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Mini Review

Metabolic and Immune Systems Are the Primary Tenets of Biological Life

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Abstract

A theory is much broader than a hypothesis or a conjecture if it can provide explanations for a wide range of observations while remaining robust to challenges through experimentation. There is a paucity of such theories in biology. The main motivation behind this research was to propose a broad theory of biological life and to explore whether it can be used as a framework for understanding health and disease conditions. A conceptual and theoretical approach was followed for this purpose. Extensive exploration and analysis of the biomedical literature in a non-systematic but purposeful manner were undertaken. They were then extrapolated using a top-down approach to identify the fundamental systems mediating life processes. Two attributes must exist for the survival of any biological life form, including the ability to grow and the ability to self-protect. These two functions are performed by the metabolic system and immune system, respectively. It is proposed that all other processes and every entity in a life form are involved in conducting these two fundamental functions. It is inferred that both of these functions exhibit the universal characteristics of duality and complementarity, features that cut across disciplines. A given life form may thus be biased toward one of the two processes mediated by the immune system and metabolic system at different stages in its life history. Identifying factors that confer bias might provide a better understanding of biology with direct implications for medicine. It is proposed that life and disease could be the result of the interplay of immune and metabolic systems acting complementarily. Other physiological systems lend support to the balancing act between the immune and metabolic systems in a biological life form.

Keywords: Biological life, Process of life, Immunology, Metabolism, Theory in biology

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Background

The fields of biology and medicine are filled with insurmountable data and observations. However, there is a paucity of theories or conceptual frameworks through which the biological data can be understood (1). Historically, the discipline of biology and, thus, medicine have benefited from theoretical knowledge (2). There is a need for a general theory in biology that incorporates the working principles of a biological life form (3,4). Biological life is characterized by its diversity. However, there must be fundamental processes that are common to all forms of life. Identifying those functions and the principles with which they operate may help formulate a general theory of biological life. Such a theory should define biological life not in the form of entities or structural elements, as they encompass wide variations, but as functions or processes. Theories abound in the physical sciences to understand a phenomenon. Physicists and their theories have provided a basis for understanding biological life (5). However, biology differs from physics and chemistry in two important aspects. Firstly, function comes before structure in biology. In other words, the process comes before the entity. Secondly, biological life is characterized by its evolutionary history compared to physical objects (6). Evolution is an essential aspect of biological life (7,8). If biological life is determined by its processes rather than the elements that it is made of, then the unit of evolution must be the process and not the entity, as described elsewhere (9). Hence, a biological life form may exist if essential conditions for survival are met. These can be met by the most essential of the processes that mediate the survival of the life form. To perform these processes, the pleiotropy and redundancy of the entities that conduct the vital processes of biological life provide the robustness required to survive the various insults from within and outside. Biological life, hence, can be defined as a process.

Entities and Processes of Biological Life

Any complex phenomenon, such as life, can be described in terms of the entities that drive the processes or in terms of the processes driven by the entities. However, research that is driven to understand the entity can never be completely helpful in understanding a process as complex as life, health, or disease. For instance, knowing the complete genome of humans, though highly crucial for our knowledge, cannot completely explain the processes of life in humans. Entities would have distinct forms and identities and can be organized at multiple levels, whereas processes would have variations in functions at multiple scales (10). An entity may perform many processes. Similarly, a process may require many entities to be performed. An entity can be described, analyzed, shown, examined, and appreciated. In contrast, understanding a process requires thinking and imagination. Understanding an entity requires a bottom-up approach, whereas understanding a process requires a top-down approach. The description of a process begins with defining its purpose, while the description of an entity is completed with a purpose. A process can be mediated by multiple entities but driven by a single purpose. Most of the research being conducted in the past century has focused on describing and investigating the entities and their role in various processes in living forms, which, in effect, sidelined the processes. This aspect has been nicely brought out by Denis Noble in the form of a central debate that needs to be addressed in physiology (11). More research needs to be directed toward understanding and investigating processes that mediate health and disease where multiple entities act together and play their respective roles, which are driven by the purpose of physiology. There are also instances of misunderstandings between entity and process, such that when referring to an entity, it is described as a process, and vice versa. For instance, the description of the genome sequence (an entity) was meant to refer to the process of life (a process) itself. The researchers' overemphasis on entities is also evident when a process such as health is discussed, and it is brought down to a perfect organization of entities that would be sufficient to describe health.

Entities can be studied at different levels, from single cells to tissues to organisms, whereas processes need to be studied at different scales. Data generated at the highest level for entities and across the scales for processes, if they are reproducible, would likely have the capacity to further the knowledge of biological systems (12). The bottom-up and top-down approaches to studying entities and processes, respectively, should be integrated somewhere in the middle, where truth is likely to be found. This would require a third class of researchers, in addition to those studying entities and processes who are good at this aspect of bringing together the findings from the two approaches (10).

Process of Biological Life

A biological life form is not merely a collection of different entities such as tissues, cells, organelles, and macromolecules. These entities mediate the process of life. A life form may perform many functions for its day-to-day existence. They would include digestion, excretion, respiration, circulation, and the like. However, the characteristic of life is survival. A life should possess two functional attributes to survive, namely, the ability to grow and the ability to protect itself in any given situation. These can be performed by the metabolic system (which helps a life form grow) and the immune system (which helps a life form protect itself). The immune and metabolic systems respond to internal and external stimuli and signals that are sensed and received by neural and hormonal systems in multicellular and complex organisms. Both the immune and metabolic systems have strong interconnections and feed onto one another, thus exhibiting the universal principles of complementarity and duality (13,14).

Role of Immune and Metabolic Systems

There are several similarities in the way the immune and metabolic systems operate in each life form. Both systems are comprised of several entities (molecules, cells, and tissues), with compartmentalization of functions. They operate in a network mode with many feedback and control elements. Moreover, they can be activated and are highly regulated. Due to these features, they exhibit high complexity, show dynamic features, undergo evolution, and are characterized by adaptive and emergent functions. No other system in a life form can be thought of as having all these features that are shared by the metabolic and immune systems.

It is crucial to understand how these two systems function in an organism (13,14) The straightforward understanding of the metabolic system would be that it is concerned with the growth of the organism, while the immune system's primary function is to defend against any threats. However, there are possibly other functions that these two systems perform. The immune system, in addition to defense, is also involved in the development of the organism and its components. In that case, the metabolic system would lend its hand in an opposite fashion, whereby instead of storing the metabolic fuel and building the entities, they would undergo catabolic reactions to provide the metabolic fuel necessary for immune functions. Thus, the role of the metabolic system could be different when the immune system defends the host than when the host undergoes development. Growth is not the same as development, which possibly occurs through the metabolic system and immune system, respectively.

An important aspect of two vital processes mediating the process of life is the creation of bias. The bias would most likely be present due to the dual and complementary nature of these two processes. This is because a given life form may be unable to simultaneously grow and protect itself, as the demands for these two processes might be highly different from each other. Either one of the processes would be operating at a higher capacity at any given point in time, while the other process would be expected to be compromised, depending on the physiological needs of the life form.

The balancing act between the immune and metabolic systems in a biological life form is an important concept to be understood. If an organism is biased toward its growth, then it will be biased toward the process mediated by the 'metabolic system'. For effective growth, increased synthesis of proteins and nucleic acids is essential, along with large amounts of energy (14). These can be obtained by the oxidation of fatty acids and the diversion of glycolysis to the hexose monophosphate shunt pathway for the generation of precursors for the synthesis of nucleic acids. Thus, optimal growth is achieved in an organism that is biased toward the processes of the metabolic system. This may take a toll on the 'immune system', which must be in a 'tolerant' mode and thus may be unable to effectively mount immune responses. This catabolic state is observed in immune cells, so that growth can occur in the organism. Hence, in metabolic bias, the immune system may be biased toward immunotolerant responses. Hence, the chances of infection may be high, and if infected, there may be a higher probability of rapid/severe disease.

Overall, a given biological life form may have a bias toward one of the processes of life. The bias may also exist at different levels in each life form, such as organisms, tissues, cells, and molecules. Bias at the organism level can be understood by studying the life history of a biological life form. The initial periods of a lifetime are biased toward growth (metabolic bias), followed by the reproductive periods where organism fitness for reproduction (immune bias) becomes critical, and finally at the later stages of life where there is a reversal of growth processes (metabolic bias inversed). The tissues can be categorized based on the predominant fuel used by them. Thus, tissues that preferentially use glucose (e.g., brain, red blood cells, lungs, and kidneys) could be considered biased toward the immune system, and those that utilize fatty acids (e.g., heart, skeletal muscle, and gastrointestinal tract) are biased toward the metabolic system. The above speculations would need to be confirmed by experimental studies.

Learnings From the Field of Immunometabolism

The field of immunometabolism, which has actively investigated the integrated interactions between the immune and metabolic systems over the past couple of decades, has enormously contributed to increasing our understanding at the molecular level in different contexts (15,16). Metabolic responses in immune cells determine the fate of immune cells in quiescent and activated states (17,18). Cytokines and interferons produced by the immune cells in turn alter the metabolic state of the organ, influencing whole-body metabolism (16,18). These adaptations occur in the context of infections, inflammation due to cellular stress, and altered tissue architecture in the case of cancer (19-22). Not all these adaptations are without costs, as it can be inferred that failure to mount adaptative or excessive/maladaptive responses can result in undesirable consequences, leading to disease states (21,22). Although in some cases, diseases occur despite these adaptations of the immune and metabolic systems, it is conceivable that there might be innumerable situations at every moment that must have been tackled effectively by a coordinated action of these two physiological systems.

Re-thinking the Roles of Immune and Metabolic Systems

The classical roles of immune and metabolic systems in a host should be updated to incorporate the learnings emerging from the field of immunometabolism. For example, it is common to think of immune systems acting against infectious agents and thus protecting the host. However, the metabolic system can also function to defend the host against the infectious agent by altering the production of metabolites such as itaconate or preventing the availability or access of essential nutrients and metabolic fuel required for the pathogens to survive (23-26). The host-microbiota that resides in the intestine, for example, illustrates the common metabolic adjustments that facilitate mutual existence, benefiting both the host and the commensals (24,26). Similarly, the immune system does not act only against the microbes but also plays essential physiological roles in maintaining the health of the host and can be activated in response to cellular stress, leading to inflammation such as obesity, atherosclerosis, and aging (27-31). These arguments again attempt to prove the fundamental roles that the immune and metabolic systems play in a host.

Unique Aspects of the Immune and Metabolic Systems

What makes the immune and metabolic systems perform the process of life in living organisms is the increased variations and redundancies within each of these systems in terms of their components and the interdependence between these two systems to support and defend the host (Figure 1). No other physiological system works at such a fundamental level but instead attempts to drive or support the adaptive responses that occur. For instance, dietary intake of various nutrients can modify the immunometabolic responses due to the differences in the requirements and availability of metabolic fuels such as glucose, fatty acids, and amino acids (18,23,31). Neural and endocrine responses can be altered because of immune responses, which in turn may contribute to changes that occur in metabolic states as well (20). The respiratory system may influence the functions of the immune and metabolic systems by modifying the availability of oxygen to tissues in combination with the vascular system (27). The digestive and renal systems are critical regulators of environmental exposure and excretion of nutrients and other toxins, which can modify the functions of the immune and metabolic systems (26). The potential roles and interactions of the immune and metabolic systems with other physiological systems in an organism are provided in Figure 2.

Applications of This Proposal to Clinical Medicine

The reciprocal interaction of metabolic and immune systems in a host is not only an important milestone in understanding the fundamentals of physiology but can also pave the way in terms of applications in clinical medicine (32-34). Advances in single-cell and omics technologies can facilitate and expand the understanding of the interconnectedness between the metabolic and immune systems in various disease contexts (35-37). These can pave the way for personalized medicine, which again demonstrates the effectiveness of efforts to collectively understand the adaptations of these two fundamental systems (33,37). The identification of suitable metabolic markers in infectious diseases and immunologic markers in chronic inflammatory diseases (e.g., obesity and atherosclerosis) and a combination of both these markers in complicated diseases (e.g., cancer) are important avenues for future research efforts (32,36). The discipline of biochemistry must significantly contribute to such efforts.

Conclusion

To summarize the model presented in this study, any biological life form can survive by possessing the dual and complementary processes performed by the metabolic and immune systems (Table 1). A perfect balance between these two systems would result in an ideal life form (Figure 1). However, a bias exists toward one of the attributes that contributes to meeting the demands of life in the life history of the organism in a way that makes it vulnerable to certain threats that manifest as diseases. Further attempts should be made to completely characterize the elements and the properties of both the immune and metabolic systems that sustain life and to identify factors that can favor the bias toward one system over the other.

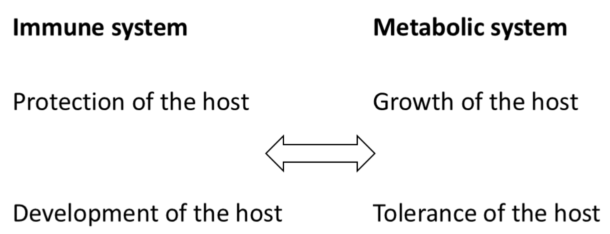

Figure 1. Basic Tenets of Biological Life. *Note*. The process of biological life is primarily mediated by the interdependent functions of the metabolic and immune systems. A bias may exist toward one of the two systems at different stages in the life history of an organism

This theoretical work can be considered a speculative hypothesis, which is not uncommon in the history of biology, or an intuitive deduction, or at best, somewhere between these two (2). Theory-based approaches have been suggested to provide a broad definition of what life is (38). Such approaches would help in the discourse of teaching biology and enhance practice in biology-related disciplines. If biology is considered a complex discipline, then it would not be due to the variation that is observed, which is the nature of biology itself, but because of the intricate, complex, and redundant processes conducted by the immune and metabolic systems. The model presented in this study is consistent with the principle of organization in biological life described earlier (39). This may further help understand the complex issues of cause and effect in biology. (40). Studies have shown how changes in metabolism may affect biological organization (41). Similar efforts with advanced technologies should be made to understand the role of the immune system in mediating biological life. Further work is required to delineate the components and functions of the metabolic and immune systems and to decipher factors that affect the overall bias of a given biological life form at different levels (organisms, tissues, and cells) and in specific contexts.

An important characteristic of any biological life form is its organization at various levels, from cells to molecules (42,43). In fact, the complexity of biological life could arise from such sophisticated systems, which are essential to performing the processes of life. If the fundamental processes mediated by immune and metabolic systems drive life, then deviations from normal could be because of failure in either of these systems to cope with challenges that can form the primary causes of diseases. A top-down

Table 1. Three Postulates of the Process of Biological Life

	Postulates of Biological Life
1	Biological life can be understood as a process performed by the metabolic and immune systems for its growth and protection, respectively.
2	Both metabolic and immune systems are interdependent on each other and exhibit characteristics such as duality and complementarity.
3	Every life form is biased toward one of the two systems.

ENTITIES	LINKER FUNCTIONS	FUNCTIONS	PROCESSES
Cells	Neural function	Digestion	Immune system
Organelles	Endocrine function	Respiration	Metabolic system
Macromolecules		Circulation	
Monomeric units		Excretion	
Molecules			

Figure 2. Entities, Functions, and Processes That Define Life. *Note*. Biological life forms are made up of various molecular entities that are organized into cells and tissues. The primary processes are mediated by the immune and metabolic systems, while the other physiological systems provide support for these two systems

approach can then be applied to identify causal elements, rather than the other way around (44,45).

Competing Interests
None declared.

Ethical Approval
Not applicable.

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