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Evolutionary Aspects of the Host - Parasite Relationship

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The host - parasite associations exhibit very diverse characteristics that may be examined at the different levels of biological organization. They are very common in nature, affecting in many ways every biological system (animals, plants or the microbial world).

The analysis of these problems parallel the complexities of studying life.

Human beings are a good example of this situation. It is very possible that each one of us carry more microorganisms in and on our body than the number of cells we have. In fact, it is difficult to imagine how we could live without our association with many microorganisms that are able to do many things that we have lost in our evolutionary history. Many microorganisms help us in the processing and transformation of our food ; they produce some of the vitamins and aminoacids we need, etc. In nature, microorganisms are essential for the biodegradation of many substrates, including the waste materials that are

eliminated by other organisms. These resources need to be recirculated to maintain their life cycles, etc.

On the other hand, microorganisms also produce many disruptions or diseases that affect our living conditions. So, they are good and bad, leaving to us the task of balancing these two types of effects.

In presenting some basic ideas about the mechanisms that regulate the host - parasite relationship, I will mainly concentrate on the association between pluricelular organisms and microparasites, specially, viruses, bacteria and fungi. I will focus some considerations on to the role that the genetic material play in this matter. I consider that at this primary level we may have a chance to understand, in some way, the complexities involved, and the evolutionary perspectives that emerge in our efforts to deal with the threat of epidemics, a problem that has been with us for millions of years.

Every organism is the result of very dynamic interactions between its genome (its genetic material) and the environment. The permanent or transient characters of living forms are the expression of differential gene activities in a variable environmental setting. In fact, the genome of each organism contains a program with information and instructions to be expressed at a certain time and for a certain duration. In this way, the physiology of genes is interwoven with the impact of environmental factors at every stage of development.

Also, living organisms are constantly changing as a result of spontaneous or induced genetic modifications. These changes are tested in different

environmental conditions, and, as a consequence, organisms experiment evolution of their characters.

The eventual adaptation or accomodation of the organisms to different environments come down to the results of chance mutations, genetic recombination and selective processes that favor specific forms of macromolecules (nucleic acids, proteins, etc.) that play basic roles in their reproduction and vegetative functions.

A very important feature of all living forms is that their genomes are chemically made of the same type of molecules, the nucleic acids (DNA , RNA). They also share a genetic code similar in structure, although, as a result of evolution, there may be differences at the level of operation of the code.

It is really surprising that, in spite of the tremendous variations produced by evolution in living forms, speciation has been very conservative with the nature and processing of the genetic information. This is the fundament to consider that the genetic code is "universal" to all living things. Nevertheless, variations in the code for aminoacids have been found. There are also differences in the molecular recognition processes that are the basis for regulating gene activities.

In 1973, Salvador Luria said that "Life has two scientific aspects : Life in action, meaning the function of living organisms ; and Life in time, meaning the persistence and disappearance or replacement of organisms by individual deaths and by the generation and proliferation of different species". In both aspects, it is essential to consider the role of the genome.

Genome to genome interactions in the host - microparasite relationship.

Microparasites are those organisms that carry on its reproduction, usually with a high intensity, within the host. They generally have generation times that are rather short (minutes) when compared with the host's life span.

If the host recovers itself from infection, its genomic potential provides him a temporal immunity against re -infection. So, we may consider that most microparasite infections are transient in individual hosts. Nevertheless, they may last longer when analyzed at the population level.

Comparatively, macroparasites, such as parasitic helminths and arthropods, may not have a direct reproduction within the host. They generally live longer than microparasites and, usually, they rarely leave a lasting immune response, allowing continuous re - infections of the host.

The microparasites, generally, seek to be commensal or to live in harmony with their host, sometimes helping its metabolism. It is the case of many bacteria in our digestive tract. The host tries to keep them confined or behind protective barriers under the control of its own regulatory systems.

Nevertheless, microparasites may take advantage of changes in their genome or changes in the inner or outer environment of the host and increase their virulence (reproduction), and,penetrating the host's barriers (skin, mucous membranes, cell walls, etc.), they overrun the existing defenses (immune system) and cause infections.

Very often, in order to carry on these attacks, microparasites work in alliance, expanding the interactions to more genomes. The whole process could be considered as an exercise of adaptation between these biological partners, in which several genetic and physiological strategies are used.

Some of these strategies are :

a) The appearance of spontaneous mutations that may occur at low frequencies, but considering the very large size of the populations they may become a very important factor. As an example it is possible to indicate that the rate of spontaneous mutations leading to streptomycin resistance in E. coli is 4 in 100.000 cells. The spontaneous mutation for penicillin resistance in Pneumococci is 1 in 100 cells. Since a colony of these bacteria may have several millions individuals we may see that the number of these mutants may be quite significant. They also will have an advantage for selective survival in a medium in which these antibiotics are present.

b) The use of enzymes that cut DNA or RNA. They are called restriction enzymes and its role is to cleave nucleic acids, making possible the incorporation or exclusion of DNA into or from an already existing genome. More than 1200 endo and exonucleases are already known. They recognize and cleave DNA or RNA at specific regions and are very important for the incorporation of foreign DNA into a host.

c) A very important source for changes in the genome are diverse mechanisms of recombination. These mechanisms are very important for the reorganization of the genome within an organism. They also play an important role for borrowing

or sequestering genetic material from other microorganisms. It is already known the role of phages and plasmids for transporting pieces of DNA between bacteria.

The similarities in genome organization facilitates this transversal gene transfer, which may overcome large taxonomic differences. These similarities may date back to common ancestors of the microorganisms involved.

The main outcome of these processes is the appearance of new genome characteristics, increasing variations in microparasites and the possibilities for evolutionary changes.

Still at the molecular level and immediate to primary gene activities, bacteria also produce a variety of agents that kill or inhibit the growth of potential enemies. These molecules, called antibiotics, are able to attack a wide range of microorganisms and, of course, are coded in the bacterial genome.

Similarly, bacteria have or develop sophisticated mechanisms to outwit or counterattack their antibiotic opponents. They may do this by reorganizing their genomes or by selecting new forms of genes produced after mutations.
These changes may create mechanisms to prevent the arrival or entrance of offensive molecules by modification of the characteristics of their target, so the attacking molecules are not able to recognize it.

Bacteria, in fact, might be symbolically considered as the best "spies" in nature. Their strategy for infection is to fit in the host in the best way possible, trying to be nice by using a similar molecular language in order to gain the confidence of the host.

Over millions of years, bacteria have learned how to survive or to penetrate well protected pluricellular organisms, evading their defenses and keeping a low profile when approaching the cells they are interested in.

An example to illustrate this bacterial behavior is Bordetella pertussis, a microorganism that causes whooping cough, a disease that kills more children than any other bacterial infection in developing countries. Humans are the only hosts for Bordetella.

Scientists at the Rockefeller University in New York, U.S.A. have been able to discover how Bordetella pertussis is able to infiltrate our body cells by cheating their molecular recognition system that allows cells of the same organ to stick together, leaving other cells in a mobile situation to continue their paths to their targets in other organs.

Molecules made of glycoproteins and glycolipids take part in this cellular recognition and the subsequent cell adhesion processes.

Bordetella has two cell surface proteins, pertussis toxin (PT) and hemoagglutinin (FHA) that are able to read the recognition code of the lung cells, and then to adhere to and colonize those cells.

Besides, the pertussis toxin has structural and functional similarities with other human body molecules, called selectins, able to be attached to sugar molecules in order to direct white blood cells (macrophaghes) of the body defensive system to go around to deal with other bacterial infections.

Bordetella infiltrates these cells, called macrophages, inducing its ingestion by them, but remaining intact once they are inside the cells.

For the penetration into the macrophage, pertussis toxin requires the help of the FHA bacterial surface protein . Once inside the macrophage, the bacteria has the advantage to be hidden from the main body defenses and is able to travel where the macrophage goes.

In brief, it is possible to see how Bordetella is able, not only, to adhere to the lung cells, but also to destroy the main body defenses, the immune system, making it easier for other bacteria to attack, generating new possibilities of parasite cooperation.

Knowing the mechanism of adherence used by the bacterium, it is possible to create vaccines that will prevent the sticking of Bordetella to the lung cells.

Although there is a vaccine widely used in more affluent nations, whooping cough is still a very important health problem.

Bordetella, spying on us for millions of years, has achieved a good knowledge of our body being able to penetrate in it and to produce a disease.

Knowing how Bordetella attacks us, we are able to protect and to know ourselves better.

A similar situation occurs with Pneumococci, a bacteria that produces pneumonia. These bacteria have a cell wall, mainly made of polysaccharides, to protect themselves, but penicillin attacks them by using a mechanism suitable to bind itself to the cell wall.

Pneumococci protects its life by means of genetic changes (mutations, regulating gene activities or developing gene recombinations) that modify the

activities of enzymes involved in the building of the cell wall. In this way, cell wall composition is changed and penicillin is not able to stick to it.

A similar strategy is used by Neisseria gonorrhea to resist penicillin. As a consequence important scientific efforts are developed to create vaccines that confer immunity against the bacteria. It is estimated that 1 million persons are infected every year in the U.S. , with a cost of 1 billion dollars spent in diagnosis and treatments.

Enterococci and Staphylococcus aureus are also becoming more and more resistant to available antibiotics, creating the need to search for new ones in other bacteria.

Parallel to this,drug designers also increase their efforts to find new targets for antibiotics in bacteria but without harming our cells.

Bacteria counterattack with new genetic or physiological changes in a process of continuous adaptation to the new conditions. This is a situation that may be compared to a real arms race going on within these biological interactions. At the moment, bacteria seem to be winning due to their enormous genetic plasticity, allowing its accomodation through millions of years of evolution, in which antibiotic opponents have been present either as a natural process or by human design.

Viruses. A similar picture may be drawn in the interaction of viruses and the cells of more complex organisms. Here, the viruses' genetic material may be RNA or DNA,and they also may be unharmful, infective or tumorigenic. The essence of

these possibilities is how the viral genome interacts with the genome of the host cell.

The viral genome may stay as a separate entity in the cytoplasm of the cell, or it may be incorporated into the cell genome where it behaves as another group of genes. Eventually, it may recover its freedom from the host genome and multiply so intensively that destroys its host. This is usually achieved under the influence of some environmental factors such as ultraviolet light. In doing this the viruses are able to transport host genetic material which may be introduced into other cells.

One type of virus are the retroviruses, in which the genetic material is RNA. As part of their life cycle, retroviruses are integrated into cellular DNA. While there, they may incorporate a cellular gene into their genome or they may interact with the cell's normal regulatory mechanisms. This is something we may call parasitism at the genetic level. Normal genes, after incorporating retroviruses RNA, may be transformed into an oncogene and may be responsible for starting a certain form of cancer. The mechanism may be the production of the protein coded by the gene at a higher than normal rate or by changing the structure of the protein.

The retrovirus may incorporate the oncogene and transport it to other cells.

In a similar way to bacteria, specific attachment of viruses to the cells requires receptors on the cell surface and combining sites on the viral protein capsule. Each virus multiplies by reproducing its own nucleic acid, a process he

partially controls with its own genetic information and corresponding enzymes. Specific inhibitors of these processes have been found. One of these inhibitors is the antibiotic puromycin, which blocks the synthesis of a protein essential to make the viral nucleic acid.

Our cells are full of potential antiviral and anti - cancer weapons. One of these weapons, recently discovered, is the Rnase Pribozyme (Rnase P) that is present in our cells. These enzyme molecules have RNA as a constituent and are able to cut RNA in a routine process for refining the tRNAs necessary for protein synthesis in our cells.

Appropiately guided, the ribozymes may be used to cut and destroy RNA strands made by disease causing viruses, such as AIDS, or the abnormal RNA made by oncogenes.

Since RNA is considered to be one of the first precursors of the genetic material, RNase P could be looked upon as a living fossil of this world in transition. In fact at the evolutionary level it may be considered a real relic of the genetic material in the primeval era, before the appearance of the DNA double helix.

Fitness and Evolution.

The genome to genome interactions in host - microparasite relations, eventually may be translated into estimations of the relative fitness of these organisms.

The host's fitness depends on the relative gene frequencies of the parasite population. In the same way, the parasite's fitness depends on the host's gene

frequencies. In this scenario, gene polymorphism in the gene frequencies of both organisms arise and may be maintained.

These polymorphisms may be stable, cyclic or chaotic as a result of the parasite virulence and the mechanisms of host resistance. This genetic diversity may vary from generation to generation due to fluctuating environments.

One of the factors that may influence this change is the overuse of drugs, which may be eventually reflected in antibiotic resistance.

As already mentioned, bacterial cell wall components, specially bacterial cell surface proteins, may, mimic those found in the human host and are part of the mechanism of bacteria to infect and dominate cells. These cell wall components are made, of course, under the control of the genotype of each organism. Their relationship is, of course, of evolutionary relevance for host - bacterial interactions.

Scientific advances in understanding the physiology and genetics of microorganisms have been important to deal more successfully with these problems. Unfortunately, sometimes we have not been very wise to apply the new knowledge, which soon is neutralized or exploited by microorganisms for their own advantage. This situation requires that knowledge must be continuously reviewed and expanded because the biological arms race or competition continues.

Bacteria are organisms that are beneficial to human beings in many different ways. One of these is that they are ideal organisms in which to study ecological and evolutionary problems of our habitat. Their adaptations may be understood at

the molecular level and can be tested experimentally, thanks to the better knowledge we have about the organization and physiology of their genomes.

Virulence of pathogenic bacteria, is a character under genetic control, with all the perspectives to be modulated by selective pressure associated with the maintenance and evolution of virulence determinants. So, we should be permanently vigilant and prepared to deal with these friendly enemies.