invasion* in ecology.	Cancer cells are considered as invasive, endemic (native), and/or endangered species. Which one (X-species) is accurate? It may depend on cancer stage and possibly cell lineages. Metastases account for 90% of cancer mortality. Metastatic cancer may be considered as *speciation* event, in which one or multiple cells of a multi-cellular organism (e.g., animal or human) propagate (proliferate) and become the unit of natural selection, similar to a new protozoan.	Gatenby and Brown, 2018; Peplinski et al., 2021
3	Cancer vs. parasite (pathogen)	Cancer is in fact a successful "parasite (pathogen)" that for the most part does not cause the host death. A key to understanding many cancers as parasites is to recognize them being evolving ecosystems, which maximize the fitness of the tumor-propagating cells and advance toward eventually destroying its environment (host) and thus committing evolutionary suicide.	Kareva, 2011, 2015
4	Cancers vs. infectious diseases	Given that the culmination of cancer evolution is the death of host and disappearance of cancer cells, the cancer is more like intra-species competition rather than inter-species competition as in the cases of infectious diseases, where one or both parties may actually win. There is virtually no winner in cancer driven death given cancer evolution is somatic evolution. From this perspective, cancer is more like human aging than many other human diseases. The commonalty is the cell death, and the difference seems to be the programmed, somewhat "selfless" death vs. "selfish" but ultimately suicidal destination.	Korolev et al., 2014
5	Evasion of immune system vs. predator–prey interactions: metabolic adaptation and evasion of the predator (the immune system)	In the local microenvironment of the tumor, both predator (immune cells) and the prey (cancer cells) compete for a shared resource (e.g., glucose), and both may have the same adaptation—upregulated nutrient transporters. When the prey outcompetes the predator for the shared resources, cancer cells will be able to escape the immune system attack and progress further to a malignant state. The adaptations may involve the modification of the microenvironment (known as niche modification/creation).	Kareva, 2011, 2015
6	Cancer stem cells (CSC), as tumor-initiating cells, are similar to "keystone species" in ecological communities.	In ecology, keystone species refer to species that can exert an effect on ecosystem functionality that is disproportionate to its abundance or biomass, with a similar role a keystone playing in an arch. They have potentially limitless duplicative and self-renewal capacities, with the ability to seed new tumors. The CSC can be considered as keystone species of cancer and driver of tumor progression, and they are more resistant to most therapies.	Kareva, 2011, 2015
7	Cancer evolution at cell population level = ultra-microevolution.	The origin of each genetically distinct cancer cell lineage is similar to the sympatric origin of a new asexual species, competing with its progenitors and neighbors for cellular resources. Nevertheless, cell lineage evolution is fundamentally different from conventional organismal evolution. Somatic selection of cancer is driven by differential duplication of cells that are different phenotypically due to genetic mutation and/or epigenetic changes. Two stages can be identified: evolution between tumors and normal tissue and the evolution within tumors. At this level, natural selection is usually a rather weak force, and cancers usually evolve divergently even in similar tissue environment.	Crespi and Summers, 2005; Wu et al., 2016; Maley et al., 2017
8	Cancer evolution at individual host level = microevolution of cancer	Somatic evolution of cell lineages (populations) that have escaped regular cellular control mechanisms (renegade cells) at the individual host level: *the ecological theater of carcinogenesis*. The climax of host-level evolution is the death of host. At the individual level, the "predation" by immune system and "competition" among normal and cancerous cells act as selection force in driving the microevolution of cancer.	Crespi and Summers, 2005; Wu et al., 2016; Maley et al., 2017
9	Cancer evolution at population of host level = *macroevolution* along the human lineage.	Changes in human environments (e.g., diet change from 3,000+ types of plants and fruits to 20+ main types mainly of grains and sugars; from lean game to domestic animal meat and dairy products) and culture changes (e.g., increased lifespan and female reproductive life history) seem to be associated with rising cancer rates in past centuries. Development of most cancers is tightly linked to aging.	Crespi and Summers, 2005; Maley et al., 2017

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BOX 2 | (Continued)

No.	Key concepts/hypotheses in cancer ecology	Evo-eco-oncology interpretations	References
10	Cancer macro-evolution along animal kingdom: beyond humans and extends to other mammals, and possibly invertebrates or even to metazoans	Anticancer selection has lead to tumor suppression systems, tissue designs that slow down somatic evolution, constraints on morphological evolution and even senescence itself. Since anticancer adaptation should be more or less unique to each species, animal models may have less applicability to humans. Two important anticancer selections in organ architecture include: (1) Separation of stem cells and transit cells, optimal stem cell to transit cells within compartments. (2) Compartments of tissues: optimal compartment size.	Crespi and Summers, 2005; Somarelli, 2021
11	Holobiont theory and gene regulatory networks vs. species interactions in community ecology. Metazoans are "holobionts" consisting of the host plus all of its commensal and mutualistic microbiomes, as well as a diversity of pathogens/parasites.	Some scholars have argued for including a third category of symbionts in holobiont: the community of altered "selfish" cells, malignant cells (oncobiota). The total genes contained by holobiont are termed hologenome (host genome plus microbiome metagenome) is subject to natural selection. Cancer is believed to be an ancient phenomenon that is linked to the appearance and evolution of multi-cellular organisms (metazoans). The latter requires the sophisticated, higher-level cooperation of cells with complementary behaviors. Although the emergence of genes facilitating cooperation led to the evolution of stable multi-cellularity, optimal functioning of metazoans requires precise regulation of overall cell proliferation levels and cell numbers, and a constant control of neoplastic cells. When the balance is toppled, neoplastic cells that acquire genetic and/or epigenetic mutations conferring high fitness are selected and expanded, followed by oncogenesis and neoplasm/tumor formation.	Clavel et al., 2017; Rosenberg and Zilber-Rosenberg, 2018; Li and Ma, 2019b; Simon et al., 2019; Ujvari et al., 2019; Somarelli, 2021
12	"Ecological theater and evolutionary play"	Ecological theater = setting of changing and constraining environments; cancer evolutions are playing at different scales from ultra-, micro-, macro-, global-scales, at different kinds of "theaters" that may have different selection pressures.	Adler and Gordon, 2019
13	Dynamic fitness landscape is also termed dancing landscape or seascape.	In evolving cancer system, one can consider micro-environmental changes as forming the fitness landscape on which the cancer cell population evolves dynamically. Growing tumors actively engage in metabolically driven modification of their microenvironment. The fitness peaks "move" as a result of metabolically induced niche modifications. The tumor growth, progression and dissemination depend on the dynamic (dancing) fitness landscape.	Kareva, 2011, 2015
14	Allee effects: population growth thresholds and evolutionary thresholds: Allee effects are invoked to explain the *low rates* of cancer initiation, invasion, and metastasis in many cases in which many tiny tumors are not clinically relevant.	On the other hand, recurrence of cancer after treatment, and the experimental observation that a single progenitor cell in some transgenic mouse model could initiate cancer raises the complex intricacies of Allee effects. Still, some other inspirations from Allee effects make sense. First, total eradication of cancer cells is not necessary for successful cure, or reducing the density of cancer cells below some critical threshold would be sufficient. Second, a radically new strategy could be to focus on the size of the threshold, rather than on the population size. For example, if a new therapy that can raise the magnitude of the Allee effect by stimulating tumor evolution toward this outcome, an immediate effect can potentially lower the probability of metastasis. Third, an increase in the Allee threshold could also be followed by a traditional treatment that would push the primary tumor below the critical threshold and cause a rapid population "meltdown." In addition, high growth threshold also make it difficult for new mutations to rescue the population.	Ewers and Didham, 2007; Swift and Hannon, 2010; Korolev et al., 2014
15	Tipping point theory	The topic of detecting the thresholds of critical events is known as tipping point theory, which means that dramatic change (such as tumor out of dormancy) could occur when system approaches or crosses the tipping point. If a treatment can push the tumor dynamics to cross tipping-point (threshold), two contrasting outcomes may occur, either goes extinct or escape from the treatment. The Allee effects can be considered as one kind of tipping point.	Liu et al., 2019; Creemers et al., 2021
16	Ecology of information is a field of behavioral ecology, which explicitly considers information in an ecological context.	While biology tends to focus on information dynamics in the genome, survival, and proliferation of each organism requires continuous assessment of myriad types of cues and signals, which provide information from their environment to which they must respond physiologically and behaviorally. Uniquely in nature, living systems must acquire, store, and act upon information. Studies revealed that cancer cells and normal cells obtain and process information differently. Cancer cells must constantly obtain information from their environment to ensure survival and proliferation. Whelan et al. (2020) propose to eradicate cancer cell by information disruption, similar to habitat fragmentation driving population extinction.	Schmidt, 2017; Whelan et al., 2020; Bukkuri and Adler, 2021; Miller et al., 2021
17	Cancer heterogeneity and genome instability: *Heterogeneity* is a fundamental property of cancer cells within a tumor, both genetically and phenotypically.	Most mutations are likely to be neutral. Strongly beneficial or deleterious mutations usually have shorter lifetimes, because they either quickly spread or get eliminated by natural selection. However, large tumors with high mutation rates may have several mutations segregating at the same time, a phenomenon known as clonal interference. Clonal interference can reduce the rate of adaptation because of their	Korolev et al., 2014

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BOX 2 | (Continued)

No.	Key concepts/hypotheses in cancer ecology	Evo-eco-oncology interpretations	References
		mutual interference (competition). Genetic heterogeneity is a determining factor for the evolutionary potential of the tumor, which could reflect the important aspects of the internal tumor dynamics including mutation rates, effective population size, generation time, and spatial structure. This mutation diversity of cancer cells is similar to a principle in natural ecosystem, in which biodiversity is often positively correlated with the stability (resilience) of ecosystems.	
18	Nine major themes for cancer ecology and evolution	(1) The ways to use eco-evolutionary concepts to understand initiation of cancers; (2) the eco-evolutionary principles (e.g., cooperation theory) for understanding metastasis; (3) the methods to identify selective pressures in the tumoral microenvironment; (4) the contribution of the holobiont to cancer initiation and progression; (5) the immune system contribution to oncogenic processes; (6) use evolutionary principles to design treatments against cancer; (7) mathematical modeling; (8) the ways that cancer shapes the ecology and evolution of species (e.g., adaptive therapy); and (9) the lessons learnable from the cancer of wildlife.	Pacheco et al., 2014; Klement, 2016; Dujon et al., 2021; Pressley et al., 2021
19	Why curing cancer is difficult? Four factors explain why curing cancer is difficult:	(1) Limited cellular and tissue-level knowledge. (2) Cancer cells and normal cells are similar, making the targeted killing hardly possible. (3) Cancers can evolve rapidly, and can quickly develop resistance to anti-cancer drugs. (4) Cancer cells possess extraordinary heterogeneity and is often hardly possible to develop therapies that can eradiate all types of cancer cells. Besides the first one, any relief in addressing the other three challenges is likely to first require advances in strategic thinking, and eco-evolutionary dynamics perspective should play a critical role.	Korolev et al., 2014
20	Cancer Treatments: Treatment strategies for cancer parallel those for invasive species (such as a new insect pest) inspired researchers to develop therapies that attack targets but with few side effects or that delay or evade resistance.	(*i*) Surgery and physical removal eliminate the most visible parts of the invasion but rarely fully eradiate pest, and therefore often must be complemented with other treatments. (*ii*) Chemotherapy and pesticides seek to kill only their targets, but their very effectiveness creates/induces side effects through damage to non-target individuals and strong selection for resistance. (*iii*) Immunotherapy and biological control utilize the *power* and *specificity* of biology against itself, with exceptional outcome in some cases but with unexpected failures in other situations, making integrated treatment necessary again. (*iv*) Other treatments such as differential therapy (DTH). If the usage of some molecular agents can induce differentiations in cancer cells, then the differentiated cells that are a terminal branch of development essentially remove cancer cells from the proliferative compartment. Integrated usages of DTH and traditional cytotoxic therapy (CTH) can kill cancer cells either DTH or CTH alone cannot. The integrated strategy was inspired by the insights from the ecological studies on habitat fragmentation, namely that habitat reduction along with stochasticity in mortality could trigger species extinction.	Ewers and Didham, 2007; Adler and Gordon, 2019; Hansen and Read, 2020; Araujo et al., 2021; Dua et al., 2021; Gregg, 2021; Solé and Aguadé-Gorgorió, 2021

of constraining and changing environments (Hall, 2017). The cancer cell environment includes other host cells, microbiomes, and the biochemical and physiological environments. Obviously, virtually everything in cancer environment is dynamic, and for this reason, cancer evolution, which is played out at ultra-micro-, micro-, macro-, and global scales as explained in **Box 2**. Environment also supplies the energy and materials that allows cancer cells to survive and evolve, until they evolve to their maximal fitness, which kills its host but ironically themselves too, or they are suppressed and/or eradicated by competitions from other somatic cells, predation by immune cells, and/or various medical treatments. For the interwoven nature between cancer ecology and evolution, evo-eco (or eco-evo) paradigm for cancer research has been suggested to play a similar role as the popular evo-devo in evolutionary developmental biology.

Another point to note is the somewhat mismatch between theoretical studies and clinic applications. Although the recognition of cancer as an evolutionary process occurred more than a half-century ago and the recognition of ecological theories have also occurred since the new century, and evo-eco thinking has indeed generated tremendous impacts on cancer research, we must admit that much of the research remain are at the stage of discussions on their parallels. Indeed, much of the ecological and evolutionary concepts in cancer ecology are analogies (parallels) drawn from ecology and evolution. For this reason, evo-eco thinking has not achieved tangible clinic success. As indicated by Korolev et al. (2014), it is crucial to pursue the identified parallels further by making them quantitative, testable, and eventually useful insights for devising therapy strategies and methods (Plutynski, 2021). DNA sequencing technologies, and experiments with microbes and animal models have created unprecedented opportunities to revolutionize the eco-evolutionary studies on cancers.

Cancer is so closely related to genes that it is considered to be a disease of human genome; recent findings suggest that human metagenome is also involved in cancer development (Poore et al., 2020). For this reason, beyond the points summarized in **Box 2**, in the remainder of this sub-section, we briefly discuss a more recent topic in cancer ecology, the relationship between cancer and human microbiomes. Human microbiomes are distributed not only within and on human bodies, but also within the tumor tissues. They can be neighbors of cancer cells as well as "insiders"

within cancer cells. Therefore, microbiomes should have far reaching impacts on the cancers. Nevertheless, the field is still in its infancy stage with a history of slightly longer than a decade.

Bacteria and virus within tumors are localized within both cancer cells and immune cells. However, exact diagnostic implications of microbial contributions to different types of cancer were largely unknown until Nejman et al. (2020) and Poore et al. (2020). Poore et al. (2020) reanalyzed microbial reads from 18,116 samples from 10,481 patients belonging to 33 cancer types deposited in TCGA databases by utilizing machine learning algorithms. They found that there are unique microbial signatures in tissue and blood within and between most cancer types. In some cases, microbiome signature can be more sensitive than human genomic signature. Nejman et al. (2020) took largely experimental approaches to investigating the 1,526 tumor and adjacent normal tissues across seven cancer types covering breast, lung, ovary, pancreas, melanoma, bone, and brain tumors. Their findings are similar to those obtained from the bioinformatics (machine-learning) approaches by Poore et al. (2020). For example, Nejman et al. (2020) demonstrated from their 1,526 tumor microbiome samples that the beta-diversity within a given tumor type is smaller than the beta-diversity between tumor types, i.e., the within cancer type similarity (between tumor tissue and adjacent normal tissue) is larger than between cancer types.

Although bacteria were first detected in human tumors more than a century ago (Nejman et al., 2020), the studies on the relationship between microbiome and cancer is still in its early infancy, and answers to many of the fundamental questions are still open. The most intensively studied microbiome-cancer relationship has been focused on gut microbiome, but in recent years, attentions have been increasingly paid to tissue microbiome such as lung-tissue microbiome and lung cancer relationship. Understanding how microbes in the respiratory tract might influence lung carcinoma development and treatment efficacy may be instrumental for forecasting the risk of cancer development and to improve treatment efficacy and safety (Ramiìrez-Labrada et al., 2020). Cooperative interactions between microbiome and host might lead to microbial participation in host functions such as defense and metabolism. Furthermore, the same microbes that promote human health, under one circumstance, might induce disease and cancer development in another circumstance. In some other circumstances, the change of microbiome composition may cause disease.

In the case of lung cancer, it has been postulated that altered lung microbiome and chronic inflammation in lung tissue contribute to carcinogenesis (e.g., Clavel et al., 2017). The lung microbiome dysbiosis may modulate the risk of malignancy at multiple levels including chronic inflammation and oncogenes (e.g., Tsay et al., 2021). The correlation between repeated antibiotic exposure and increased risk of lung cancer has been investigated. Several bacteria including *Mycobacterium tuberculosis* have been found to relate with lung cancer.

The coevolution of the host immunity-microbiome interaction may have led to the development of regulatory pathways that modulate self-tolerance and tolerance against non-cancerous agents vs. elimination of pathogens and tumor cells. The delicate balance between tolerance and lung immune activation may be interrupted by changes in immunity-microbiome cooperation due to the antibiotic overuse, changes in diet, or chronic infections, and the loss of balance might raise the risk of lung cancer (e.g., Woodhams et al., 2020).

MEDICAL ECOLOGY OF HUMAN MICROBIOME ASSOCIATED DISEASES

General Introduction on Medical Ecology

The term *medical ecology* was coined nearly a century ago by eminent microbiologist, Rene Dubos.[1] Dubos discovered gramicidin in 1939, together with Alexander Fleming's discovery of penicillin in 1928, and their findings opened the way into the modern era of anti-microbial therapy. Inspired by their findings, in which soil microbes played a dominant role, Dubos embraced the concept that natural ecosystems, if explored properly, would provide for many of our needs, including treatments for diseases. Therefore, the ecological principles, if applied to the human condition, will provide a resolution to the dichotomy of the "man vs. nature" paradigm. According to the website of http://www.medicalecology.org/, "the *medical ecology* is an amalgam of principles borrowed from a wide variety of basic and applied sciences. This new hybrid science focuses on issues of human health in which environmental disturbances plays a central role."

Ma (2012b, 2017b, 2021a) proposed a narrowed definition for medical ecology, with diseases limited to microbiome-associated diseases. As mentioned previously, medical ecology of human microbiome can be defined as cross-disciplinary studies of human microbiomes for the objectives to understand their implications to human health and diseases from the ecological perspective, which are supported by bioinformatics and computational biology, theoretical ecology, clinical medicine, and medical microbiology. In the case of medical ecology for human microbiomes, community ecology occupies particularly important position (Gilbert and Lynch, 2019). **Figure 4** and **Box 2** are aimed to illustrate the selected key concepts and aspects of medical ecology of human microbiome associated diseases.

To the best of our knowledge, the term human microbiome associated diseases do not have a formal definition for its scope. Nevertheless, many human diseases are indeed associated with the human microbiomes, indirectly at the minimum. To illustrate this opinion, in the remainder of this section, we review the evidence supporting the relationship between COVID-19 and human microbiomes.

COVID-19 and Human Microbiomes

COVID-19–Virome Interactions

It is estimated that the size of human virome is approximately 380 trillion, which is approximately 10 times of the size of bacterial microbiome, and the later is approximately 10 times of the somatic cell number of human body. The human virome may regulate host immunity and pathophysiology (Brown et al., 2019). Nevertheless, there are few reports on the interaction between

[1] http://www.medicalecology.org/

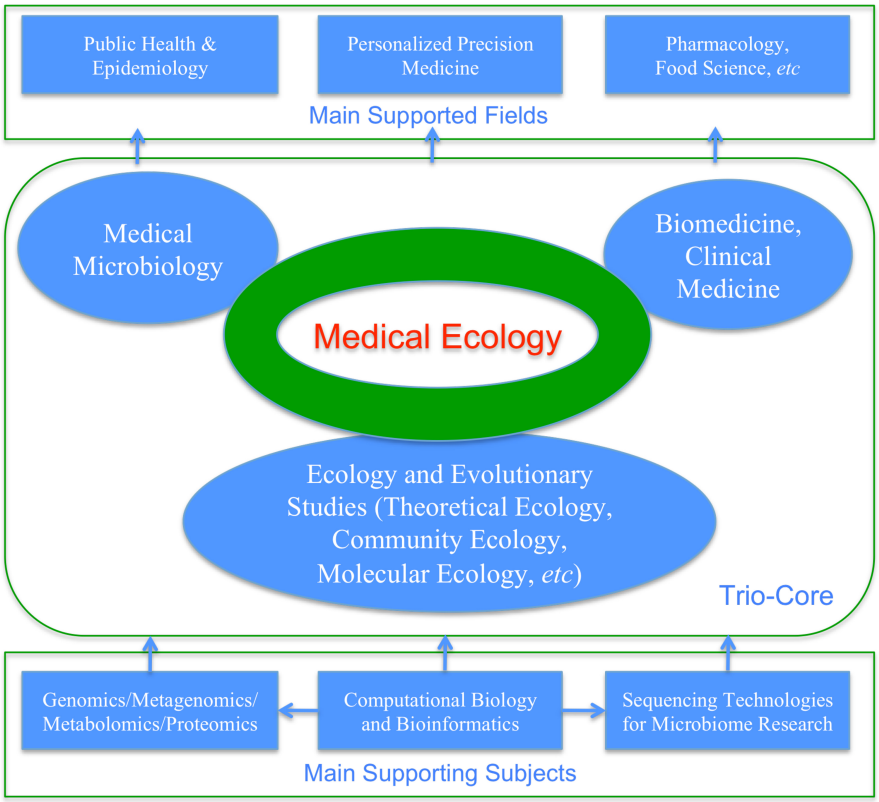

FIGURE 4 | Medical ecology: its trio-core, as well as its supporting and supported fields.

COVID-19 and human virome, and to the best of our knowledge, Zuo et al. (2020b) may be the only exception. They found that both enteric RNA and DNA viromes were perturbed by SARS-CoV-2 by comparing stool samples from 98 COVID-19 patients with those from 78 healthy controls. They also suggested that gut microbiome may calibrate host immunity and regulate severity to SARS-CoV-2 infection (Zuo et al., 2020a).

SARS-CoV-2 and Gut Microbiome

Patients with COVID-19 may experience gastrointestinal disorders preceding or following the respiratory symptoms. Studies have confirmed that, alongside the respiratory tract, the gastrointestinal tract can be an entry and replication site for SARS-CoV-2 (Dhar and Mohanty, 2020; François and Harry, 2020). Since gut microbiome plays major roles in maintaining host homeostasis. It has been reported that many respiratory viral infections may alter the gut microbiome, including influenza virus and respiratory syncytial virus, and SARS-CoV-2 is, by no means, an exception (Zuo et al., 2020c).

Gu et al. (2020) found that SARS-CoV-2 infection may influence the composition of gut microbiome, e.g., leading to a significant reduction of bacterial diversity, a significantly higher relative abundance of opportunistic pathogens such as *Streptococcus*, *Rothia*, *Veillonella*, and *Actinomyces*, and a lower abundance of beneficial symbionts, compared with the control group.

It was revealed that the gut microbiome of COVID-19 patients demonstrated increased functional capacity for nucleotide and amino acid biosynthesis and carbohydrate metabolism (Tang et al., 2020; Zuo et al., 2020b). Depleted symbionts and gut dysbiosis persisted even after the patient recovered from COVID-19. It was suggested that the differences in microbiota composition might be harnessed to differentiate the severity of COVID-19-related infections (Zuo et al., 2020a). SARS-CoV-2-induced shedding of angiotensin-converting enzyme II (ACE2), which is the cell surface receptor that virus binds to when entering host cells, may drive the dysbiosis of gut microbiota (Viana et al., 2020). In the meantime, gut microbiome dysbiosis, in turn, may raise the COVID-19 severity, particularly in elderly or obese patients (Belani, 2020; Viana et al., 2020). Furthermore, improving the profile of the gut microbiome may help to alleviate the COVID-19 symptoms in elderly and immune-compromised patients.

SARS-CoV-2 and Lung Microbiome

Lung microbiome is associated with several respiratory diseases and immunity; by activating an innate and adaptive immune response, it may change the risk and symptoms of COVID-19 disease. However, few existing studies have investigated the lung microbiome of COVID-19 patients (Fan et al., 2020). Shen and Bo (2020) found that COVID-19 patients experienced the enrichment of pathogenic and commensal

bacteria. Han et al. (2020) suggested that the COVID-19 patients might have higher diversity of bacteria than the healthy controls. The abundance of lactic acid bacteria, including *Lactobacillus fermentum*, *L. reuteri*, *L. delbrueckii*, and *L. salivarius*, appeared to be higher in the COVID-19 patients than in the healthy control (Han et al., 2020).

The diversity of human oropharyngeal and intestinal microbiomes may influence the progression of pulmonary viral infection. The SARS-CoV-2 may aggravate lung disease by interacting with the lung or oral microbiota, and the aggravation mechanisms involve changes in cytokines, T cell responses, and the effects of host conditions such as aging, and the oral microbiome changes owing to some systemic diseases (Bao et al., 2020). For instance, *Capnocytophaga*, *Veillonella*, and other oral opportunistic pathogens have been found in the lung of the COVID-19 patients (Chen et al., 2020; Peddu et al., 2020; Ren et al., 2020; Shen and Bo, 2020; Wu et al., 2020). The nasopharyngeal bacterial population in COVID-19 patients differed with viral infection lengths, e.g., significant decline of *Fusobacterium periodonticum* 3 days after infection (Moore et al., 2020).

SARS-CoV-2 and Environmental Microbiome

Coronaviruses may live on in marine plankton with wastewater effluent. Mora et al. (2020) analyzed the metagenomic data from the dried-out Aral Sea basin in Uzbekistan and found that coronavirus-like sequences (including SARS-CoV-2 match) had existed in environmental samples before the current COVID-19 pandemic. Mordecai and Hewson (2020) suggested that SARS-CoV-2 might be present in coastal marine waters affected by sewage effluent, and the rates of their physical decay and loss of infectivity may be similar to other aquatic viruses.

The risk of COVID-19 infections may be influenced by the *environmental microbiome* diversity. Higher diversity of *human microbiome* is thought to render better immunity against external infections. *Human microbiome* diversity is in turn strongly influenced, if not dictated by environmental microbiome diversity. Kumar and Chander (2020) argued that high microbial exposure, particularly to Gram-negative bacteria, may induce interferon type-I that might have a protective effect against COVID-19. Their argument is that the countries with lower mortality also tend to be sanitation poor and to have high incidence of attendant diseases. Kumar and Chander (2020) continued that the populations of developing and underdeveloped countries might have higher resistance to COVID-19 due to high microbial load exposure and resulting microbial interference and/or immunity. They concluded that, high diversity of environmental microbiome appears to have a protective effect against external infection such as SARS-CoV-2 (Kumar and Chander, 2020).

TOWARD A UNIFIED MEDICAL ECOLOGY OF HUMAN DISEASES

Is an Ecological Unification Necessary?

At present, majority of studies in medical ecology has been centered on human diseases that are associated with human microbiomes. However, whether or not medical ecology approaches should play an important role in studies beyond human-microbiome-associated diseases are still open. We argue that ecology, especially *theoretical ecology*, should play a significant role in studies on human diseases, which should be similar to the role that medical genetics has been playing in bio- and clinical medicine since the 1960s. Therefore, *medical ecology*, in our opinion, should become a foundational discipline of modern medicine, similar to today's medical genetics (Harper, 2004). Broadly speaking, disease ecology of zoonoses, IPM for agricultural and forest pests, and cancer ecology all have demonstrated the importance of ecology in the medical enterprises we humans have been endeavoring. Whatever terminologies from disease ecology, cancer ecology to medical ecology may be used, the common threads of ecological science are obvious. We suggest the term "medical ecology" is used for human diseases, while preserving the term "disease ecology" for wildlife and zoonoses. As to the ecology of plant and animal diseases (pests), there is no need to change their terminologies since we do not believe there is a need to extend the unification to the areas of plant protection (entomology, nematology, and plant pathology). Regarding the veterinary science for livestock diseases, our limited knowledge suggests that the ecology of livestock diseases should be situated somewhat between the medical ecology for human diseases and disease ecology of wildlife theoretically, and should also be similar to the ecology of IPM for plant protection from a practical perspective. For example, on the one hand, monitoring the emergence and/or reemergence of zoonoses should be conducted through the practices across wildlife conservation, veterinary service, and public health system; on the other hand, some practices in veterinary medicine such as the control of insect and mite pests are similar to the IPM for plant protection. Still, if one feels that a unified terminology is necessary, either disease ecology or medical ecology or their interchangeably usages can be useful; **Figure 5** is a sketch from our attempt to view disease and medical ecology from a unified ecological perspective.

Box 4 summarizes the key commonalities and unique aspects of disease ecology, IPM, cancer ecology, medical ecology, and ecology of COVID-19 (as an example of infectious diseases). Although, we realize that it is neither feasible, nor necessary to unify all of the terminologies for ecological sciences compared in **Box 4**, we reiterate a common ecological perspective is critical for the studies of medical enterprises humans endeavor.

Perspective—Areas for Promising Novel Breakthroughs

According the Ecological Society of America (ESA),[2] "*Ecology is the study of the relationships between living organisms, including humans, and their physical environment; it seeks to understand the vital connections between plants and animals and the world around them.*" Traditionally, ecology includes several disciplines: autecology, population ecology, community ecology, ecosystem ecology, and landscape ecology in terms of the scale (level) of ecological entities, corresponding to individual (organism), population of individuals (organisms from same species),

[2]www.esa.org

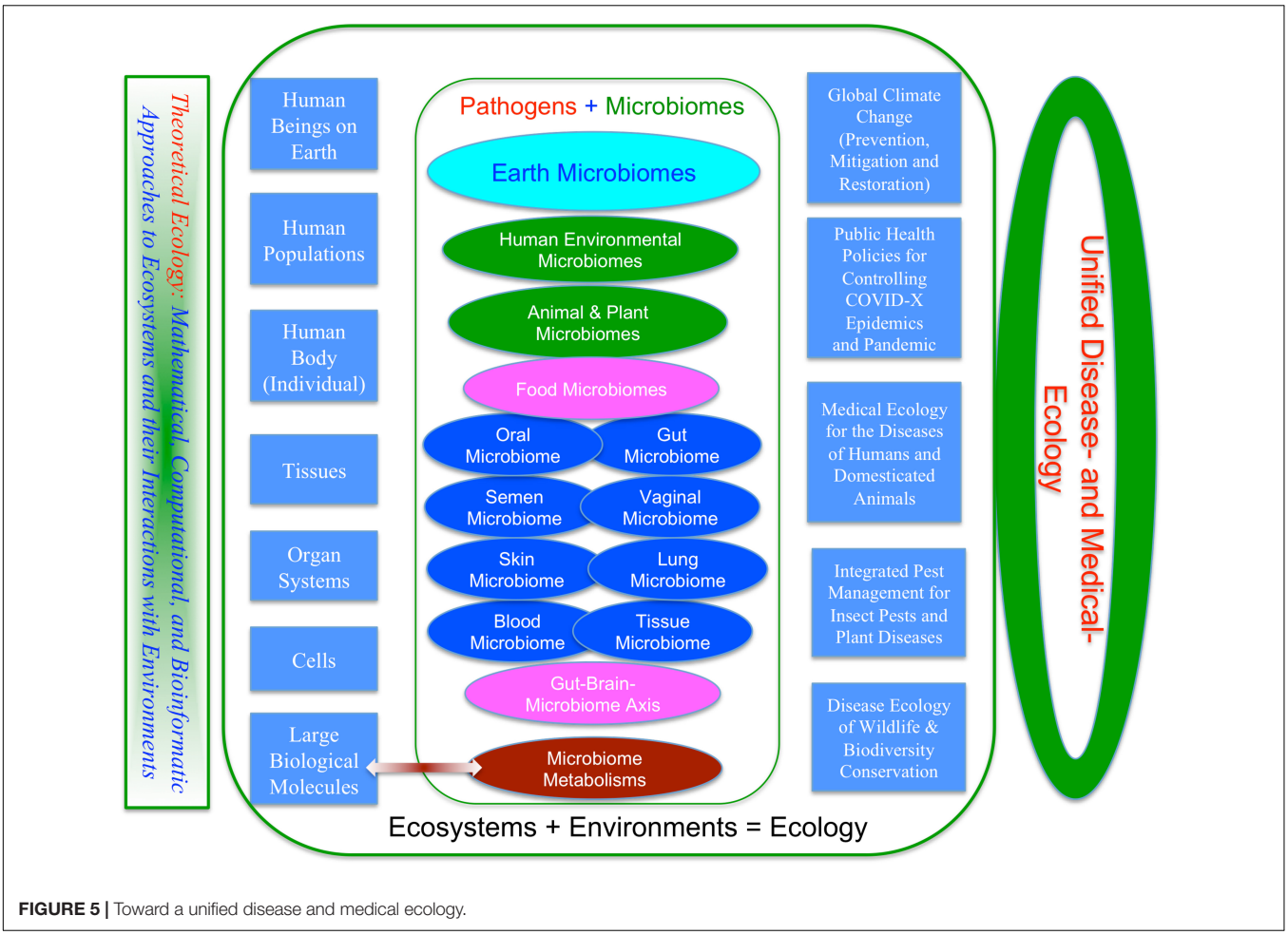

FIGURE 5 | Toward a unified disease and medical ecology.

community of species (assemblage of populations from different species), and landscape (a cluster of interacting ecosystems). This is just one classification scheme for the ecological science, and other alternative schemes exist. For example, there are microbial ecology, plant ecology, insect ecology, and animal ecology in terms of taxa; molecular ecology, physiological ecology, chemical ecology, mathematical ecology, and evolutionary ecology in terms of cross-disciplinary classification. To fit cancer ecology into the ESA definition for ecology, we need to add cells to the list of ecological entities. To add *medical ecology* as a cross-disciplinary field of ecology, we need to add human host to the list of ecological environments, and, of course, recognize *microbiomes* as the counterparts of *macrobiomes* (or *biomes* in traditional literature) in the ecology and biogeography of plants and animals traditionally. The systematic studies of microbiome started in the new century, while the history of biome research can be traced back to 18th century at a minimum (von Humboldt, 1799, cited in Sanmartín, 2012). Studies in recent years have demonstrated that both microbiomes and macrobiomes should follow the same or similar ecological principles and laws. One such example is the extension of classic species–area relationship (SAR) in plant biogeography (Watson, 1835) to general diversity–area relationship (DAR) (Ma, 2018a, 2019), which was first demonstrated with the human microbiomes.

Cells are building blocks of life except for viruses, from single-celled prokaryotes through to metazoans (multi-cellular organisms). To understand a multitude of biological processes, it is required to understand how cells behave, how they interact with each other and with their environment (Richards et al., 2019), which is obviously the mission of ecology. Richards et al. (2019) presented a working definition for *single cell ecology*: "the use of state-of-the-art approaches, often informed by physical and molecular methods, to study biological phenomena at the scale of a single cell with a focus on how individuals or groups of individuals of the same species interact with their environment, each other and cells of different species."

One may wonder what is the relationship between the *single cell ecology* and *cancer ecology*. Cancer ecology has a history of near three decades; however, until the recent decade, the technology that is implemented at *single-cell* level for exploring ecological interactions was not available. Single cell sequencing methods refers to sequencing protocols that can sequence a single-cell genome or transcriptome, rather than sequencing the genome from mixed-cell samples as done traditionally (Tang et al., 2019). Compared with traditional sequencing technologies

BOX 3 | Twelve selected key concepts and topics of the *medical ecology* of human microbiome associated diseases (*H*-MAD) (H, healthy treatment; D, diseased treatment) (also see **Figure 4**).

No.	Key concepts/aspects	Interpretations
1	Diversity, shared species analysis, and diversity scaling	Microbial diversity analysis, in particular, of human microbiome, has been a *de facto* standard in studies of *H*-MAD. Hill numbers are well recognized as the most appropriate metrics for alpha-diversity and their multiplicative partition is advantageous over additive partitions of many other diversity metrics. Besides measuring the OTU diversity, Hill numbers can also be applied to measure *metagenomic gene* (MG) diversity, and its various assemblages, most notably, metagenome functional gene cluster (MFGC) and metagenomic species (MGS) (Ma and Li, 2018). Diversity, however, is usually entropy-based, community-level metrics that summarize the species abundance distribution, but it can be insensitive to changes of species identities (composition). In this aspect, *share species analysis* (SSA) by Ma et al. (2019) can detect the species composition changes between treatments (e.g., healthy and diseased samples). Classic SAR (species–area relationship) and STR (species–time relationship) in biogeography have been extended to general DAR (diversity–area relationship) and DRT (diversity–time relationship), which provide tools for investigating cohort (population) level diversity scaling, as well as potential (dark) diversity of a cohort (population) of the human microbiomes (Ma, 2018a,b,c, 2019; Li and Ma, 2019b; Ma and Ellison, 2021b).
2	Diversity–disease relationship (DDR)	Although diversity analysis has been a *de facto* standard procedure for microbiome analysis, a rigorous statistical comparison revealed that in only approximate 1/3 of the *H*-MAD cases, there were significant differences between the healthy (H) and diseased (D) treatments (Ma et al., 2019). However, currently, there is not a hypothesis on mechanisms underlying the diversity–disease relationships (DDR) in *H*-MAD, unlike in the field of zoonoses where the hypotheses of dilution/amplification effects have been well established (Ma, 2020a; Merrill and Johnson, 2020).
3	Population-level DDR (*p*-DDR)	The DAR (Ma, 2018a,b,c, 2019) can be extended to investigate the *population-level* DDR (*p*-DDR) (Li and Ma, 2021). It was found that the differences between the *H* & *D* treatments in *p*-DDR parameters, that is, the DDR at population scale, are slightly less than 1/3. It is conceived that the slightly weak *p*-DDR relationship might be due to cancelation effects among individuals within a population (Li and Ma, 2021).
4	Heterogeneity, power law, asymmetrical interactions	As argued previously (**Box 1**), *heterogeneity* and *diversity* should be considered as "*Two roads diverged in a wood. . .*" rather than both sides of the same coin. However, unlike diversity analysis, there is relatively little consensus on measuring heterogeneity. Since the focus of heterogeneity is interactions, which often leads to divergence or dispersion in phenotypic data. In this venue, Taylor (1961) power law (TPL) that relates variance (*V*) and mean (*M*) of population abundances can be a rather useful heterogeneity measure. Ma (2015) extended TPL to community level with four extensions (TPLE) including community spatial heterogeneity, community temporal stability, mixed-species population aggregation (heterogeneity) and mixed-species population temporal stability. The TPLEs have been applied to measuring microbiome heterogeneity of humans and other environments such as hot springs (Ma, 2012b, 2015, 2020b, 2021a,c; Oh et al., 2016; Li and Ma, 2019a).
5	Heterogeneity–disease relationship (HDR)	The above-mentioned TPLE can be applied to detect the differences in heterogeneity between the *H* & *D* treatments (Ma, 2020b). It was revealed that the differences in HDR (heterogeneity–disease relationship) are similar to the DDR (Ma et al., 2019, Ma, 2020b). The TPLE and HDR can also be applied to gene abundance from whole-genome metagenomic sequencing (Ma, 2020f).
6	Mechanisms of community assembly and diversity maintenance. Niche-neutral continuum and hybrid modeling. Four-process synthesis of community ecology.	How microbiome is assembled and how its diversity is maintained are questions of fundamental importance both theoretically and practically. Theoretically, four processes or mechanisms (selection, neutral drifts, migration, and speciation) are considered to drive the spatiotemporal dynamics of microbiome (biogeography) (Vellend, 2010, 2016; Hanson et al., 2012). However, quantitatively characterizing the four processes is challenging. Practically, understanding the mechanisms is critical for understanding the etiology of *H*-MADs. Assessing and interpreting the neutral drifts with Hubbell's unified neutral theory of biodiversity (UNTB) (Hubbell, 2001; Harris et al., 2017; Ning et al., 2019), even though imperfect, play a significant role in understanding the dynamics of microbiome diversity and the disease effects. Furthermore, niche-neutral hybrid modeling and network analysis, particularly core/periphery network (CPN) and high-salience skeleton network (HSN) (see below for separate introduction on CPN and HSN) can be integrated with the UNTB to more effectively assess the relative importance of the previously mentioned four processes (mechanisms) and especially the select effects of diseases (Li and Ma, 2016, 2020a,d; Ma, 2020a,c,e, 2021b,d,e; Li et al., 2021).
7	In silicon motifs: trios and PN ratio	Complex network analysis can be a powerful approach to analyzing microbiome data given that microbiome datasets, whether it is OTU (operational taxonomic unit) tables or MGA (metagenomic gene abundance) tables, are multi-dimensional data and are particularly suitable for network analysis. Species (OTU) interaction (strictly speaking species co-occurrence) network can be constructed conveniently based on the correlation relations between OTUs. Nevertheless, basic correlation network analysis offers relatively little biomedical insights. For this reason, some special motifs, especially arguably the simplest network motifs (trio motifs) can actually offer very useful information on the disease effects, so does the P/N ratio (the ratio of positive to negative correlations in a network) (Ma, 2017a; Ma and Ye, 2017). For example, Ma and Ellison (2021a) identified 12 trio motifs that are specific to BV (bacterial vaginosis) patients and they have the potential to act as *in silico* biomarkers for BV diagnosis and as targets for personalized treatments. The PN ratio may indicate the balance (shift) between positive interactions (cooperation) and negative interactions (antagonism) within microbiome, and may reflect the effects of microbiome-associated diseases.
8	Core/periphery network	Arguably the most important reason (also the advantage) why network analysis has been experiencing explosion is its capacity in reducing the complexity of complex systems (networks) while preserving their certain key features. The so-termed core-periphery network (CPN) and high-salience skeleton network (HSN, see the next block) reduces the complexity of network nodes and edges (interactions), and allow us to focus on critical nodes and paths, respectively. Informally, the network core usually denotes a centrally and densely connected set of network nodes, while the network periphery refers to a sparsely connected, usually non-central set of nodes that are linked to the core (Csermely et al., 2013). Ecological communities/systems are typical complex systems (networks), which can be formulated as core/periphery network (CPN). The core/periphery structure was found to be ubiquitous in the species dominance network (SDN) of the human vaginal microbiome and the structure plays an important role in controlling the community diversity–stability relationships (Ma and Ellison, 2018, 2019, 2021a). The CPN structures were found not only ubiquitous in the human microbiomes, but also may be influenced by the microbiome-associated diseases (Li and Ma, 2020b; Ma, 2020a, 2021b).

(Continued)

BOX 3 | (Continued)

No.	Key concepts/aspects	Interpretations
9	High-salience skeleton networks	While the previous CPN distinguishes the different structural and functional roles between core and periphery nodes (species), the high-salience skeleton network (HSN) makes distinctions among the links (edges). The HSN allows us to focus on critical paths (interactions) in complex networks. High salience skeletons or backbones reduce the number of links in the network while preserving the nodes (Grady et al., 2012; Shekhtman et al., 2014; Ma, 2021b). The so-termed high-salience skeletons constitute the backbones ("highways") of the network, and the emergence of backbones is the result of the interplay of broadly distributed node degrees and link weights, i.e., the mix of node and link heterogeneity, which is virtually ubiquitous in the human microbiome networks. Ma and Ellison (2018, 2019, 2021a) demonstrated the detection of core/periphery nodes and high-salience skeletons in species dominance networks, and further investigate the influences of microbiome-associated diseases on the critical network structures.
10	Species Dominance Network for diversity-stability paradigm	Ma and Ellison (2018, 2019, 2021a) proposed a new dominance concept that is applicable at both population and community scales with unified mathematical metrics. Based on the new dominance metrics, they developed the concept and methods for building and analyzing the species dominance network (SDN). A primary application of SDN is to investigate classic diversity-stability paradigm, actually dominance-stability relationship by replacing diversity with dominance. Conceptually, dominance is closer to heterogeneity than to diversity since both dominance and heterogeneity stress interactions, rather than stressing partitions as diversity does. Mathematically, dominance is a function of classic mean crowding that can be computed from mean and variance, which can be used to build Taylor's power law (TPL) model. As mentioned previously, TPL parameter can be used to measure heterogeneity. Therefore, dominance-stability relationship should be similar to heterogeneity-stability relationship. A recent consensus has been that heterogeneity seems more closely related to stability than diversity to stability. In Ma and Ellison (2018, 2019, 2021a) species dominance network paradigm, previously mentioned core-periphery and high-salience skeleton networks are the main tools for performing the network analysis.
11	Integration of ecological and network analyses	The previously described methodologies can be classified into two categories: ecological analyses based on classic ecological theories (1)–(6) and complex network analyses (7)–(10). Both categories can be integrated to obtain more comprehensive insights. One such example is to integrate network analysis with classic neutral theory to assess and interpret the relative importance of the four processes (mechanisms: drift, selection, migration, and speciation) underlying the microbiome structure and dynamics (Ma et al., 2015, 2016; Ma and Li, 2019; Li and Ma, 2020b,c; Ma, 2020a, 2021b).
12	*Ad hoc* approaches: e.g., AKP	The AKP (Anna Karenina principle), which refers to observations inspired by the opening line of Leo Tolstoy's Anna Karenina: "all happy families are all alike; each unhappy family is unhappy in its own way," predicts that all "healthy" microbiomes are alike and each disease-associated microbiome is "sick" in its own way in human microbiome-associated diseases (*H*-MADs). The AKP hypothesis predicts the rise of heterogeneity/stochasticity in human microbiomes associated with dysbiosis due to *H*-MADs. Ma (2020c) proposed to use beta-diversity measured in Hill numbers to test the AKP principle. It was found that approximately 1/2 of the analyzed *H*-MAD diseases follow the AKP, while about 1/4 follow anti-AKP principle. There are potentially numerous applications of classic ecological theories that can be applied to medical ecology, and the previous introduced ones are those that have formed systematic approaches that are generally applicable to most, if not all, *H*-MADs. One more *ad hoc* approach for disease ecology is the applications of previously mentioned TPL, DAR and their integrations in predicting the turning points of COVID-19 infections (Ma, 2020d, 2021c). Finally, the previous approaches can be equally applied to study the microbiome-associated *animal* diseases, although the field seems to have received relatively little attention until today. However, many studies on healthy animal microbiomes have been performed, including some big-data tests of ecological theories with animal microbiomes (e.g., Ma, 2012a, 2013; Ma, 2021d,e; Ma et al., 2022).

that can only produce the "average" genome of many cells, the single cell sequencing methods (e.g., Xu and Zhao, 2018; Tang et al., 2019) can assess *heterogeneities* among individual cells, make distinctions among a moderate number of cells, and delineate cell maps. When the single-cell sequencing methods are applied for microbiome/metagenome studies, they can easily link metabolic functions to specific species (hence providing both microbial species and functional diversities), generate a high-quality genome for species with relatively low abundances, which may be rather difficult to capture with traditional metagenomic sequencing (Xu and Zhao, 2018). After the microbial genomes are assembled, one can study genome rearrangement, gene insertion, deletion, duplication, and loss, intra-species variations (strains or sub-species diversity) and virus-host infection of uncultured microbes (Xu and Zhao, 2018). This enabling technology has been changing many fields of biology since its invention, for example: the heterogeneity in antibiotic responses within population of cells, evolution of cancer cell lines, transcriptome expression profiles during viral infection, cell cycles, physical properties of a cell, and microbial interaction with each other and their environment (Richards et al., 2019). In fact, many of the projects have been aimed to investigate diseases at single cell level (Tang et al., 2019). We expect that the single cell sequencing technology is likely to revolutionize the studies of cell ecology and consequently offers unprecedented opportunities to advance medical ecology, in particular, cancer ecology and studies on microbiome-associated diseases.

In the remainder of this review, we try to identify the additional disciplines or fields that are of critical significance for medical ecology, besides cell ecology. The completion of landmark human genome project (HGP) helped to transform the material basis of biological research into big, portable datasets; and simultaneously led to the full establishment of bioinformatics and computational biology (Ma, 2017b; Grote et al., 2021). It appears that biology research has turned from molecularization of life to perceived big-data- and omics-centric present (Grote et al., 2021). Somewhat ironically, this trend is opposite to the ancient question of how to relate ideas of "life" to those of "matter," which may have to do with the traditional representations widely adopted by biologists, from imagery, metaphors, and scale of explanatory reasoning (Grote et al., 2021). Nowadays, biologists may often be subconscious

BOX 4 | Comparing the cancer ecology, medical ecology of human microbiome-associated diseases, medial ecology of COVID-19, disease ecology of livestock, IPM of plant pests, and disease ecology of wildlife.

Characteristics of disease system	(1) Cancer ecology	(2) Ecology of microbiome-associated diseases	(3) Ecology of COVID-19 and infectious diseases	(4) Disease ecology of livestock	(5) IPM (disease and insect pests of plants)	(6) Disease ecology of wildlife
Host	Humans; animals; plants (rarely)	Humans; animals (few studies); plants (few studies currently)	Humans, animals (zoonosis)	Livestock	Crops, forests, vegetables, fruits, grains, shade trees, flowers.	Wildlife and spillover to humans (zoonoses)
Pathogen (parasite)	Cancer cells; cancer stem cells.	Infectious or opportunistically infectious agents (bacteria, virus, fungi); metabolism syndrome; autoimmune; microbiome dysbiosis; COVID-19		Virus, parasite, bacteria, fungi, mites, etc.	Insect and mite pests, fungi, bacteria, and virus; nematode	Virus, bacteria, fungi, mites, insects
Direct "Neighbors"	Normal cells; immune cells (predators); microbiome cells.	Normal cells, immune cells ("trainee," symbiosis); opportunistic pathogens	Normal cells; immune cells (predators); phages.	Normal cells, immune cells (predators); phages	Natural enemies (predators, parasitoids, phages); microbiomes	Similar to (3) and (4), cancer may occur in wildlife, but is usually not a human concern.
Focal populations	Cancer cell population; human population.	Microbial populations; human population.	Pathogen population; human population.	Pathogen population; human population.	Populations of insects, pathogen, and natural enemies.	Populations of pathogen, vector, Wildlife.
Focal community	Assemblage of normal cells, cancer (stem) cells, microbiomes, and immune cells.	Microbiome = communities, which may include opportunistic pathogens.	Largely missing in current paradigms	Largely missing in current paradigms	Plant (forest) community, assemblages of insects and their natural enemies; microbiomes	Plant (forest) communities; microbiomes.
Focal environment	Host + microbiome + immunity + nutrition, etc.	Similar to (1)	Similar to (1); + weather + transportation + cold-chain trade + sewage	Similar to (1)	Weather; climate; Soil, microbiomes; fertilizers; biodiversity.	Weather; climate; microbiomes; biodiversity conservation.
Focal ecosystem	Cancer cells + host environment	Microbiome + host environment	COVID-19 + host environment	Similar to (3)	Focal community + focal environment	Pathogen, wildlife + local habitat (environment).
Focal landscape	Fitness landscape of cancer cell evolution	Microbiome landscape of host population	Meta-population of infectious agent and its carrier (hosts)	Similar to (2) and (3)	Agricultural (crop) landscape; forest landscape; landscape changes from deforestation, urbanization, and agricultural intensification; biodiversity loss, etc.	
Treatment (control) measures	Surgery; chemotherapy; immunotherapy; others such as differential therapy (DTH)	Modern clinic medicine; traditional Chinese medicine; microbiome transplantation.	Prevention and containment (quarantine, contact-tracing and testing, mask, and lockdown); immunization; anti-viral drugs.	Similar to (2) and (3)	Bio-control using natural enemies and microbial agents such as BT; pesticides; crop rotation; mixture forest plantation; quarantine; resistant cultivars.	Various measures to prevent and contain the emergence, reemergence and spillover of zoonoses such as biodiversity conservation.
Key ecological disciplines (in the order of importance)	Population-, evolutionary-, community-, and theoretical ecology	Community-, theoretical, and molecular ecology	Population ecology, epidemiology; theoretical ecology	Similar to (3)	Insect ecology; community ecology; biogeography; theoretical ecology.	Epidemiology, public health, and conservation biology; medical biogeography.
Key ecological theories (see **Boxes 1**–**3**) and their strategic, tactical, and etiological implications	See **Box 2** (e.g., metastasis is similar to *migration* and *invasion* in ecology and *speciation* in evolution).	See **Box 3**, e.g., dysbiosis = loss of equilibriums of microbiome, and is related to disease etiology.	E.g., R_0 [persons infected per person infecting is similar to the intrinsic rate of increase (R_0) in ecology (**Box 1**)]	Similar to (3)	IPM is strategically aimed to manage (keep) pest population dynamics below economic threshold (ET)	See **Box 1**, e.g., biodiversity loss is more likely to raise the likelihood of emergence and spillover of zoonoses.
Fields of special interests	(1) *Theoretical ecology*, especially cooperation theory (e.g., five paradigms of cooperation) and communication theory (e.g., handicap principle) and evolutionary game theory, e.g., for devising cancer treatment strategies, or for anti-dysbiosis. (2) *Molecular ecology* demonstrating the studies of ecological problems based on molecular biology techniques. (3) *Computational ecology* and *bioinformatics*, AI and machine learning for big genomic/metagenomic/transcriptomic/metabolomic data analyses. (4) *Evolutionary medicine* should be integrated with medical ecology. (5) *Personalized medicine* requires inputs from medical ecology, because the "environment" for the same disease system can be personally different. (6) *Disease ecology* of zoonoses, together with epidemiology, is critically relevant to clinic medicine and biomedicine. (7) *Cell ecology* (see out-box explanation).				(1) Bioinformatics and computational ecology. (2) Omics ecology: genomics, metagenomics, etc. (3) Metagenomic, metagenetic sampling of ecosystem/landscape with GIS-based biodiversity monitoring, aided by AI and big-data analytics. (4) Ecosystem health and services should be maintained and planned in coordination with multiple human medical enterprises. (5) Integration with forest management, conservation biology, etc.	

that gene as code of life is essentially a metaphor and therefore bioinformatics is only a tool to link the code or information with the experimentally known underpinnings (Reynolds, 2018; Grote et al., 2021). Therefore, a point we wish to make is that bioinformatics, big-data analytics, and even arguably computational biology are more like microscope to biologists. They usually do not offer *theories* to develop hypotheses to explain the experimentally known underpinnings. A follow-up question is then what science can fill the gap to offer the theories? Our answer is the ecology, especially theoretical ecology.

The critical importance of physical sciences (including chemistry) to biology, and particularly molecular biology, has been well recognized, whether it is microscope, electron microscope, to today's DNA sequencing technology. Nevertheless, virtually all the landmark contributions physical scientists made to biology seem to be on practical sides, rather than on theoretical sides. Arguably, the most important theory in biology, Darwin's evolutionary theory appeared to have little connections with physical sciences. Instead, ecology and evolution are often perceived as *twin* in biological sciences (e.g., Department of Ecology and Evolution in many universities, and in sections of many academic journals). Hutchinson's "*Ecological Theater and Evolutionary Play*" is another example, which also highlights the dependence between ecological and evolutionary sciences. As illustrated by Kingsland (1995) in her classic "*Modeling Nature*," and many others, it is theoretical ecology or mathematical ecology that turns out to play a role similar to what theoretical physics (mathematical physics) does in physics. Indeed, many mathematical models in theoretical physics have been adapted to ecological modeling. Nevertheless, the mathematical models based on the principles of physics (such as thermodynamics) only achieved limited success in ecology. This should be due to the reality that life is fundamentally different from physical world, and physical environment is only part of ecosystem. Therefore, while bioinformatics and computational biology offer necessary supportive tools for medical ecology partially, theoretical ecology (mathematical ecology) present inspirations for constructing and testing important hypotheses (theories) in medical ecology.

In summary, we expect that cell ecology, bioinformatics and computational biology (including big-data analytics and AI), theoretical ecology should be among the most critical supporting disciplines (fields) for advancing medical ecology of human diseases, and equally important to disease ecology of wildlife and livestock, and the IPM of plants. A question slightly beyond the scope of this review is what are the significant contributions medical ecology can make to clinic- and biomedicines. Here, we list four fields that medical ecology can support: (1) etiological insights, especially for human microbiome associated diseases (e.g., Li and Ma, 2020d; Ma and Ellison, 2021a); (2) personalized precision medicine (e.g., Ma et al., 2011); (3) devising innovative treatment strategies and measures such as the immunotherapy and differential therapy (DTH) of cancers (Adler and Gordon, 2019; Solé and Aguadé-Gorgorió, 2021), and microbiome transplantations; (4) epidemiological forecasting of disease outbreaks and pandemic (e.g., Ma, 2020d).

Finally, a slightly off-topic to this review is the field of *complexity science*, which has enormous potential applications to medicine and medical/disease ecology such as those demonstrated with complex network analyses (e.g., Ma and Ellison, 2019, 2021a) and evolutionary game theory (e.g., Ma and Krings, 2011; Ma and Zhang, 2021; Ma and Yang, 2022). Ecosystems are typical complex systems, and ecological science is arguably one of the most successful scientific disciplines where complexity science has achieved extraordinary successes. We further argue that medical/disease ecology can help to establish strong and broad bridges between medical enterprises and complexity science.

AUTHOR CONTRIBUTIONS

YPZ and ZSM conceived and outlined the review topics. ZSM wrote the draft. Both authors revised the draft and approved the submission.

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