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Parasitomimetics: Can We Utilize Parasite-Derived Immunomodulatory Molecules for Interventions to Immunological Disorders?

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Because our immune system has ability to expel microorganisms invading our body, parasites need evolution to maintain their symbiosis with the hosts. One such strategy of the parasites is to manipulate host immunity by producing immunomodulatory molecules and the ability of parasites to regulate host immunity has long been a target of research. Parasites can not only manipulate host immune response specific to them, but also influence the host's entire immune system. Such ability of the parasites may sometimes bring benefit to the hosts as many studies have indicated the "hygiene hypothesis" that a decreased opportunity of parasitic infections is associated with an increased incidence of allergy and autoimmune diseases. In other words, elucidating the mechanisms of parasites to regulate host immunity could be applied not only to resolution of parasitic infections but also to treatment of non-parasitic immunological disorders. In this review, we show how much progress has been made in the research on immunomodulation of host immunity by parasites. Here, we define the word 'parasitomimetics' as emulation of parasites' immunomodulatory systems to solve immunological problems in humans and discuss potential applications of parasite-derived molecules to other diseases.

Keywords: parasites, hygiene hypothesis, immunological disorders, immunomodulatory molecules, therapeutic interventions

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INTRODUCTION

Parasitism, one form of symbiosis, is a relationship between species where one species receives benefit from the host while causing harm to the host. Infection with parasites causes parasitic diseases which have been major health threats to humans for a long time. There are three main classes of parasites that can cause disease in humans: protozoa, helminths, and ectoparasites. Even in this modern era, more than 1.5 billion people, or 24% of the world's population, are infected with soil-transmitted helminth infections worldwide (1).

Majority of parasites cause chronic infections, i.e., sustained survival in their hosts. This means that the hosts have enough time to recognize the invading foreign bodies and establish immunity to expel the parasites. The host immune response can be classified into innate and acquired immunity, and the host defends itself against pathogens with a variety of strategies. In contrast, parasites, which

require chronic infection of the host, have often been able to escape the host immunity by inducing immune modulation in the host. In other words, as the host evolves its own immune mechanisms, the parasite evolves its own mechanisms to evade immunity. The ability of these parasites to regulate host immunity has long been a target of research.

Helminths are the representative parasites that regulate host immunity with diverse strategies. One of the strategies is to mimic host molecules which are involved in immunosuppression. An example is TGF-β which induces regulatory T cells and inhibits effector functions in NK cells and macrophages to suppress host immunity (2), and it is known that helminths have a homologue of a mammalian TGF-β; a TGF-β homologue was discovered in *Brugia malayi* and named Bm-TGH-2 (3). Other helminth-derived molecules such as FhTLM from *Fasciola hepatica* and HpTGM from *Heligmosomoides polygyrus* have been identified and are involved in T cell suppression through binding to TGF-β receptors on T cells and its signaling (4, 5). Furthermore, FhTLM binds not only to TGF-β receptors on T cells but also to TGF-β receptors on macrophages and induces IL-10 secretion by macrophages (4). Interestingly, although HpTGM is a protein with cytokine-like functions, it has no homology to mammalian TGF-β or other members of the TGF-β family (5). Thus, parasites have molecules that functionally play similar roles to host molecules, even though they are not structurally conserved.

Another example of parasite secretory molecules mimicking host molecules is macrophage migration inhibitory factor (MIF). MIF is a cytokine that causes inflammation and migration of immune cells, and is mainly expressed by pituitary corticotropic cells, monocytes/macrophages, and T cells (6, 7). MIF causes allergic reactions by inducing pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-8 (8, 9). Many homologs of MIF have been discovered, such as Bm-MIF from *B. malayi* (10), TsMIF from *Trichinella spiralis* (11), AceMIF from *Ancylostoma ceylanicum* (12), and AsMIF from *Anisakis simplex* (13). However, functions of the parasite-derived MIFs are respectively diverse. Bm-MIFs, like host MIFs, induce IL-8 and TNF-α, leading to inflammation (10). Bm-MIF also induces host MIF, enhancing MIF-mediated immune responses (10). On the other hand, TsMIF and AceMIF are known to bind to host MIF receptors, but their detailed functions are not known (11, 12). Furthermore, AsMIF not only regulates macrophages by reducing Th2-related cytokines, but also induces regulatory T cells and immunosuppression by production of IL-10 and TGF-β (13). Thus, even if parasite molecules have sequence homology to host molecules, their functions are not necessarily conserved.

Parasite molecules that resemble host molecules are not limited to cytokines. Cystatin acts as a cysteine protease inhibitor *in vivo*. In the immune system, cystatins inhibit cysteine proteases involved in antigen processing such as lysosomal cathepsins and asparaginyl endopeptidase (AEP) (14). Some homologs of cystatin have been identified in parasites. Bm-CPI-2 and Al-CPI from *B. malayi* and *Ascaris lumbricoides*, respectively, inhibit host cysteine proteases and suppress antigen presentation (15, 16). Hp-CPI from *H. polygyrus* inhibits antigen and MHC class II molecule processing and induces immunosuppression (17). LsCystatin from *Litomosoides sigmodontis* reduces nitric oxide production (18) and onchocystatin from *Onchocerca volvulus* induces IL-10 production and suppresses antigen-stimulated cell proliferation (19).

As mentioned earlier, it has also been reported that parasite molecules structurally dissimilar to host molecules may act directly on the host immune system to induce immunomodulation. Omega-1 is a glycoprotein which is secreted from *Schistosoma mansoni* eggs. Omega-1 acts as T2 ribonuclease (RNase) and prevents protein synthesis by decomposing of ribosome RNA or messenger RNA (20). This RNase activity plays a role in conditioning DCs to prime Th2 responses (21, 22). CP1412, a close homolog to omega-1 from *Schistosoma japonicum*, also induces Th2 cell polarization through the RNase activity (23).

Although it has been reported that *S. mansoni* soluble egg antigen prevents type 1 diabetes in non-obese diabetic (NOD) mice (24), the identification of omega-1 leads to possibility to utilize parasite-derived molecules as therapeutic agents of type 1 diabetes. Injection of recombinant omega-1 into NOD mice induces expression of IL-4 and Foxp3 (25). Moreover, injection of the molecule into obese mice improves insulin sensitivity by IL-33 release from white adipose tissue (26). These results indicate that parasite molecules, even structurally dissimilar to host molecules, can be useful for therapy of immune-mediated diseases.

Together, parasites have potential to manipulate the host immunity. Here, we would like to shift the focus to protozoa. One of the characteristics of protozoan parasites is their intracellular parasitism to various types of host cells, and especially those living in phagocytic cells may require the highest level of immune escape by immunomodulation. Here, we focus on protozoa that parasitize phagocytic cells (macrophages, DCs), *Toxoplasma gondii*, *Leishmania* spp. and *Trypanosoma cruzi*, and review immunomodulatory molecules and their mechanisms of action and potential of the parasite-derived immunomodulators as drugs for immunological disorders.

IMMUNOMODULATORY MOLECULES AND THEIR MECHANISMS OF ACTION

Toxoplasma gondii

Toxoplasma gondii is a eukaryotic parasite that can only grow in host cells. *T. gondii* is one of the most widespread apicomplexans and is a common parasite of animals and humans. It is well known to cause serious opportunistic infections. Tachyzoites of *T. gondii* can infect any cell types but erythrocytes and can evade host immunity of macrophages or DCs (27, 28).

Rhoptry proteins of *T. gondii* are secreted from rhoptry and are associated with invasion of the parasites into host cells. ROP16 is one of the rhoptry proteins which was originally identified as a serine-threonine kinase (29), and then was shown to directly phosphorylates host STAT3/6, suppresses innate immune cytokine secretion (29, 30), and to induce macrophages to become M2 macrophages (30, 31). Other rhoptry proteins that directly act on host immunity include ROP18, which inhibits IRG-mediated clearance of macrophages (32).

ROP18 phosphorylates p65 and inhibits NF-κB, resulting in suppression of inflammatory cytokines (32, 33).

Dense granule proteins secreted by *T. gondii* may manipulate host inflammatory responses. GRA18 has been identified as the parasite's anti-inflammatory molecule; once released in the host cell cytoplasm, it forms complexes with regulatory elements of the β-catenin destruction complex and prevents β-catenin from being destroyed (34). Within macrophages, GRA18 induces expression of a specific set of genes commonly associated with anti-inflammatory responses, including genes encoding the chemokines CCL17 and CCL22 (34). *T. gondii* inhibitor of STAT1 transcriptional activity (TgIST) binds to activated STAT1 dimers in the nucleus of IFN-γ-treated cells and represses the IFN-γ–mediated STAT1-dependent proinflammatory expression (35).

Leishmania spp.

Leishmaniasis is a disease caused by protozoan parasites of the genus *Leishmania*. The parasites are transmitted to the mammalian host by sand fly. There are three main forms of leishmaniasis, cutaneous leishmaniasis, mucocutaneous leishmaniasis and visceral leishmaniasis. *Leishmania* proliferates within macrophages in their mammalian hosts. Because macrophages have ability to kill internalized pathogens, it is likely that *Leishmania* has acquired a sophisticated system for evading the host immunity by directly controlling the immune system.

Leishmania GP63 is a metalloprotease that causes cleavage of various peptides. It has already been reported to cleave several host immune-related proteins such as MARCKS-related protein (36), mTOR (37), NF-κB p65 (38), PTP and SHP-1 (39). Cleavage of PTP results in stimulation of phosphatase activity, which leads to rapid downregulation of Janus kinase and mitogen-activated protein kinase signaling (39). GP63 also cleaves mTOR and dephosphorylates 4E-BP1, resulting in transcriptional repression and macrophage suppression (37). SHP-1-mediated suppression of macrophages is dependent not only on cleavage by GP63, and another leishmanial protein elongation factor-1alpha (EF-1α) binds to and activates SHP-1, which in turn inhibits macrophage activation (40, 41). This ability of *Leishmania* to inhibit macrophage effector functions may result from direct interference by *Leishmania* molecules such as GP63 and EF-1α with macrophage signal transduction pathways.

TGF-β prevents macrophage activation and exacerbates *Leishmania* infections (42). Some species of *Leishmania* have been known to trigger the production of biologically active TGF-β by macrophages (42, 43). The latent TGF-β1 is activated by treatment with proteases such as plasmin and cathepsin D. It has been reported that *Leishmania* parasites contain high levels of cysteine proteases, belonging to cathepsin L and cathepsin B families (44). Cathepsin B-like cysteine protease from *Leishmania donovani* is able to cleave latent TGF-β1 into an active form releasing latency-associated protein (45).

Arginase encoded in *Leishmania* may manipulate the polarity of host macrophages. Macrophages harbor two competing pathways for arginine metabolism initiated by the enzymes inducible NO synthase (iNOS) and arginase, respectively. Mammalian arginase-I hydrolyzes arginine to urea and ornithine, and macrophages dominated by the arginase pathway, in other words alternatively activated macrophages, have suppressed iNOS production resulting in defects in nitric oxide-mediated parasite killing. Parasite-derived arginase seems to cause local depletion of the iNOS substrate arginine and to enhances parasite survival (46, 47).

Similar to helminths, *Leishmania* and *Toxoplasma* also encode MIF homologs (48). *Leishmania* MIF upregulates inflammatory and innate immune signaling in infected macrophages including inflammatory genes such as cxcl1, tlr2, and tnf (49). *Toxoplasma* MIF induces IL-8 production by human peripheral blood mononuclear cells and activates the ERK/MAPK pathway in mouse bone marrow-derived macrophages (50).

Trypanosoma cruzi

Chagas disease is a chronic disease caused by infection with *Trypanosoma cruzi*. The parasites are transmitted to the mammalian host by reduviid bug. Some people with chronic *T. cruzi* infection eventually develop clinical disease including predominantly cardiac dysfunction.

One of the characteristics of *T. cruzi* infection is polyclonal activation of B cells (51). The polyclonal B cell activation could restrict optimal development of antigen-specific lymphocytes involved in protective responses to the infection by increasing competition for activation and survival signals in the lymphoid tissues (52). *T. cruzi* proline racemase was identified as a B cell mitogen which activates B cells polyclonally (53). Moreover, its racemase active site is necessary for mitogenic activity and it was a new finding that the eukaryotic amino acid racemase has potential to activate B cells (53). *T. cruzi* trans-sialidase (TcTS) is also known as a B cell mitogen that causes T cell-independent B cell activation and induces non-specific immunoglobulin secretion (54). TcTS also promotes IL-17 production by activated B cells (55). *T. cruzi* P21 binds to CXCR4 and activates actin polymerization and macrophage phagocytosis through PI3-kinase signaling pathway (56, 57). This favors phagocytosis of the parasites by macrophages. Furthermore, P21 induces recruitment of leukocytes to the site of inflammation and up-regulates expression of IL-4 inducing Th2 immune response (58).

T. cruzi trypomastigotes are complement-resistant (59, 60). *T. cruzi* calreticulin (TcCRT) inhibits both the classical and lectin complement pathways (61, 62). It binds and inactivates the first complement component C1 and mannose-binding lectin (62). TcCRT prevents C1 formation by interfering binding of C1r and C1s to C1q (63). TcCRT also binds to the L-ficolin collagenous portion and prevents the human complement lectin pathway activation (62). Moreover, in mammals, the binding of C1q to calreticulin is a so-called "eat-me signal" that can recruit macrophages and initiate the apoptotic process (64). TcCRT promotes infectivity of *T. cruzi* and is essential for the parasites to invade host macrophages (65). Together, TcCRT, which mimics host calreticulin, may be important for survival of *T. cruzi* by ensuring efficient entry to macrophages without inducing their parasite-killing activities.

The main cysteine peptidase from *T. cruzi* is cruzipain, a papain-like endopeptidase expressed in all life cycle stages of the

parasite (66). Cruzipain is able to activate latent TGF-β *in vitro* (67). Activation of TGF-β is required for parasite entry into the mammalian cells and play an important role in cardiomyocyte invasion by *T. cruzi* (68). A moderate oxidative environment is advantageous for *T. cruzi* proliferation (69) and Chagas disease is known to cause an increase in reactive oxygen species (ROS) in infected tissues and cells (70). Intracellular *T. cruzi* forms release in the host cytosol its major cyclophilin of 19 kDa (TcCyp19) (71). TcCyp19, causes the increase in ROS required for parasite growth in the mammalian host (71).

POTENTIAL OF PARASITE-DERIVED IMMUNOMODULATORS AS DRUGS FOR IMMUNOLOGICAL DISORDERS

Though parasites' skills to modulate host immunity are beneficial for their own survival, situations where such immunomodulatory molecules are highly appraised may go beyond infections. The "hygiene hypothesis" states that as exposure to pathogens decreases due to improved sanitation, the risk of allergic and autoimmune diseases increases. This hypothesis is based on the fact that the large increase in the frequency of allergic and autoimmune diseases observed in developed countries over the past 40 years is negatively correlated with an overall decrease in the frequency of infectious diseases (72). In experimental models, the occurrence of autoimmune disease is prevented by infection with distinct pathogens, such as bacteria, virus and parasite (72).

There have already been attempts to treat immune-mediated diseases by artificially infecting them with helminths. Because *Trichuris suis* can be obtained from experimentally infected pigs, the parasite has been used in immunotherapy research to artificially infect people. There are some clinical reports that patients who ingested *T. suis* had a reduction in several immune disorders such as Crohn's disease (73) and ulcerative colitis (74). However, some clinical trials have shown no therapeutic effect (75, 76) and in a large study using meta-analysis, *T. suis* showed no apparent benefit for inflammatory bowel disease patients (77). Besides, therapeutic benefit by parasites may be limited to the infection sites but not systemic. A clinical trial of artificial infection with *T. suis*, a parasite of the intestine, did not provide relief from allergic rhinitis (78). Furthermore, infection with live parasites for therapeutic use may not be practical, and can sometimes cause other unintended consequences. There is also a risk of inadvertently transmitting pathogenic parasites. For this reason, it is imperative to identify immunomodulatory molecules and apply them to treatment of immune-mediated diseases rather than using live parasites. In order to ensure safety, it is also necessary to elucidate the detailed mechanism of how the molecule regulates immunity.

Using helminth molecules that regulate host immunity could have the potential to alleviate the symptoms of immune disorders. As mentioned above, helminth cystatins exhibit host immunosuppression through a variety of mechanisms. Recombinant proteins of *B. malayi* and *Clonorchis sinensis* cystatin showed anti-inflammatory activity and significantly reduced symptom of dextran sulfate sodium (DSS)-induced colitis in mice (79, 80). The recombinant cystatins down-regulated expressions of IFN-γ and TNF-α and up-regulated IL-10 expression in the DSS-induced colitis mice (79, 80). Administration of recombinant *S. japonicum* cystatin also reduced inflammatory parameters and ameliorated the severity of the trinitrobenzene sulfonic acid (TNBS)-induced colitis (81). HpTGM from *H. polygyrus* is a TGF-β mimicry and suppresses intestinal inflammatory response (5, 82). In Smyth's study (2020), active HpTGM was recombinantly expressed by *Chlamydomonas reinhardtii* in order to be safely consumed orally in mice and humans. Oral administration of recombinant HpTGM regulated immune cells and ameliorated weight loss, lymphadenopathy, and disease symptoms in a mouse model of DSS-induced colitis (82).

This section explains the status of research on how the protozoan parasites introduced in the previous chapter can be applied to the treatment of immune-mediated diseases. *T. gondii* can be divided into distinct clonal lines: types I, II and III and each strain has a different virulence (83–85). ROP16 of *T. gondii* type I and III (ROP16 I/III) induces M2 macrophages to ameliorate inflammatory bowel disease (86). This study was based on the fact that ROP16 I/III induce deflection of RAW264.7 to M2 macrophages and suppress M1-related inflammatory responses (86, 87). In fact, Caco-2 intestinal epithelial cells co-cultured with M1 macrophages underwent apoptosis, but Caco-2 cells co-cultured with ROP16-transfected macrophages induced to M2 showed suppressed apoptosis (86).

When *Leishmania* is taken up by macrophages, LPS-induced proinflammatory cytokines such as IL-12, IL-17, and IL-6 are specifically suppressed by the parasite (88). *L. donovani* infection of monocytes causes suppression of TLR2 and TLR4-stimulated IL-12, with an increase in IL-10 production (89, 90). Because chronic secretion of inflammatory cytokines is one of the causes of immune-mediated diseases such as atherosclerosis (91), Crohn's disease (92), and rheumatoid arthritis (93), identification of the leishmanial immunosuppressive factors (components) will lead to the development of therapeutic agents for the immune-mediated diseases in the future. *L. infantum* infection also induces down-regulation of NLRP3 inflammasome activation in $A\beta_{42}$-stimulated cells (94). Activation of the NLRP3 inflammasome is a major play in the neuroinflammation that accompanies Alzheimer's disease (95) and the down-regulation could prevent disease development.

The potential of parasite-derived molecules is not only to suppress host immunity and alleviate immune diseases. They can also be used to manipulate host immune cells and to prevent other pathogen infection. TcTS may have a potential to remove sialic acid from cellular membranes, and TcTS treatment decreases mycoplasma infection through preventing of adhesion to the glycoproteins which require sialic acid (96). This study was based on the observation that chagasic patients was are less likely to be infected with mycoplasma (96).

CONCLUSIONS

With a recent increase in the prevalence of immune disorders, such as allergic disorders (97, 98), rheumatoid arthritis (99), ulcerative

colitis and Crohn's disease (100, 101), there is an increasing demand on therapeutic interventions for such diseases. Since many of currently available drugs are derived from natural resources, it is also reasonable to seek clues for novel immunomodulatory interventions in parasites, the professional immunomodulatory organisms. Biomimetics is an emulation of models and systems living organisms have and their applications to solve various issues we face. We here propose a new term 'parasitomimetics', which is made up with 'parasite' and 'biomimetics', to represent research activities focusing on parasites' unique skills and their utilization for tackling medical issues including immune disorders. Parasites have acquired amazing abilities in the process of evolution, e.g., cell adhesion, cell invasion, escape from host cells, and morphological changes/metamorphosis. Among them, parasites' abilities to regulate host immunity may be one of the most practical for medical applications. However, parasites' harmful effects to the hosts should be seriously considered when applying them to other diseases. Unlike the usage of live parasites, an approach to mimic parasites' immunomodulatory skills by identifying the responsible molecules and synthesizing them for administration will lead to more controlled product development/standardization and minimize a risk of adverse events. On the other hand, immunomodulatory effects of parasites are often achieved by more than one molecules and active components can be missed during the identification process if we conceive that the immunomodulatory effect is derived from a single molecule. Besides, immunomodulatory molecules of parasites are not limited to proteins, which are covered in this review. For example, trehalose was identified as a molecule derived from *H. polygyrus* that induce $CD8^+$ Treg cells leading to prevention of autoimmune-mediated diabetes (102). Some cautions and novel systematic methods in identifying divergent and/or multi-component immunomodulators may increase the success rate of parasitomimetics.

Like helminths, there is also progress in identifying molecules from protozoa parasites that manipulate host immunity and elucidating their mechanisms. On the other hand, attempts to use them for treatment of immune-mediated diseases are lagging when compared with helminths. Immunomodulatory abilities of the protozoan parasites that have evolved to parasitize within immune cells should be unique and divergent from those of helminths and may be applied to resolving human immune-mediated diseases where helminth-derived molecules cannot cover.

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KN and YG contributed to conception. KN wrote the first draft of the manuscript. YG reviewed the draft. KN and YG contributed to manuscript revision. All the authors read and approved the submitted version.

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