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Host-parasite Interactions; From Co-evolutionary Changes to Genomic Insights

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Abstract

Host-parasite interaction belongs to the association between two biologically different organisms in which the host delivers food and shelter for the parasite and in return the parasite reproduces itself in the host body. There are many kinds of host-parasite relationships including parasitism, mutualism, and commensalism. The potent interaction between the host and parasite is regulated by the evolutionary changes over space and time. Host-parasite interconnection is the basic feature of the maintenance of ecology and biodiversity. The association between the host and parasite establishes an equilibrium in which the host unfolds protective strategies against parasites and the parasites develop mechanisms to elude the host's defenses and spread infections. This dynamic interaction between the host and parasite mainly depends on the host's immune system, the severity of infection, the load of parasites in the body, and the ecological requirements. Moreover, environmental conditions, locomotion, and genetic factors of the host also influence host-parasite interactions. The pathogenicity of parasites is determined by the sensitivity and resistivity of the host's immune response. As parasites evolve, they employ diverse strategies to manipulate the host's behavior and adapt to changing atmospheres. The education of the host-parasite association is essential for proper control and surveillance of parasitic diseases. For the prevention of parasitic infections, different therapeutic measures have been devised. Researchers are performing many types of procedures to sustain the ecosystem and fitness of individuals using host-parasite interactions. The purpose of this review was to enhance the importance of the host-parasite interaction in our environment.

Keywords:

Co-evolution, the evolution of parasites, molecular mechanisms, the immune response of the host, genetic makeup of the host, environmental factors, therapeutic strategies

Introduction

In the circumstances of geography, evolutionary revolutions take place with time [1, 2, 3]. With time, gene modifications occur that strongly influence organisms of various species [4]. The formation of molecular tags has proved to be beneficial for analyzing genetic data. Phylogeography is a new field of research that has been used to detect the chronological background of inhabitants and species [5]. Researchers handled the structure and genome of various lineages. By incorporating the modern and ancient studies of population, an innovative domain of comparative phylogeography emerges [6, 7]. In this area of research, a comparison of gene changes occurs within species that have the same habitat and ecological traits. The variation of disease within time and space develops modifications in the choice of organisms (that evolve as prey) and parasites (that appear as predators). The evolutionary and epidemiological data guide us to the relationship between the host and parasite which mainly depends on the geometrical (varying from people to the mainland) and terrestrial (from a person's life to hundreds of eras) rankings. Within hosts and parasites, diseases also alter patterns due to changes in the gene pool of organisms. The pressures of fitness, selection, and time among living creatures evolved disorders that originate from the interrelation of the host, parasite, and the adjacent living or non-living atmosphere [8, 9, 10].

The severity of the infection and outcome of the illness solely depends on the variations of the host characteristics such as opposition and forbearance to infection. Also, the transmission power, pathogenicity, and surroundings linked with the parasite spread diseases. Moreover, different infecting variants of parasites play an important role in specifying the consequences of sickness in hosts [11,12]. So, a living host is an environment where bloodsuckers, mutualistic organisms, and immune particles correspond and participate in the shelter and other materials [13]. The interaction studied between cultivated bacterial cells and lytic bacteriophage viruses from the phyllosphere of the horse chestnut tree, *Aesculus hippocastanum* [14]. The distribution of bacteria on the upper surface of a plant or leaf is favorably speckled [15]. The sensitivity of infection has been established to change geometrically covering all trees. Almost 10-40% of the parasite is isolated from the host plant with the panoramic rise of parasitic load in the growing season of July [16]. Indeed, the occurrence of disease mainly differs with the spatiotemporal variations. At larger scales of space and time variations, diverse studies assess the pattern of diseases about the diversity of hosts and parasites and their interconnection with the divergent environment. Dispersal of populations allows parasites to stabilize and duplicate themselves to determine the genetic configuration of the host and parasites among diverse populations [17].

There are different types of host-parasite interactions in which hosts and parasites depend on each other for nutrition, shelter, and protection. These relationships demonstrate how pathogens depend on the host and how they induce infections, some parasites provide beneficiary characteristics to their hosts and sometimes both host and parasite get an advantage. The term *holobiont* refers to the extended somatic interaction between living entities [18]. Hypothetically, this term covers all symbiotic interactions including mutualism, commensalism, and parasitism but it is more restricted to mutualistic associations between host and parasites. According to the evolutionary theory of hologenome, it is considered natural selection among organisms is evolved through holobiont [19,20]. Mutualism is the development of a healthy relationship between host and parasite in which both of the organisms are profited. According to studies, some mutualistic symbionts are helpful in the growth of the immune system [21,22,23]. For example, a tsetse fly that causes sleeping sickness carries a mutualistic bacterium, *Wiggleworthia glossinidia*, and this bacterium is important for the development of the immune system [23,24]. In higher organisms like vertebrates, bacteria inhabiting the gastrointestinal tract are responsible for the establishment and improvement of a healthy defense system for the body [21,25,26,27,28,29,30]. Sometimes, pathogenic microbes can be beneficial in strengthening the immune system of the host, and this interaction is called conditional mutualism [31]. For example, the hepatitis A virus can limit the infection of the hepatitis C virus [32].

Similarly, the microbes that are linked with the host can enhance the wellness of their hosts. For instance, gastrointestinal bacteria resist pathogenic bacteria by producing chemicals and as a result, they decrease the growth of pathogens [26].

Parasitism is a complex symbiotic association between hosts and parasites in which the parasite is favored and damages the host. The parasite depends on the body of the host and destroys the host's immune system by causing diseases. At the start, the parasite enters the host body and induces disease but the sensitivity and resistivity of the host's immune systems decide whether the parasite will develop an infection or not. Furthermore, the host parasitic relations are greatly dependent on environmental components like temperature, competition in population, and niche variations the symbiotic associations are influenced by host explicitness and the variety of diverse organisms found in one species [33, 34, 35, 36]. Host-related microbes are contrived by the parasites residing in an individual's body. HIV infections are usually linked to gut diseases because the microbial flora is altered by the parasitic community [37, 38, 39]. As a result, parasites contribute to the pathogenesis of disease.

In the past few decades, several studies have been conducted to investigate the molecular mechanisms of host-parasite interactions to determine the intricacy and variety of molecular strategies [40, 41, 42,43]. The techniques of molecular interactions are functional in two phases of animal and plant defenses including border protection and innate immunity. First of all, the barrier securities inhibit the entry of parasites into cellular compartments and tissue spaces [44]. Once a parasitic component adheres to the host cell, it can easily cross the cell or tissue hindrance. The parasite performs molecular mimicry on the prey of the host cell for nourishment, refuge, and symbiosis. So, this step is important for the attachment and access of parasites in the host's body. The second phase of parasitic infection begins with the activation of the innate immune system of herbage, mammals, and spineless creatures. The inherent molecular mechanism can be classified into three widespread scenarios: (1) identification of signals that are specifically linked with parasites. (2) Distinction of altered identity, evolving microbial modification, or deterioration. (3) Scarcity of self-acknowledgment signs in a cell [40, 41].

In host-parasite interactions, immunity is the major contributor. Every individual has a unique immune system and they respond to pathogenic microorganisms according to the nature and variability of immunity. When a pathogen attacks a host, the immune corresponds with the parasite and takes action against them. The nature of the host's immune system depends on the type and intensity of infection. When a parasite infects a host, the immune system of the host commences to develop a defensive immune reaction against a specific pathogen. The essential cells responsible for immune response are T helper cells that prey on the parasites. After some time, T-helper lymphocytes differentiate into Th1 and Th2 cells that modulate the immune system and synthesize cytokines (chemical mediators). The Th1 cells release interleukin-2 which stimulates the secretion of cytotoxic T cells and interferon-gamma aims at the triggering of macrophages. Th2 cells stimulate the production of IL-4, IL-5, IL-10, and IL-13 and induce the initiation of B lymphocytes for the synthesis of antibodies [45]. Cytotoxic T cells are suitable for the deterioration of viral pathogens, INF-gamma is important for the inhibition of microbes present inside the cells whereas antibodies are involved in the killing of parasites present outside of the cell. Nevertheless, the immune response of an organism changes from time to time according to the stage of disease [46].

The burden of parasitic diseases greatly influences the health of hosts. Deficiency of nutrition or malnutrition is an emerging problem in developing countries resulting in both child morbidity and causality [47]. Among various parasitic infections, worm and malarial infections affect the growth and nutrition of hosts with various mechanisms including atrophy, severe blood loss, and digestion of nutrients from food. Seven out of ten children are affected by parasitic infections and experience long-term growth impairment in regional parasitic diseases [48]. Schistosome infections are linked with malnourishment and stunt growth in children [49, 50]. Secondly, cestode infection is associated with the entry of worms into the gastrointestinal tract. Low infusion of food occurs in *A. lumbricoides* disease where the parasite resides in the small intestine of the host causing difficulty in the absorption of nutrients from food and impaired development [51, 52, 53]. Other parasitic infections also collaborate with anemia, hepatomegaly, and splenomegaly. Irregular immune reactions are highly related to liver and spleen enlargement as a consequence of eosinophilic inflammation [54, 55, 56].

In our atmosphere, different kinds of microorganisms are present that constantly react with living organisms. Pathogenic infections are a major cause of death globally. The molecular mechanism of host-parasite interaction is important to understand the virulence of parasites to formulate parasite-specific biomarkers and to develop effective vaccines and therapies. The evolution of interactions among hosts and parasites has become complex due to DNA splicing, the addition of cap and tail to the mRNA as well as interception of genes and proteins through post-translational modification. The genomic data of the host-parasite interactions indicated that DNA provides information on physical and molecular processes between the host and parasite [57, 58]. When a parasite attacks an organism, it reacts by expressing the protein molecules. Various biomarkers are produced by the host's body in reaction to a pathogenic disease. These biomarkers may include natural body liquids like blood serum, saliva, urine, and cerebrospinal fluid. "Parasito-proteomics" is the study of the tea room between the genomes of the host and parasite through the manifestation of the host and parasitic proteomes during their molecular crosstalk. In the 1990s, several proteomic tools have been devised to analyze the proteins associated with host-parasite interactions. In the future, various new ways are recommended to deal with the complexities of host-parasite genomic relationships to acknowledge the problems associated with the environment and human health.

1. Co-evolutionary processes of host-parasite interaction:

Host-parasite coexistence is a process in which appointed parasites stimulate different hosts to inhibit the expenses of infection. The body of the host allows pathogenic microbes to adjust to a new environment. Over the past 3 billion years, this mechanism has evolved as a generator of biological assortment which comprises the sustainability of genetic variation within communities and generations [59,60,61,62,63,64,65,66,67]. Antagonistic co-occurrence takes place as a corresponding interaction between two similar organisms. This type of evolution highlights the physical composition of two opposite species that have a pessimistic effect on one another [68,69]. In antagonistic interaction between the host and parasite, genetic variation stretches out quickly throughout the population and goes to fixation [70]. Consequently, this interaction leads to recurrent selective sweeps or RSS. It consists of a sequel of occasions in which alleles are present constantly in the host and parasite population. On the other hand, when genetic variant persistence alters in most populations, it also induces a change in allelomorph abundance in the parasitic inhabitants guiding to constant negative frequency-dependent selection or NFDS [71]. Host-parasite relationships are determined by genomic divergence, epidemiological traits, changes in the surrounding atmosphere, phenotypic variations, sociable relations of hosts, and multiplicity of parasites [72, 73, 74, 75]. The major factor linked with the host-parasite interaction is the population size. When a parasite attacks the host, it finishes the health, viability, and propagation of the host. When the overall fitness of the host reduces, the facilities for the parasite also decrease.

2. Types of host-parasite interactions:

In a host-para relationship, a host is an organism that provides protection and nutrition to a parasitic organism whereas a parasite is a living thing that survives at the expense of the host. The term "symbiosis" is a Greek word meaning living in collaboration with two different species for longer periods. In 1877, Albert Frank formulated the word symbiosis to explain the synergistic association between lichens. In 1879, Heinrich explained symbiosis as a process in which two biologically different organisms live together [76, 77]. The word symbiosis contains vast relations between the host and parasite from synergistic interaction to the antagonistic or harmful association [78]. There are four different kinds of symbiotic interactions:

- Parasitism
- Mutualism
- Commensalism
- Phoresis

2.1. Parasitism:

A relationship between two organisms in which a parasite gains shelter and food from the host by harming it is called parasitism. Parasites can be seen by the naked eye as nematodes and cestodes or they can be microscopic objects like viral particles and bacteria [79]. Each parasite is specific to its host and can impose damage by drilling a hole in its host (*Schistosomes)*, destroying the immune system of the host (*Microfilariae),* and stealing the nutritive substances of the host (*Taenia sodium).* Parasites are normally smaller in size than their host but they can replicate more rapidly and reside inside the host for an extended time [80].

2.1.1. Types of parasitic relationships :

The following few kinds of parasitism are:

2.1.1.1. Kleptoparasitism:

It is a type of interaction in which parasites utilize the food collected by the host. This association has been seen in many species of cuckoo and cowbird which avoid building their nests but laying their eggs in the nests of other birds and leaving them there. The host bird (owner of the nest) takes care of the cuckoo eggs and if the host bird wants to eradicate the eggs, some cuckoo pounces on the nest to force the host bird to complete their desire.

2.1.1.2. Intraspecies social parasitism:

It is a type of nursing parasitism in which some partners of the species haul milk from irrelevant mums. It happens in the wedge-capped capuchins where dignified females take milk from low-ranking females and take advantage of the minor ones [81].

2.1.1.3. Parasitoids:

During this process, the parasitic larvae grow inside the host cell causing the expiration of the host. The feature of killing the host discriminates parasitoids from parasites. The phenomenon of parasitoidism resembles predation because both conditions cause the death of the host.

2.1.1.4. Autoinfection:

It is a type of parasitic infection in which the parasite concludes its life span in one primary host without passing it to another secondary host. For example, *Strongyloids* transform nontoxic larvae into infectious nymphs that penetrate the intestinal tract and later on cause infection of the skin to the host.

2.2. Mutualism:

Mutualism is a type of symbiotic interaction in which two living entities of dissimilar genera survive together and benefit from one another. Mutualism increases the rate of fitness as compared to parasitism. Some common mutualistic associations include interaction between bovines and intestinal bacteria. The bacteria provide cellulose in the host to speed up the process of digestion and in return, the host provides bacteria with many essential nutrients. Mutualistic interactions are very important for the maintenance of the ecosystem but they gain less awareness as compared to pillage and parasitism [82].

2.2.1. Types of mutualism:

2.2.1.1. Recourse-resource mutualistic relationship:

It is the most frequent type of mutualism where one set of supplies is bartered for an unlike resource such as a relation between plant roots and *mycorrhizal* fungi. Plants deliver carbohydrates to the fungus and the latter facilitates plants with phosphorus and nitrogenous substances.

2.2.1.2. Service-resource mutualistic association:

It is an association in which one organism endows for a service with a resource. Examples include the oxypecker (bird) that feeds on ticks present on zebra skin. As the bird gets nutrition, the zebra acquires the facility of pest check.

2.2.1.3. Service-service mutualistic interaction:

Service-service relationships are complex to understand as they are rare in nature and occur in cooperation with the service-resource association [83]. An example of this type of relationship is between ants (genus *Pseudomyrmex)* and the whistling thorn trees. The former species build nests inside the thorns of trees to get protection whereas the trees get security from herbivores and competition for trimming as compared to other plants.

2.3. Commensalism:

The symbiotic association is where the parasite gets the benefit and the host is neither benefitted nor harmed.

2.3.1. Types of commensalism:

2.3.1.1. Facultative commensalism:

The type of commensalism in which the host may not involved in the association. For example, stiff ciliates grow on small arthropods but they can also live in ponds.

2.3.1.2. Obligate commensalism:

The relationship in which both host and parasite certainly demand each other to grow and live like *Epistylis* ciliates cannot survive without decapods.

2.4. Phoresis:

A type of symbiotic interaction in which two organisms are physically and biologically independent of each other. The smaller living creature (parasite) is taken away by the bigger organism (host). For instance, tiny arachnids on mammals and diplopods on birds [84].

3. Molecular mechanisms in host-parasite interactions:

Living things are continuously disclosed to parasites. In any particular environment, a molecular war starts when an organism (host) meets a parasite [59]. The interrelation of the host with the parasite began million years ago and the organisms adapt themselves according to it. Because of the pressure and competition between the host and parasite, most of the host organisms achieve suitable mechanisms to eradicate parasites whereas in some cases, parasitic species cross the defense barrier of the host and become able to complete their life cycles. These molecular mechanisms enable hosts to operate different mechanisms and pathways to deal with parasitic attacks. In host-parasite relationships, the latter induces changes in the host's behavior by changing the substrate concentration, fluctuations in temperature, biological clock, termination of proper nutrition, and alterations in the growth and transfer of pathogenic particles [85,86,87,88,89]. The central nervous system (brain and spinal cord) processes the data it obtains from the sensory organs and corresponds with all body parts to interpret the information. The central nervous system is responsible for managing the host's external stimuli and activity patterns. The molecular base of the central nervous system is associated with the changes in host behavior. By altering the functionality of the central nervous system, a parasite can induce changes in the behavior of the host. It can be done by integrating with the host's neuromodulatory components (chemical messengers and endocrine secretion) [85,90]. The production of neurotransmitters and hormones by the host is responsible for the behavior change. When the parasite is not physically connected to the CNS of the host, it produces higher amounts of neuromodulators. The analysis of the genomic and proteomics of the host and parasite is a promising tool for understanding the molecular mechanism of host-parasite association. Parasito-proteomics is a powerful approach to examining the complete set of proteins expressed by the host and parasite during the host-parasite molecular cross-talk [91].

4. Host immune response against parasites:

In a parasitic attack, T cells are activated to respond against the pathogenic parasites. When symptomless helminth infection occurs, the immune system activates T cells that release chemical mediators along with interleukin-4 and interferon-gamma [92]. On the other hand, in individuals who develop systematic parasitic disorders, their immune system allows helper T-1 and T-17 cells to arbitrate the infection [93,94]. In our immune system, the equilibrium resilience to self-antigen is sustained by regulatory T cells [95]. Dendritic cells are factors in the adaptive immune system that transfer information. They present antigens to the major histocompatibility complex. When the concentration of antigen increases, dendritic cells display the expression of inhibitor molecules such as programmed cell death ligands PD-L1 and PD-L2. In addition to the activation of dendritic cells, the stimulant of IL-12 stimulates the production of helper T cells, and a stimulus of IL-10 differentiates into Treg cells [96,97]. Toll-like receptors and C-type lectin receptors are the common types of dendritic cells that are involved in the recognition of parasites. Dendritic cells perceive the toxic antigens of parasites and kill them. Lipid molecules obtained from *Schistosoma* eggs and *Asacris* worms were recognized as TLR- 2 ligands. These lipid molecules induce the activation of dendritic cells to bring about the Th2 response. Furthermore, it is reported that the TRL2 expresses PD-L2 on the surface of dendritic cells which reduces the effect of T cells in *Schistosoma* infection. Recent studies demonstrate that helminth antigens are recognized and attacked by dendritic cells TRL2 and TRL4. The immune system of the host stimulates the production of immunoglobulin E molecules. Immunoglobulin molecules bind to the Fc receptors and exhibit an immune reaction on basophils and eosinophils resulting in the release of chemical mediators (cytokines) (Fig 2).

5. Effect of environment on host-parasite interaction:

The changes in biotic and abiotic components of the ecosystem bring along modifications in the genetic makeup of living organisms. The progressive changes and biological evolution among living things are liable for geological expansion (biodiversity). In host-parasitic relationships, parasites depend totally on their host, and environmental changes affect both of them. Thus, the existence of parasites from climate change depends on the parasite selectivity, the complications of the life cycle of the parasite, the distribution of living things in the ecosystem, and the number and motility of hosts. In extreme weather conditions, the parasites become more sensitive and will not be able to infect another host. The consistency of the host decreases in drastic conditions that will be hazardous for holoparasites. Whereas facultative parasites are more sensitive to direct variations in the atmosphere [98,99]. The motility of the host in different geographical areas helps parasites adopt new environmental conditions and develop diverse interactions with the host [100,101,102]. By changing the atmosphere for hosts and parasites, there may be competition for food, and the individuals under stress have jeopardized their health [103,104] (Fig 1). The three main characteristics of extreme changes in host-parasite interactions are (I) factors that influence the stability of host-parasite association are biological diversity, distribution of population, and immunosuppression (II) the problem in predicting the host-parasite relationship because of the change in environment (III) the execution of management strategies in developing nations to inhibit the effect of universal infections.

6. Genetic basis of host sensitivity and resistance against parasites:

According to the studies, it is understood that the parasites are responsible for the genetic development of the host. Although parasitic infections are caused by various environmental factors, genetic makeup varies depending on the type of infection. Genomic epidemiological analyses are responsible for determining the nature of the host-parasite relationship [105]. After the sensitive alleles of genes from the host are recognized, they can be utilized to devise strategies like defensive immunity against parasitic infection. So genetic epidemiology is the experimental analysis of immunity in nature [106]. In the case of arthropod infection, it is evident that a single gene or loci in the host are susceptible to distant species of parasites. For example, malaria is caused by the biting of the female *Anopheles* mosquito. Different researches have shown that genetic elements in the human body are sensitive to malarial phenotypes, an association of genes in the occurrence of infection, and antibody reactions against malarial antigens. Some studies demonstrate the interrelationship between red blood cells and malarial species and the results show that hemoglobin S is a protective factor. Interaction of 56 single nucleotide polymorphisms reported resistant material genes in 12 various destinations of Asia, Africa, and Oceania. Highly remarkable consortiums were seen in hemoglobin A and C observed in *HBB* and ABO, CD40 ligands interact with platelets and induce an inflammatory response, and *ATP2B4* [107,108,109]. The weaker connection of resistant loci was observed in *CD36, IL1A* (activated by cytokines), and *Interferon regulatory factor 1* (transcriptional activator of IF-beta) [110,111,112,113,114]. Furthermore, a new oppressive gene locus APT2B4 has been discovered that encodes for calcium efflux of erythrocytes. The plasmodium variants affect protein structure and balance of calcium in the body and also the viability of parasites in the host's cell. As a result, genetic factors play a role in the resistance to parasitic diseases.

7. Therapeutic applications for host-parasite interactions:

Every year different antiparasitic drugs are developed by the pharmaceutical industries but very few of them are effective against pathogenic parasites. These medications not only deter the growth of parasites but also protect the host and they avoid cross-resistance with other drugs. Moreover, drug preparation is a costly and time-consuming process because experiments are done on laboratory animal models which must exhibit high antiparasitosis activity and be less toxic for experimental human models. For the proper evaluation of newly synthesized drugs, it is preferable to cultivate and reproduce parasites. Some studies have been conducted that prove that immunomodulatory drugs inhibit the replication of parasites. It is essential to comprehend the biotic characteristics of sex steroids and their inhibitory effects on the parasitic cells. Due to the evolution in the field of genomics, investigators have improvised tools for target recognition, authentication, and screening for anti-parasitic drug detection. As we discussed earlier, sexual hormones and their derivatives are useful in the prevention of parasitic disorders. The administration of testosterone in mice decreases the parasitic load by 50%. This hormone induces the secretion of IL-2 and IFN-gamma that provide resistance against parasitic infections [115,116]. HE2000 is an artificial androstane steroid that reduces the concentration of *Plasmodium falciparum* by 60% in the blood. Genistein, an isolation of soybean attaches with the endoplasmic reticulum and exhibits estradiol effects. This drug reduces the secretion of chemical mediators in the central nervous system. Hence, genistein has been used as a novel anti-parasitic drug.

8. Conclusion:

This review concludes that parasites are present everywhere in the environment and they dramatically affect the health of organisms, especially humans. The phenotypic and genotypic characteristics of the host and parasite determine their associations in nature. The diversity of spatiotemporal measures plays an important role in sculpting the host-parasite relationships and method of evolution. The different living and non-living factors of the environment induce competition among hosts and parasitic variants. With time, hosts and parasites evolved, and they developed prolonged relationships that depended on the type and extent of parasitic infection. The immune reaction shown by the host is highly specific to the type of the pathogen. Various environmental and genetic factors are important in displaying the resistance and susceptibility of the host genome. Parasites mainly influence the structure of communities resulting in the maintenance of the ecosystem. Some parasitic infections increase the disease burden globally and hence, serious interventions are needed to eradicate their risk. For this, appropriate strategies should be adopted to evaluate the host-parasite interactions and maintain biodiversity.

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