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The first embryo, the origin of cancer and animal phylogeny. IV. The neoplastic basis for the formation of the innate immune system

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The formation of the innate immune system of animals can only be envisioned after the development of the first metazoan embryo. The decisive role of Embryology in understanding the evolution of the immune system has been inexplicably disregarded in the history of science. Some characteristics of our holozoan ancestors, including macrophage-like movement and enteric phagocytosis, were suppressed by the formation of chains of physically attached cells in the context of embryo multicellularity. The formation of the archenteron during morphogenesis of the first embryo resulted in a meta-organism whose survival was dependent on the ability to perform enteric phagocytosis (nutrition on bacteria). By recognizing the neoplastic basis of embryo formation, it is possible to venture a glimpse at its other face, a process that becomes evident when the extracellular matrix and cadherin junctions are destroyed. What ensues is metastasis (in the case of cancer) or an alternative version controlled by cell differentiation (during embryogenesis). In the context of innate immunity, the development of mesogleal cells by epithelial−mesenchymal transition and differentiation into cells specialized in bacterial recognition allowed the newly formed animal to preserve homeostasis, an innovation that has been maintained throughout evolution. In this article, I will share my first reflections on the embryonic origin of innate immunity and its close relationship with cancer. Innate immunity arises naturally during embryogenesis, which explains why the immune system typically does not react against cancer cells. In its essence, the immune system was created from them. Here, I argue that the first embryo can be understood as a benign tumor nourished and protected by the innate immune system.

Introduction

The embryo conceived as a benign tumor nourished and protected by macrophages

Innate immunity is common to all multicellular organisms. The innate immune system acts by producing responses to microbes recognized as exogenous through the detection of highly conserved antigens (Haney et al., 2014; Cao and Kagan, 2023). The evolution of the innate immune system, and of macrophages in particular, has been thought of as a functional repertoire brought on from the unicellular ancestors of animals. The system is believed to have expanded with the evolution of multicellularity and the increasing complexity of tissues and organic systems (Bajgar and Krejčová, 2023). What is undeniable is the lack of any embryological basis in discussions of the origin and evolution of the immune system in a multicellular context.

Another neglected aspect when discussing multicellularity and metazoan emergence is that the multicellular organization of animals could not have evolved without the formation of the first embryo (Cofre and Saalfeld, 2023). In this context, the innate immune system emerges and evolves linked to embryonic development. In this article, I discuss the idea that some of the characteristics of holozoan precursors, including amoeboid movement (macrophage-like movement) and phagocytosis (enteric phagocyte), were initially repressed by the formation of chains of physically attached cells in the creation of the first multicellular embryo. However, these repressed characteristics reappear in the embryonic context when the bonds that connect cells during morphogenesis are broken in a process known as epithelial–mesenchymal transition (EMT). This moment of evolutionary history is of great importance, being considered as one of the points of convergence (commonplace) between clinical pathologists/oncologists and embryologists, as evidenced by the enormous similarity between gastrulation and metastasis (Thiery and Sleeman, 2006; Kalluri and Weinberg, 2009; Micalizzi et al., 2010; Nakaya and Sheng, 2013; Ribatti et al., 2020).

In this article, I also discuss the idea that the evolutionary engine of metazoans is a Neoplastic force (Cofre, 2024); therefore, I will try to demonstrate how cancer (also a biological process) is intertwined with the emergence of the innate immune system during embryonic development. With the destruction of the extracellular matrix (ECM) and separation of cadherin junctions during embryo morphogenesis, a controlled metastasis was generated. This allowed cells to be projected and differentiated into the mesoglea by EMT, with the new animal having specialized functions of bacterial recognition and homeostasis protection. This innovation was maintained and enriched throughout animal evolution.

Thus, I propose in this article that the first embryo can be regarded as a benign tumor protected and nourished by the innate immune system. Embryological and neoplastic perspectives on the emergence of the innate immune system may elucidate some of the behaviors of macrophages that seem counterintuitive, protecting tumor growth (da Fonseca et al., 2016). The immune system might not be able to react against cancer cells, because, in essence, it was created from such cells during embryogenesis.

Nutrition or defense: primordia of the innate immune system in unicellular holozoa

Phagocytosis, the central function of innate immune responses, first appeared in primitive unicellular eukaryotes. Unicellular holozoan genomes encode homologs of key components of the immune system, including Toll-like receptor (TLR) gene homologs (Suga et al., 2012; Richter et al., 2018; Ros-Rocher et al., 2021). Among the Protozoa, the amoeba *Dictyostelium discoideum* is often regarded as a primitive macrophage (Cosson and Soldati, 2008). Human phagocytic cells and *D. discoideum* share several unique functions, such as the ability to migrate over a substrate, the capacity to ingest microorganisms by phagocytosis, and a notably high degree of proteome conservation (Eichinger et al., 2005). Perhaps unsurprisingly, it was in *D. discoideum* that the first evidence of modifications in the phagocytic activity of bacteria for exclusively nutritional purposes (Clarke and Maddera, 2006), that is, for purposes other than defense, was found. Some types of bacteria can escape phagocytosis and infect *D. discoideum* (Skriwan et al., 2002; Cosson and Soldati, 2008). To counteract this threat and survive bacterial infections, *D. discoideum* developed different strategies that include specialized sentinel cells and expression of gene products involved in bacterial death (Eichinger et al., 2005; Benghezal et al., 2006).

Human macrophages must detect and recognize specific pathogen-associated antigens on the surface of foreign cells in order to effectively distinguish pathogens from the body's own cells. Such antigens are identified by immune cell receptors called pattern recognition receptors (PRRs) (Akira et al., 2001). *Dictyostelium* is equipped with a broad array of surface receptors that exhibit substantial homology to mammalian PRRs, such as scavenger receptors (LIMP-2), TLRs (tirA, tirB), leucine-rich repeat receptors (LrrA), and C-type lectin receptors (Bajgar and Krejčová, 2023). Activation of such receptors triggers intracellular signaling cascades initiating phagocytosis, phagosome maturation, and bacterial death, as well as cascades related to stress and detoxification responses (Dunn et al., 2018). Metchnikoff's seminal observations shed light on the intimate connection between Biology (physiology) and Pathology (defense) (Metchnikoff, 1893). I speculate that bacteria began to explore a "wide new universe" with the multicellular experiences of Protozoa, culminating in the emergence of the immune system. From then on, a metazoan embryo was all that was needed for the immune system to perpetuate itself throughout animal evolution.

I consider that a theory encompassing bacterial development (a process that allows bacteria to develop into different cellular states, directly or indirectly interfering with host–pathogen interactions) is essential in order to understand the intimate connection between Biology (physiology) and Defense. Bacteria specifically exploit adhesion molecules (i.e., cell surface proteins involved in cell–cell

and cell–matrix adhesion) to endeavor to enter into the multicellular world of Protozoa and Metazoa (Sansonetti et al., 1994; Kerr, 1999; Boyle and Finlay, 2003; Bonazzi et al., 2009). Proteins such as cadherins, integrins, selectins, and immunoglobulin superfamily molecules are well-known targets of a large number of bacteria and other classes of pathogens. A possible reason for this selectivity appears to be the intracellular signaling cascades that such receptors activate, which, in most cases, leads to remodeling of the actin cytoskeleton (Boyle and Finlay, 2003). This argument is very important for the hypothesis raised in this article. Thus, for pathogenesis, bacteria "utilize" the primordial cellular basis of the construction of the first metazoan embryo (Cofre and Saalfeld, 2023). Given that the NFM is an evolutionary engine (Cofre, 2024) and that bacteria interact with its main components (cadherins, integrins, and actin remodeling), it will be very useful to understand the co-evolution of microbes and metazoans.

The first embryo as the first step in the evolution of the immune system

By comparing the genome of ctenophores, sponges, and other basal animal phyla with those of non-metazoan eukaryotes, it can be inferred that most components of signaling cascades, including innate immune system receptors, evolved after the appearance of metazoans. In most cases, these proteins are composed of specific domains (e.g., Pellino) or architectures (e.g., association of a death domain with a Toll/interleukin-1 receptor, TIR, domain in myeloid differentiation factor 88, MyD88) that are found exclusively in metazoans (Gauthier et al., 2010). Yet more relevant is the finding that the dynamic expression of TLRs during embryogenesis and larval development of *Amphimedon* is consistent with a role in both embryonic development and immunity (Gauthier et al., 2010). In other words, embryogenesis and immune system are closely linked.

Today, it is known that basal metazoans such as ctenophores did not have prototypical TLRs. It is hypothesized that prototypical TLRs arose from the fusion of TRR (a hydrophobic leucine-rich region ectodomain) and TIR (an intracellular Toll/interleukin-1 receptor domain), resulting in the so-called mccTLRs (TLRs with multiple cysteine clusters in their ectodomain) from Cnidaria to Nematoda (Brennan and Gilmore, 2018). With the expansion of TLRs in mollusks, sccTLRs (TLRs with a single cysteine cluster in their ectodomain) emerged. The developmental (convergence extension, planar polarity, and invagination) and immunity functions of Toll (Kuebler and Paré, 2023) were first identified in studies with *Drosophila* (Gerttula et al., 1988). These embryological functions were also demonstrated in more basal Arthropoda (Benton et al., 2016), indicating that they are highly evolutionarily conserved biological functions, being present in basal groups of animals. An example of such functions is seen with TLR knockdown, which results in abnormal embryonic development in *Nematostella vectensis*. The species has NF-κB-dependent innate immune system signaling (Brennan et al., 2017). On the other hand, the expression patterns of TLRs in *Amphimedon* (Gauthier et al., 2010), from an embryonic standpoint, are suggestive of a developmental function that, in my view, serves to facilitate

morphogenetic movements. This function has been reported in *D. melanogaster* (Gerttula et al., 1988).

Surprisingly, the developmental functions of TLRs in vertebrates appear to have been taken over by Wnt/PCP (Roszko et al., 2009), and TLRs became mainly, but not exclusively, restricted to immunity (Leulier and Lemaitre, 2008). Regardless of the participation of Wnt/PCP or TLRs in gastrulation, the invagination process seems to reflect a highly evolutionarily conserved mechanism involving mechanotransduction (Brunet et al., 2013; Pukhlyakova et al., 2018). Such a mechanism was widely discussed in the proposal of NFM as a true evolutionary engine (Cofre, 2024). Therefore, the separation of the embryological and immune functions of TLRs could explain the differences between vertebrate Toll and *Drosophila* Toll (Hibino et al., 2006). Such a view seems to challenge the idea of a common ancestor in the origin of the innate immune system (Leulier and Lemaitre, 2008). Therefore, in the current hypothesis, there exists a common ancestral origin of TLRs. The decisive embryological events that explain TLR dissociation (gastrulation dissociation) are recent in metazoan evolution. I believe that the decoupling of TLRs and gastrulation in vertebrates has a developmental basis and was crucial for the emergence of the adaptive immune system, a topic that I will cover extensively in a separate article.

Animal evolution played a determinant role in refining the innate immune system. An efficient "digestive" cellular system for ingested material represents only the primary function (Gotthardt et al., 2002) through which phagocytosis extends its functional capacity throughout evolution (Desjardins et al., 2005). A previously formulated hypothesis proposes that many of the characteristics of pro-inflammatory macrophages evolved in the unicellular ancestors of animals, and that the functional repertoire of macrophage-like amebocytes was further expanded with the emergence of multicellularity and the increasing complexity of tissue and organ systems (Bajgar and Krejčová, 2023). As argued by Bajgar and Krejčová, there is a link between the emergence of embryonic morphogenesis and the expansion of possibilities and complexity of the innate immune system. Other authors also acknowledged that the history of the immune system has been shaped over billions of years of bacteria–metazoan co-evolution (Li and Wu, 2021) or by beneficial symbiotic associations with complex communities of microbes (Gerardo et al., 2020), shedding light on the relevant role that bacteria might have played in animal evolution (Hughes and Sperandio, 2008; Alegado et al., 2012). Some bacteria are even able to induce multicellular behavior in choanoflagellates, which appeared before the evolutionary radiation of animals (Alegado et al., 2012).

Capsaspora owczarzaki is a unicellular eukaryote—a protist. Phylogenetically, *Capsaspora* belongs to the clade Filasterea, one of the closest unicellular relatives of animals, together with choanoflagellates, ichthyosporeans, and corallochytreans (Ferrer-Bonet and Ruiz-Trillo, 2017). Based on this close evolutionary relationship, Capsaspora is becoming pivotal to understanding the origins of animal multicellularity. Recent investigations revealed that C. owczarzaki and some choanoflagellates contain genes encoding nuclear factor-kappa B (NF-κB)-like proteins (Sebé-Pedrós et al., 2011; Suga et al., 2013; Richter et al., 2018). NF-κB

is a molecule extensively studied for its role in embryonic development and immunity, from the first animal to modern humans (Gilmore, 2006; Ghosh and Hayden, 2012; Williams and Gilmore, 2020). It should be noted, however, that functional NF-κB-like proteins (DNA binding and transcription activators) vary considerably in general structure, activity, and regulation mechanisms, both between protists and in comparison with animal NF-κB (Williams et al., 2021). The emergence of metazoans seems to have been essential for the definitive configuration of the NF-κB protein, further supporting the view that the emergence of the first embryo was a fundamental step in the development of the immune system.

Considerations on the trophic conditions of the first animal

Let us ponder on the trophic conditions of the first metazoan (multicellular embryo). What could this unique organism eat? It is important to point out that this primitive condition might have fostered the first parasite–host relationship. I can predict through my hypothesis that the preservation of phagocytic capabilities from unicellular holozoans in the archenteron of the first embryo would be a matter of survival (Figure 1A). Likewise, the differentiation of specialized macrophages can be seen as a matter of preservation of homeostasis and integrity in this new multicellular metazoan niche, as will be discussed later.

Although body plan is not the focus of this article, it is possible to affirm that the first embryo likely subsisted on picoplankton (planktonic microbes measuring 0.2–2 µm in diameter) and dissolved organic matter (Mills and Canfield, 2017). At the time of their emergence, the first metazoans would be the only representatives of complex multicellular clades (without cell wall) with the ability to phagocytose particles and other cells for nutrition purposes. The first embryo, therefore, probably occupied similar trophic levels and niches as its unicellular flagellate ancestors

(Richter and King, 2013). To clarify, the appearance of the first animal was not necessarily accompanied by major changes in prey preferences (Valentine and Marshall, 2015).

What food would be available to the first metazoans? Bacteria, flagellates, multicellular structures, and phytoplankton would likely have been their primary prey (Lenton et al., 2014; Leys, 2015). Without wide availability of animal life, primitive seas would unlikely be rich in bacteria and fecal aggregates, which contain high levels of dissolved organic carbon. Filtration as a feeding mechanism would have been energetically costly (Leys et al., 2011; Leys, 2015), so it is unlikely to have originated in oxygen-poor oceans. Even if the hypothesis of the emergence of the most basal animal taxon (Ctenophora) turns out to be correct (Ryan et al., 2013; Moroz et al., 2014; Arcila et al., 2017; Shen et al., 2017; Whelan et al., 2017), the first animals could not have been carnivores like modern ctenophores. Thus, the most likely feeding strategy during embryonic and early animal development is bacterial phagocytosis.

On the first animal and its immune system

Although the traditional view is that sponges form the first branch of the animal tree (Linden and King, 2021), several studies suggest the Ctenophora as the basal-most animal lineage (Ryan et al., 2013; Moroz et al., 2014; Arcila et al., 2017; Shen et al., 2017; Whelan et al., 2017). Also, there remains no doubt that ctenophores have a well-developed innate immune system (Traylor-Knowles et al., 2019; Arroyo Portilla et al., 2021). Two TLR homologs identified in *Mnemiopsis leidyi* and *Hormiphora californiensis* contain LRR domains that mediate interactions with microbial pathogens in humans (Ng et al., 2011). Furthermore, both species were found to express perforin-2 (MPEG-1) (Traylor-Knowles et al., 2019), suggesting an older role in attacking Gram-negative bacteria (McCormack and Podack, 2015). On the other hand, a single homolog of NOD-like receptor (NLR), Jun, and Fos was
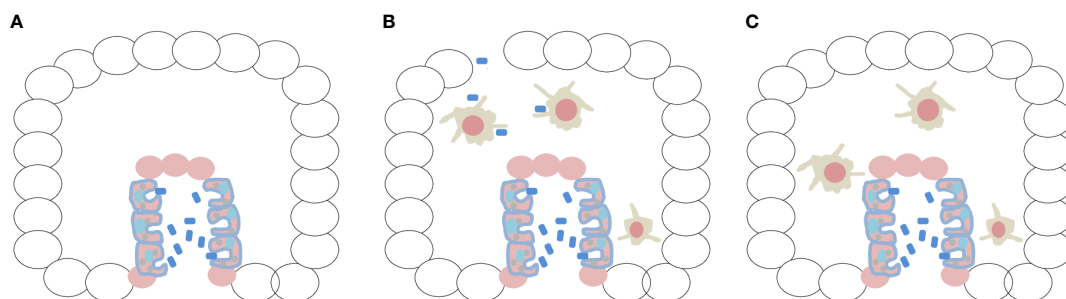

FIGURE 1
The first embryo would be a benign tumor, protected and fed by the innate immune system. **(A)** Creation of a meta-organism after invagination and archenteron formation, linked to the conservation of the ability to recognize bacteria, would have been essential for the nutrition of the first embryo, being a matter of survival. Ciliated digestive cells lining the archenteron were identified in ctenophores (Franc 1972; Hernandez-Nicaise 1991; Presnell et al. 2016; Vandepas et al. 2017). **(B)** Animals such as ctenophores are very fragile, and their rupture or mechanical injury might have allowed bacterial invasion of the embryo. During morphogenesis, macrophages differentiated and protruded into the mesoglea by epithelial–mesenchymal transition. This created a different phase of phagocytosis (and exaptation of TLRs) represented by professional macrophages, constituting protective immunity. **(C)** The embryo would be a benign tumor nourished and protected by the immune system, and the two phenomena, enteric phagocytosis and protective immunity by professional macrophages, were formed in association with physical phenomena (invagination/EMT/gastrulation) that occurred during morphogenesis of the first embryo.

detected (Traylor-Knowles et al., 2019), potentially indicating a well-simplified cytosolic defense system against other metazoan lineages and at least suggesting that a heterodimerization interaction might have produced a functional AP-1 homolog at the base of the evolutionary radiation of animals.

An astounding finding was the identification of highly mobile cells traveling through the mesoglea of ctenophores, exhibiting amebocyte-like morphology and converging on experimentally damaged areas under the dermis (Traylor-Knowles et al., 2019). When challenged with live or heat-killed bacteria, *in vivo* and *in vitro*, these mobile amoebocyte-like cells exhibited pinocytic and phagocytic behavior. Bacteria were rapidly engulfed (within minutes) and transported to acidic compartments within the cell. Ciliated digestive cells lining the gastrovascular canal (archenteron) had already been observed in *M. leidyi* and other ctenophore taxa (Franc, 1972; Hernandez-Nicaise, 1991; Presnell et al., 2016; Vandepas et al., 2017), but ciliated digestive cells exhibiting phagocytic behavior toward bacteria were only recently reported (Traylor-Knowles et al., 2019). In my view, both observations, namely amoeboid cells in the mesoglea and phagocytic cells in the primitive gut, are a reflection of immunity (protection) and survival (nutrition) behaviors. (Hartenstein and Martinez, 2019). As will be discussed later, immunity (protection) arose from the epithelial–mesenchymal transition (EMT) of the primitive intestine (Figure 1B), constituting the neoplastic basis for the formation of the first embryo.

Considerations on ctenophores as meta-organisms and their influence on the formation of the immune system

All multicellular organisms are intimately associated with bacteria and, therefore, together constitute metaorganisms, a fact that has already attracted public and scientific attention worldwide. The scientific community has begun to elucidate the essential role of the microbiota in the functioning of humans (Rook et al., 2017) and in the life history of animals. This role becomes evident, for example, in basal marine metazoans such as corals and jellyfish. Bacteria and their exudates have a crucial impact on the induction of metamorphosis and settlement of the planula larva of *Cassiopea andromeda* (Neumann, 1979) and the coral *Acropora millepora* (Tebben et al., 2011). Bacterial exudates were also reported to induce sexual reproduction (Woznica et al., 2017) and the formation of multicellular structures (Alegado et al., 2012) in choanoflagellates.

Such discoveries enticed us to think deeper and allowed us to conclude that interactions with bacteria can moderate/modulate/mediate evolutionary processes (Reshef et al., 2006; Zilber-Rosenberg and Rosenberg, 2008; Rosenberg et al., 2009; Bosch and McFall-Ngai, 2011). There is a call for transdisciplinary collaboration in zoology (Bosch and McFall-Ngai, 2011) that should be well extended to evolution. Animals do not live in isolation but rather in complex communities that interact with environmental conditions—a highly relevant perspective when it comes to evolutionary phenomena. In the context of this article,

ctenophores, as a basal metazoan phylum (Ryan et al., 2013; Moroz et al., 2014; Arcila et al., 2017; Shen et al., 2017; Whelan et al., 2017), are considered meta-organisms (Daniels and Breitbart, 2012; Jaspers et al., 2019).

A more detailed understanding of Ctenophora–bacteria interactions at the base of the metazoan tree may reveal important information about the evolution of meta-organisms. In this article, I will make predictions about the possible contributions of bacteria to the exaptation of the neoplastic functional module (NFM) and the differentiation of the innate immune system. The next section explores the environmental conditions that enabled the emergence of these phenomena.

Ediacaran ocean

The Ediacaran fossil record reveals an intriguing pattern: the first animals inhabited only deep-water environments and experienced frequent hypoxia (Boag et al., 2018). Therefore, it appears that hypoxia resistance was acquired at the beginning of animal life, and the Warburg effect (which will be discussed in the following section) may be a remnant of the evolutionary history of metazoans. The fossil record also suggests that the Ediacaran biota initially appeared around 571 Ma in deep ocean waters before appearing in shelf environments at approximately 555 Ma (Jablonski et al., 1983; Boag et al., 2018) Thus, from an evolutionary perspective, understanding the tolerance of marine animals to hypoxia is of utmost importance for my hypothesis.

Today, it is thought that metazoan evolution was facilitated by a series of dynamic and global changes in redox conditions and nutrient supply, which sustained multiple radiation phases in metazoans, one of them in the Ediacaran Period (Wood et al., 2019). Thus, it has been proposed that changes in Ca^{2+} concentration in the Ediacaran ocean were a crucial driving force behind major innovations in evolution, including multicellularity and the origin of metazoans (Brennan et al., 2004; Kazmierczak et al., 2013).

Also, it is postulated that the ancient ocean had high alkalinity and low concentrations of Ca^{2+} and Mg^{2+}, similar to modern soda lakes, commonly associated with volcanic regions (Kempe and Degens, 1985). It is assumed that the first soda ocean gradually evolved into a sodium chloride-rich ocean through "titration," emanating volatile acids such as HCl, thereby reducing the pH and finally reaching a titration point of Ca^{2+}, allowing its relatively rapid accumulation at the end of the Precambrian (Kempe and Degens, 1985; Kazmierczak et al., 2013). In a time period of 3 billion years, the primitive concentration of calcium in the ocean increased by 1,000 to about 100,000 times (Kempe and Degens, 1985; Kazmierczak et al., 2013). A strong indicator of an early alkaline ocean is the predominance of alkaloid cyanobacteria (Cyanophycea) in Precambrian biota (Kempe and Degens, 1985).

There is evidence of alkali-tolerant and extremely alkalophilic bacteria (Padan et al., 2005) that could withstand the hostile environment of the Ediacaran ocean. Such organisms are important from the viewpoint of current medicine (Livermore, 2003; Levy and Marshall, 2004) because the emergence of

resistance to novel antibiotics is linked to alkali tolerance (Krulwich et al., 2005). The answer to this problem may lie in our evolutionary history. Systematic studies have shown that many alkalophilic prokaryotes represent separate lineages within currently accepted taxa, whereas some have no strong relationship with other known prokaryotes (Jones et al., 1998). It appears that these alkalophilic communities evolved independently in an early period of Earth's history. What is important to our hypothesis is that the first embryo and animal had access to alkalophilic bacteria as a source of nutrition.

The Warburg effect

There is still considerable debate as to whether or not oxygenation was the main factor in early metazoan evolution (Towe, 1970; Wood et al., 2019). Although all existing animals need oxygen, their demands are not always the same. The most tolerant organisms of extreme oxygen depletion on the seafloor include calcareous foraminiferans, nematodes, and annelids (Levin, 2021). A recently developed biogeochemical model revealed that atmospheric and oceanic oxygen levels in the Ediacaran Period were dissociated, indicating that the early increase in atmospheric oxygen levels in the Ediacaran might not have promoted generalized oxygenation of the deep ocean (Shi et al., 2022), which is also consistent with geochemical records (Lenton et al., 2014). Experimental results with basal groups of animal evolution demonstrated that the sea sponge *Tethya wilhelma* can withstand oxygen levels as low as 0.25% to 4% of current atmospheric levels (Mills et al., 2014).

Ctenophores also live in deep ocean waters (Harbison et al., 1978; Haddock et al., 2017) and some have been found at 7,200 m depth (Lindsay and Miyake, 2007), where there are extremely low oxygen levels. Genomic analyses of sponges and ctenophores showed that both lack important components of the hypoxia-inducible factor (HIF) pathways that maintain cellular oxygen homeostasis (Mills et al., 2018). Therefore, ctenophores might have performed aerobic metabolism under very low concentrations of oxygen.

As for copepods, which are highly resistant to hypoxia and important representatives of marine zooplankton, *Calanoides carinatus* carries out part of its embryonic development at a depth of 700 m in the ocean (Auel et al., 2005; Verheye et al., 2005; Auel and Verheye, 2007). The nauplius larvae of *Labidocera aestiva* and *Acartia tonsa* are highly resistant to extreme hypoxia conditions. Surprisingly, *Tigriopus californicus*, a resident of supralittoral rocky pools where dissolved oxygen levels can drop to ~0 mg/L (Truchot and Duhamel-Jouve, 1980), has become an excellent physiological model for the study of oxygen deprivation in animals without respiratory structures (Graham and Barreto, 2019). It is the first marine animal whose high hypoxia resistance (Goolish and Burton, 1989; Graham and Barreto, 2019) can be linked to the Warburg effect.

Surprisingly, studies on *T. californicus*, showed that these organisms can withstand prolonged exposure to extreme oxygen deprivation, despite having secondarily lost the main members of the HIF pathway, being similar to tumor systems (Graham and

Barreto, 2019). Allie Graham and Felipe Barreto predicted a shift from oxidative phosphorylation to glycolysis under hypoxic conditions. Consistent with this prediction, the authors observed a significant increase in pyruvate dehydrogenase kinase (PDK) mRNA levels (Graham and Barreto, 2019). This is the Warburg effect (Warburg, 1956) occurring in highly hypoxic animals and thereby revealing, in my opinion, a vestige of our origin in deep ocean waters. Despite a large volume of papers researching this effect in cancer, the function of the Warburg effect has remained unclear (Liberti and Locasale, 2016).

Another expected prediction for the Warburg effect is that elevated glucose metabolism decreases the pH within the cell due to lactate formation (Estrella et al., 2013), thereby requiring greater activity of H^+ extrusion mechanisms to prevent cell death (DeCoursey, 2015). Considering the animal formed in the Ediacaran ocean under hypoxic conditions (Shi et al., 2022) in an alkaline sea (Kempe and Degens, 1985), it is expected that it would show H^+ efflux. Voltage-gated proton channels (Hv1) with ΔpH-dependent regulation occur in several organisms, from protists to humans (DeCoursey, 2015), and are responsible for bioluminescence in dinoflagellates (Rodriguez et al., 2017; Kigundu et al., 2018). These channels might have helped calcify (Taylor et al., 2011; Kottmeier et al., 2022) and acidify the Ediacaran ocean (external environment).

In line with these observations, acidification of the microenvironment in tumor models has always been considered an intriguing aspect of the disease (Schlappack et al., 1991; Rofstad et al., 2006; Moellering et al., 2008). The potential benefits of acidosis to cancer cells have been discussed. Some hypotheses of acid-mediated invasion suggest that H^+ ions secreted by cancer cells diffuse into the surrounding environment and alter the stroma interface of the tumor, allowing for greater invasiveness (Gatenby and Gawlinski, 1996; Estrella et al., 2013). It is possible that the Warburg effect and acidification are a remnant of our evolutionary past linked to Neoplasia. Thus, in the first ctenophores, the Warburg effect might have promoted high proliferation and cell growth in a hypoxic and highly alkaline environment.

Unraveling the malevolent alliance of macrophages with tumor cells at its evolutionary origin

Most surprising in oncology and modern immunology is the recognition of the functional ambiguity of tumor-associated macrophages (TAMs), mainly because they seem to promote tumor evolution, which represents a challenging obstacle in cancer treatment (Ostuni et al., 2015). It is also remarkable how tumors seem to exploit the trophic activity of macrophages to survive and progress. Disrupting this "malevolent alliance" between cancer cells and macrophages might represent a crucial step toward cancer cure (Allavena et al., 2021).

Later in this article, I will present a summarized part of my hypothesis proposing that the first embryo was a benign tumor, with some cells performing digestive phagocytosis in the archenteron as a trophic survival activity. At more advanced stages of morphogenesis, macrophages are formed and, through

EMT, move into the mesoglea (in a kind of controlled metastasis by specific exaptation of the NFM) and create a different function for phagocytosis (immunity conferred by professional macrophages) (Figure 1B). Therefore, the first embryo is a tumor with macrophages that feed and protect it (Figure 1C). From the point of view of my hypothesis, rather than a "malevolent alliance," there is an intimate and common evolutionary origin with Neoplasia. The immune system cannot deny its origin.

Evolutionary remnants of the Warburg effect in the immune system and macrophages

Before describing my hypothesis on the emergence of the innate immune system, I would like to clarify the evidence of the Warburg effect in phagocytic cells. Phagocytosis uses acidification systems that nowadays involve NADPH oxidase and energy (ATP) (Lukacs et al., 1990; Nunes et al., 2013). This functioning makes sense in the context of the current environment, without alkalization and in the presence of oxygen. But the presence of voltage-gated proton channels (Hv1) with ΔpH-dependent regulation in neutrophil phagosomes (Okochi et al., 2009) is not plausible without recognizing the evolutionary history of the immune system in the first embryo. These observations point to remnants of the Warburg effect in the innate immune system. As for the adaptive immune system, I published a personal communication discussing evidence of the Warburg effect in vertebrate lymphocytes (Cofre, 2022).

The primary function of Hv1 channels, in an oxygen-free and highly alkaline environment (Shi et al., 2022), would have been to neutralize soda in the Ediacaran ocean (Kempe and Degens, 1985). Subsequently, in response to oxygenation of the Earth's atmosphere, Hv1 channels would have been co-opted for the production of oxygen free radicals, coupled to NADPH oxidase (Okochi et al., 2009). Therefore, I propose that the presence of HV1 channels in myeloid-derived suppressor cells (MDSCs) (Cozzolino, 2022; Cozzolino et al., 2023) also points to the evolutionary origin of the immune system.

Consistent with my hypothesis, traces of the Warburg effect are also found in the response of macrophages to hypoxia. Multiple studies have shown that experimental hypoxia alters cell morphology, expression of cell surface markers, cell viability, phagocytosis, metabolic activity, and cytokine release in macrophages (Lewis et al., 1999). Surprisingly, exposure to hypoxia markedly reduced cytochrome oxidase activity and increased pyruvate kinase activity in alveolar macrophages (Butterick et al., 1981), revealing the occurrence of the Warburg effect in the innate immune system. These findings suggest that macrophages can adapt to a lack of oxygen by switching to anaerobic glycolytic pathways for ATP production, resembling malignant cells under hypoxic conditions (Lewis et al., 1999).

Looking at our evolutionary history and the conditions of the Ediacaran ocean, I find plenty of antecedents of the intimate relationship between embryogenesis, cancer, and immune function. The following section presents a description of my hypothesis.

Discussion

Nothing in biology makes sense except in the light of evolution

All metazoans (animals) are produced by fertilization, so the beginning of animal life only makes sense with the formation of an embryo (Cofre and Saalfeld, 2023). Developing an embryo requires cells to proliferate physically united under an initial mechanical phenomenon that I believe would be a multiflagellate fusion event (Cofre, 2022). The initial impact of multiflagellate fusion is a determinant physical event at the beginning of animal phylogeny that left its records imprinted on the first metazoan cells in the form of cytasters (Cofre, 2022). It also promoted intense reorganization of the actin cytoskeleton in the cytoplasm and nucleus of the first "zygote" and produced a form of genomic reorganization that produced the NFM (Cofre and Saalfeld, 2023). In the context of the genesis of the innate immune system, there are at least three basic elements of the NFM that are interconnected with the genome: (i) the proliferation process (cell cycle), (ii) the adhesion process (surface molecules, such as cadherins), and (iii) the bacterial recognition process (phagocytosis).

Two important discoveries guided the field of innate immunity. The *Drosophila* Toll protein, previously known only for its functions in embryonic development (Anderson et al., 1985), was characterized as necessary for flies to mount an effective immune response to the fungus *Aspergillus fumigatus* (Lemaitre et al., 1996). TLR4 was later identified as necessary for mice to mount effective responses to Gram-negative bacteria (Poltorak et al., 1998). Therefore, the innate immune system of insects and mammals has an evolutionary relationship; TLRs were proposed to have a central role in the primary recognition of infectious pathogens throughout evolution (Beutler, 2004). This evolutionary basis was consolidated because TLRs, as discussed previously in this article, were found in protists and ctenophores.

The formation of a multicellular embryo connected by a cytoskeleton producing mechanical tension forces during morphogenesis is an extremely energy-demanding process. Therefore, it seems logical to me to incorporate TLR elements as fundamental components of the first animal, participating in its survival, a real matter of subsistence. By co-opting TLRs, this first organization ensured that the organism would be able to phagocytose bacteria and supply the necessary resources for ATP production under anaerobic conditions during embryogenesis. The first resources of our first embryo likely stemmed from multiflagellate fusion and were therefore scarce until the formation of the primitive gut (Presnell et al., 2016). It is easy to understand why TLRs (PRRs in general) are so strongly related to embryology (dorsal/ventral patterning was their first function) (Lemaitre et al., 1996), cancer (immunotherapy) (Anderson, 2000; Chen et al., 2008; Rakoff-Nahoum and Medzhitov, 2009; So and

Ouchi, 2010; Pradere et al., 2014; Shi et al., 2016; Braunstein et al., 2018), and the survival of the first animal (enteric phagocytosis) (Hartenstein and Martinez, 2019).

Animal genesis involving the co-option of the NFM led to unbridled and vertiginous proliferation limited by cadherins. This process, this initial expansive force, would be Neoplasia. Neoplasia is not simply cell proliferation but rather a force of transformation, a process that arose with the multiflagellate biophysical impact on animal genesis. Therefore, Neoplasia is an embryological process that represents the cancer side in all embryos (Cofre and Saalfeld, 2023). The disease cancer will change throughout animal phylogeny (as will be discussed in several separate articles), but, whenever cancer appears in any species, it reveals its embryonic evolutionary origin (Ben-Porath et al., 2008; Yu and Xu, 2020; Lee, 2022).

During the first growth phase of the embryo, cells learned to grow together and managed to migrate together to produce the first great revolution—epiboly—the outline of the first collective migration (Cofre, 2024). In this context, by growing together, cells held great potential for the creation of new animal forms. However, many of the characteristics of our unicellular holozoan ancestors were suppressed. For instance, in a mechanically united epithelium, amoeboid and migratory characteristics cannot manifest themselves freely. On the other hand, phagocytosis can still occur in restricted places of the plasma membrane. In primary cell cultures of ctenophores (Vandepas et al., 2017; Traylor-Knowles et al., 2019), despite the mechanical destruction of cells with trypsinization, centrifugation, and exposure to classic mammalian culture media, it is possible to observe the basic characteristics of the NFM in the first adult animal: (i) ectodermal and endodermal proliferative cells (Vandepas et al., 2017), (ii) some cellular associations (cell–cell interactions, cells that learn to grow together) (Vandepas et al., 2017), and (iii) amoeboid cells with the ability to phagocytose bacteria (Traylor-Knowles et al., 2019).

During embryo construction, the initial module undergoes exaptations, which are a representation of the physical changes (and their impact on genomic reorganization) that occur during morphogenesis of the first embryo. The second great revolution was the co-option of extracellular matrix (ECM) construction and remodeling to the Neoplastic module (Cofre, 2024). The latter has consequences on the formation of the two faces of the innate immune system (nutrition and defense); the innate immune system becomes linked to two sequential morphogenic processes that are important for embryo formation.

Constructing an ECM on a mechanically joined epithelium translates into the creation of textural gradients (Hartman et al., 2017; Zhu et al., 2023) and the onset of durotaxis (Sunyer et al., 2016) and topotaxis (Park et al., 2018), which will signal cell differentiation. But the relevant aspect for animal evolution is ECM remodeling, which will translate into shape changes, such as invagination and EMT movement. EMT is a fundamental embryonic process for embryo construction and reconstruction of the adult animal (Savagner, 2001; Arnoux et al., 2005). In the framework of my hypothesis, it represents the cancer (Neoplastic) side of the embryo revealing itself (Berx et al., 2007; Thiery et al., 2009; Cofre and Saalfeld, 2023), although always contained by ECM topology, leading EMT to cell differentiation (controlled metastasis).

Considering the first embryological event that was decisive for the formation of the innate immune system, with evidence in ctenophores (Martindale and Henry, 2015), I speculate that invagination by tensional forces began at the aboral pole (Cofre, 2024), which led to the production of a meta-organism (Daniels and Breitbart, 2012; Jaspers et al., 2019). This marked the occurrence of the first co-option of phagocytosis and TLRs to a mechanical embryonic event (which was registered in the NFM), linking the innate immune system of animals to archenteron differentiation (Figure 1A). I draw the attention of readers to the fact that phagocytosis and TLRs are of protist origin (Suga et al., 2012; Richter et al., 2018; Ros-Rocher et al., 2021) and incorporated into the NFM. Therefore, I speculate that they have an important link with cancer (Rakoff-Nahoum and Medzhitov, 2009; Pradere et al., 2014). TLRs were co-opted to the NFM during a morphogenic event, explaining their relevant role in embryogenesis throughout animal evolution (Brennan and Gilmore, 2018).

I underscore that TLRs were associated with enteric phagocytosis in the archenteron (Figure 1A). This unique moment allowed consolidating the embryonic structure by means of the energy support obtained by digestion of alkalophilic bacteria. TLR proteins changed throughout animal evolution (Patthy, 1999), and Neoplasia itself created innovations from these proteins (Cofre, 2024). Such processes will allow us to understand the emergence of the adaptive immune system at a different time point of animal history. Ctenophores have Transib transposons in their genome (Kapitonov and Jurka, 2005), which would enable the reordering and creation of new domains in TLRs, triggering exclusive innovations in animals (Gauthier et al., 2010), and bacteria in their archenteron, from which RAG recombinase is derived to mediate V(D)J recombination (Tao et al., 2022). The emergence of the adaptive immune system and its relationship with embryonic development will be discussed in a separate article.

The innate immune system rapidly underwent a second co-option associated with ECM remodeling processes. Matrix metalloproteinases (MMPs) were co-opted to the NFM, along with TLRs and phagocytosis. Some cells with amoeboid characteristics (capacity for phagocytosis and TLR expression) were able to project into the mesoglea and fulfill a completely different function for the embryo, that is, of defensive immunity (professional macrophages) (Figure 1B). Thus, phagocytosis and TLRs were co-opted to the NFM via two mechanical phenomena that occurred at different periods.

A good strategy to test the hypothesis of modular exaptation of phagocytosis and TLRs during embryogenesis is to analyze the other cells that were incorporated into the mesoglea. If the process is linked to EMT in ctenophore embryos, TLRs and phagocytosis should be found in other mesodermal cells. This behavior is observed in microglia of *Beroe cucumis*, and phagocytosis occurs in the mesoglea (Aronova and Alekseeva, 2004). In mammals, microglia (TLRs and phagocytosis) perform important functions in the context of the complexity of the nervous system (Xu et al., 2022). Are the microglia of *B. cucumis* and mammals equivalent? No. There is a long evolutionary history that explains how ctenophore microglia led to mammalian microglia. With this, it will be possible to understand the keys to phagocytosis and inflammatory responses in Alzheimer's disease, multiple sclerosis, Parkinson's disease, traumatic brain injury, ischemic, and other

brain diseases (Fu et al., 2014; Gibson and Monje, 2021; Xu et al., 2022). Are microglia part of the innate immune system of ctenophores? Yes. From an embryological point of view, in my opinion, there is no doubt that microglia are at the origin of the first embryo and linked to Neoplastic phenomena, mainly because cells perform EMT to project to the mesoglea. Also, the same malevolent alliance can be found between microglia and glioblastomas (da Fonseca et al., 2016).

Co-option of TLRs (now alone, without phagocytosis) is also associated with cells of the enteric nervous system of humans (Vicentini et al., 2022). I do not yet intend to establish any structural relationship between the enteric nervous system and the mesogleal nervous network of ctenophores (origin of the neuromesoderm) (Jager et al., 2011). However, at present, all evidence points to the importance of microbiota in neural regulation and neurogenic functions (Belkind-Gerson et al., 2017; Aktar et al., 2020) and the key role of bacteria in colorectal (Candela et al., 2014; Sobhani et al., 2019), pancreatic (Zhang et al., 2020), and gastric (Ferreira et al., 2018) cancers. One of the current challenges of science is to understand to what extent bacteria in the meta-organism influenced the emergence of immunity. Today, evolutionary biologists know that bacteria influence the multicellular experiences of protists; therefore, it is interesting to think of the microbiota of the meta-organism as an inducer of morphogenesis.

This unique condition of modular exaptation to the NFM at two different times provides diversification possibilities for the embryo. Cells will be able to eat and react to bacteria invading the mesoglea. How do bacteria invade? Ctenophores are very fragile animals, and mechanical rupture of the animal body might have led to an exhaustive invasion and homeostasis interference. Moreover, their epithelial cell–cell bonds are more tenuous (transient adherens junctions) (Tamm and Tamm, 1991; Tamm and Tamm, 1993), and, thus, invasion of the mesodermal environment would be inevitable.

Thus, the initial embryo had at its disposal a mechanism of bacterial recognition rooted and inherited from holozoans (which used this mechanism for trophic purposes). The immune system emerged via modification of the NFM, which incorporated the system at different times and structures during embryo morphogenesis. It is important to emphasize that there is no competitive fitness here; this is the only animal in the immense Ediacaran ocean. This first animal was not competing with anyone, it simply manifested a potential inherent to its holozoan origin. The first animal is a representation of how embryos imbibed DNA through their physical and environmental contexts during early embryogenesis. Was the construction of the NFM successful? NFM has been conserved so far in humans and apical groups. It is also present and conserved in the evolution of the immune system, whose evolutionary records were made through the Warburg effect.

The first animal would not be able to compete with bacteria; it would be, from any point of view, an unfair competition for the first fragile representative of metazoans. I believe that it is not possible to compare the long successful history of the phylum Archaea on planet Earth to that of animals, mainly because the two have, so far, collaborated intensely and evolved together.

To conclude my proposal, I wish to quickly and briefly address the fundamentals of reconstruction in the next generation of the innate immune system created in this hypothetical embryo, as described by Cofre and Saalfeld (2023). How would it be possible to reestablish bodily coherence and integrity throughout evolution? Any embryonic event that brings mechanical and physical consequences for the embryo "as a whole" will be exapted to the NFM, conceptually denoting a mechanical topology in the genome (Zheng et al., 2009; Fedorchak et al., 2014; Cho et al., 2017; Miroshnikova et al., 2017; Uhler and Shivashankar, 2017a; Uhler and Shivashankar, 2017b; Wang et al., 2017). Maintaining the mechanical records of these events in the nucleus, or in a restricted set of embryonic cells, was a primordial step in animal phylogeny and is one of the conceptual bases of my hypothesis. The basis is in the stress waves generated by morphogenic processes (Pajic-Lijakovic and Milivojevic, 2022) and in the bionanowires of the nuclear actin cytoskeleton (Mori et al., 2014; Okuno et al., 2020; Wesolowska et al., 2020; Hunley and Marucho, 2022), which support an integrated embryonic structure influenced by galvanotaxis directed from the apical pole (Coonfield, 1936).

Experiments on ctenophores demonstrated their incredible ability to regenerate (Martindale and Henry, 1996; Tamm, 2012; Edgar et al., 2021). Cutting ctenophores in half results in the creation of two perfectly equal animals (Coonfield, 1936). These experiments provide insight into a construction network in which the parts can generate the whole. Nevertheless, a paradigm is evident from the conclusions of Coonfield: "Halves, thirds, and fourths of Mnemiopsis regenerated the lost parts while eighths of this animal failed to regenerate." I will address this paradigm separately, because it is known that two cells (a tiny part of the whole), sperm and oocyte, can generate a whole animal.

Consistent with my proposal, basal animals in animal phylogeny belatedly separate the germline (Juliano et al., 2010; Fierro-Constaín et al., 2017; Edgar et al., 2021). This is completely expected and necessary for the beginning of animal life. In the first embryo, germ cells must first receive all mechanical and physical stimuli from embryogenesis to trigger the separation of the germ line. This brings to mind the philosophical question of what came first, the egg or a beroid-like ctenophore? The answer is unequivocal: the egg came first. But there is one caveat. It emerged only after it had been completely impregnated by its surroundings and had its physical trajectory defined inside the embryo (Cofre and Saalfeld, 2023). This first embryonic trajectory is fundamental, and I can represent it in the words of a Spanish poet, "Walker there is no path, you make the path by walking (when walking you make the path)" (MaChado, 2021). Therefore, the embryo modeled the genomic records of its construction during embryogenesis. This rule is absolute for the first embryo that will establish a topological map of Physics in the genetic material (Uhler and Shivashankar, 2017a; Uhler and Shivashankar, 2017b; Uhler and Shivashankar, 2018; Tsai and Crocker, 2022).

In line with these arguments, there is evidence of biophysical regulation of the chromatin architecture and of how the load and persistence of forces applied to the nucleus can trigger and define the trajectory of a given cell population (Heo et al., 2015; Dai et al., 2020). A long dynamic tensile loading resulted in a more robust chromatin condensation, not always related to actin cytoskeleton contractility. Scientists have avoided discussing biological (molecular/genetic) clocks as mechanical (Hubaud et al., 2017). But segmentation of somites, classically a biological clock (Dubrulle and Pourquié, 2002;

Pourquié, 2003; Andrade et al., 2007; Klepstad and Marcon, 2023), is evidently subjected to tensile forces of elongation and folding (Mongera et al., 2019; Anand et al., 2023; Yaman and Ramanathan, 2023). Thus, in the context of this hypothesis, mechanical memory (like a clock) will explain how germ cells manage to rebuild all structural coherence in the next generation; these topics are discussed in a separate article (Cofre, 2022).

Finally, I have openly said that the embryo is a benign tumor, protected and nourished by macrophages. Therefore, the embryo and macrophages are inseparable (Figure 1C). Readers should have many doubts as to why an EMT process with rupture of the basal lamina did not turn into cancer. It actually is cancer, the cancer side of the embryo, but it differentiated and was regulated/controlled by the embryonic microenvironment (Figures 2A, B).
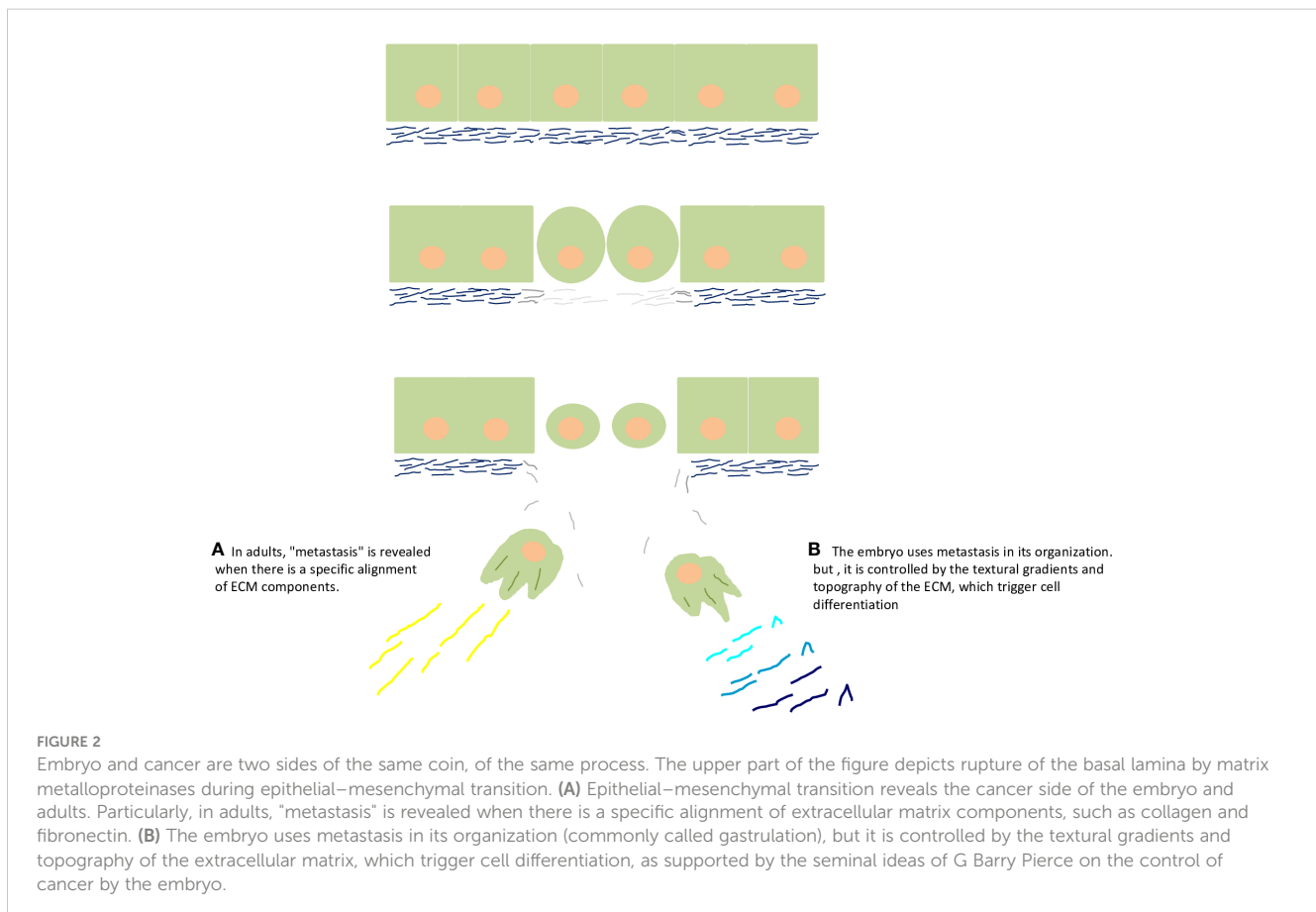
To clarify this seemingly controversial point, I highlight my great inspiration in oncology and pay tribute again to the work of G. Barry Pierce.

I propose to discuss a concept of cancer that has been formulated upon our experiments on differentiation and cancer, outline the current experiments from our laboratory in regulation of cancer by the embryo, and indicate the potential importance of this approach for therapy (Pierce, 1983).

Thus, what is controlling the cancer side of the embryo? Why did the cells that protruded into the mesoglea not turn into cancer? In his articles, Pierce suggested that it would be the "differentiation of malignant to benign cells" (Pierce and Johnson, 1971; Pierce and

Wallace, 1971; Pierce et al., 1982) happening inside the embryo (Pierce, 1983). All of us who work with cancer know that it is a disease of differentiation (Markert, 1968). So, what controls cancer in the embryo? Cell differentiation is stimulated by cadherins in epithelia (Cofre and Saalfeld, 2023) and by textural gradients in the ECM (Figures 2A, B) (Cofre, 2024).

There are strong scientific indications that alignment of ECM proteins such as collagen (linear collagen molecules) and fibronectin (linearly aligned structure) influences metastasis in several types of tumors (Conklin et al., 2011; Ao et al., 2015; Drifka et al., 2016; Yang and Friedl, 2016; Erdogan et al., 2017; Conklin et al., 2018; Dzobo and Dandara, 2023). Also, it is widely recognized that tumor progression coincides with mechanochemical changes in the ECM, providing a denser network of collagen-rich fibers (Nieponice et al., 2009; Nguyen et al., 2014; Barcus et al., 2015; Harisi and Jeney, 2015; Holle et al., 2016; McLane and Ligon, 2016; Mittal et al., 2016; Barcus et al., 2017). What the scientific community must recognize is that no one has investigated ECM and its textural gradient in embryonic models in the search for cancer cure. In my view, the best model to study gliomas, which developed within a mechanical microenvironment characterized by dense ECM and under conditions of hypoxia and HIF1α activation (Miroshnikova et al., 2016), is the mesoglea of ctenophores. The mesoglea would help to understand normal textural configuration, and this knowledge can be applied to develop new cancer therapy strategies (modeling ECM texture in cancer with physical foundations that make it look like mesoglea).

FIGURE 2

Embryo and cancer are two sides of the same coin, of the same process. The upper part of the figure depicts rupture of the basal lamina by matrix metalloproteinases during epithelial–mesenchymal transition. (A) Epithelial–mesenchymal transition reveals the cancer side of the embryo and adults. Particularly, in adults, "metastasis" is revealed when there is a specific alignment of extracellular matrix components, such as collagen and fibronectin. (B) The embryo uses metastasis in its organization (commonly called gastrulation), but it is controlled by the textural gradients and topography of the extracellular matrix, which trigger cell differentiation, as supported by the seminal ideas of G Barry Pierce on the control of cancer by the embryo.

Concluding remarks and perspectives

Nothing in biology makes sense except in the light of evolution (Dobzhansky, 1964; Dobzhansky, 2013). In a narrower sense and in an organismic context, I can now state that nothing in animal developmental biology makes sense except in the light of Neoplasia (cancer). But what would be the relevance of publishing a study on the Neoplastic origin of the innate immune system? What would be the influence on immunotherapy strategies? What are the new prospects for curing cancer?

Biophysicists have resumed a mechanical and physical glimpse at tumor and immune system formation and its application in therapeutic strategies in adults (Paiva et al., 2013; Stromberg and Carlson, 2013; Yu et al., 2021; Pratavieira et al., 2022). Today, in my view, there are incredible methods to evaluate textural gradients in a non-invasive way using embryological models (Zhu et al., 2023). I envision their urgent application to understand the tumor and its relationship with macrophages, aiming at the cure of cancer.

For this to happen, evolutionary biologists must first understand cancer evolution and all its developmental transitions. Knowing the origin of the immune system—so deeply rooted in Neoplasia since the emergence of the first animal—is the first step. It is also crucial to understand how the immune system has been modified throughout metazoan history for the creation of novel therapeutic strategies that involve advances in Physics from an evolutionary perspective.

Everything indicates, from an embryological point of view, that the great modifications of the immune system throughout animal evolution are linked to the great modifications of cancer throughout evolutionary history. Here, I can only briefly mention what will be described in another separate article, namely the adaptive immune system. In other words, if Neoplasia is understood as an evolutionary engine (Cofre, 2024), it is at the heart of the evolution of acquired immunity (Personal communication). Therefore, there is no malevolent alliance or artifices of cancer to circumvent the immune system, as it could not deny its own origin.

Finally, I want to ask an important question: Why don't biologists think like Newtonian physicists? There seems to be an explanation that is associated with the wrong idea of natural selection, that is, of a slow and gradual evolution (Saunders, 1994; Gaucherel and Jensen, 2012), and that biological phenomena need historical explanations (Quenette and Gerard, 1993). As if many of the historical explanations in embryology, evolution, and cancer had no physical foundation. There is no inherent antagonism between this "physicalist" perspective and evolution, for physics acts on matter (Newman and Linde-Medina, 2013), establishing a topological map on the genomic material (Uhler and Shivashankar, 2017a; Uhler and Shivashankar, 2017b; Uhler and Shivashankar, 2018; Tsai and Crocker, 2022). From my point of view, the empowerment of physicists (Newman et al., 2006; Tiezzi, 2006; Newman and Linde-Medina, 2013; Newman, 2016) to defend the important explanatory role of Physics in biological processes such as evolution and embryology in the context of an abrupt "emergence" of animals may quickly undo the tenuous line that divided these two areas of Natural Sciences (Murray, 1992) and our way of thinking (Rowbottom, 2009).

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics Statement

Ethics oversight was not required for this article as we look at theoretical animals. The study was conducted under strict ethical standards, respecting the scientific literature, different opinions, and citing at least two hundred authors.

Author contributions

JC: Conceptualization, Data curation, Investigation, Writing – original draft, Writing – review & editing.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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