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Short Communication

The Viruses, Latency and Malignancy

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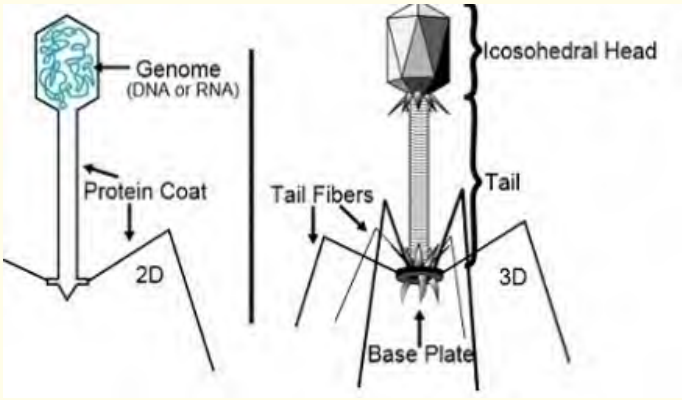
At the boundary of the living and the matter there are the viruses that look like crystals and/or machines. Since there was the first photograph of a virus (1940) one could ask different problems. The head of bacteriophage T4 is an icosahedron: the feature to optimize the volume of content in relation to the area, and then to the amount of material needed to build it with a "tail" sheathed in a spiral. The fibers attached the cell walls that the virus is about to infect. The various parts are assembled to form the virus itself. The so-called retroviruses (viruses whose genome consists of two RNA molecules) are not limited to damage the host cell but by integrating their genome into that of the host cells can propagate from one generation to the other [1]. But how did the viruses originate? The virus origins where discussed according to three possibilities, the first was concerning their origin from the cell itself, without any gene and with the functions taken from the host cell. The second one was deriving from independent cells genes that would replicate for themselves. The third chance implicates both protein and DNA or RNA independent origin, not from cellular organisms. This theory was set out in the 60's by two astrophysicists Fred Hoyle and Chandra Wickramasinghe and among the scandal of academics was endorsed in 1978 by the Nobel Prize Francis Crick, the discoverer of DNA, who theorized that oceans of viruses stay in interstellar space and from there, carried by comets or driven by stellar winds, reach the planets, which colonize and where they propagate. In support of this theory (which, among other things, could explain the explosion of complex life forms that our planet has experienced 570 million years ago) it is to be considered the astonishing ability of viruses and other microorganisms, called extremophiles, to resist on our planet in extreme environments (such as, for example, concentrated sulfuric acid discharged from mines, nuclear reactors, the ocean depths) which are somewhat similar to the interplanetary space, characterized by full vacuum, low temperatures and radiations Moreover, although controversial, traces of microorganisms have been found on meteorites.



The viral particle is shaped by DNA or RNA with at least 3 genes that are inside a shell of proteins and no chance to replicate outside an infected cell.

The viruses infect plants and animals including men and are able to replicate within the living cells for instance the varicella virus remains latent for years in neuron cells [2], but it is enough a weakness of the body as the immune defense in order that the virus moves along the nerves and causes the typical Herpes Zoster vesicles [3].

It is very interesting the evolution of the viruses because they are able to penetrate germ cells and multiply their genes into the cell genome transmitting an indelible marker across generations.

The endogenous proviruses as they are called or "fossil viruses" were found in molluscs and insects till to mammals. Even in man a total of about 80,000 fossil proviruses have been discovered. It seems that they are capable to cause diseases in chickens and mice while are inactive in men, It is also interesting to see which changes were caused by the endogenous proviruses in the evolution of our body. A gene derived from an endogenous provirus is governing the placental cell layer, named syncytiotrophoblast, that makes the main prevention in avoiding the eventual passage of toxins from mother to son.

It is since the evolution time when viruses and humans get together. The viruses can block the "sentinel antigens" found at the cell surface to alert cells against unwanted intruders or vice versa they might remove molecules so that then use to numb the defences of the host.

The history goes back to Egyptian times when it is described the first viral infection, approximately 3700 BC, with the paralytic poliomyelitis afflicting a man on the hieroglyph of a temple.

The mummy of Pharaon Ramses V (1196 BC) shows his blister lesions on the face caused by the infection of the of the variola virus that was responsible for the smallpox death. The disease passed then to India and to China (1122 BC) as sudden plague devastating and afflicting the lives of our ancestors and then disappearing. Smallpox remained endemic among the affected population after each epidemic wave.

Humans recovered from smallpox did not show to get sick again since an Asian old observation. Therefore in 590 AD for the first time the variolization was introduced as a practice of conscious intervention with the purpose of immunization considered a kind of target to reach by causing a mild illness from Indians who had the first idea to protect people against the severe disease. Then China, Arabia, Pakistan and Africa followed this practice.

A distinctive sign, part of a ritual mystical ceremony, was to infect healthy individual by smallpox pus of sick people for preventing the real illness. Then a long time passed away before a proper methodology was developed until 1796, when the English naturalist and physician Edward Jenner developed the first vaccine. Jenner noticed that milkmaids who lived in his county and had contracted a non-severe form of disease, known as the cowpox, did not get sick even when smallpox was spread in an epidemic in the community.

On May 14, 1796 Jenner inoculated an eight years child by the use of material obtained from a milking machine contaminated by the virus spreading cow-pox. Then in July, two months later, the English doctor inoculated again that child using the smallpox material from a sick patient.

The success of this from of vaccination was shown by the child who did not develop any disease. Since the nineteenth century this vaccination was adopted in all the world and the WHO (World Health Organization) made the statement in 1979 that smallpox was completely eradicated from the people of the earth.

One century later the vaccination of Jenner, at the end of 1800 the viruses were known and their existence was admitted after the spreading of diseases not only caused by bacteria, fungi and protozoa.

A coworker of Pasteur, Charles Chamberland, in 1884 used a porcelain filter to block any known bacteria and in 1892 Dimitri Iwanowski, Russian pathologist was able to demonstrate by this filter some new studies showing that extracts of ill tobacco plants could transmit the disease to other plants even after being filtered.

Therefore one could postulate that some agent, that was not seen at the microscope, was filterable and smaller than a bacterium, furthermore able to cause pathologies. The concept of viruses was confirmed and developed in 1898 by Martinus Beijerinck who extended the results on TMV (Tobacco Mosaic Virus) obtained by Iwanowski referring to a "contagium vivum fluidum", or a soluble living agent.

The mechanism of virus-host relation is complex. In an acute infection the virus penetrates into the host cell, it is replicated by the body cells, causes lysis and is fully eliminated. In a latent infection the virus can persist till the end of the host life, giving chances to be replicated according to the capacity of the host to leave time and space for a chronic infection and even continuous replication. The onset of the virus depends on its belonging to a specific viral family and to the capacity of the host body to tolerate it. For instance the family of Herpesviridae [4] is characterized by the viral latent infection in men and after the first establishment the chance to "wake" more or less frequently, and to yield clinical manifestations of varying severity, depending on the virus and the host immunity.

The herpesviruses are able to select a different site of latency in the host body and according to their subfamily are protected in nerve cells or lymphocells from the attack of the immune system, which makes eradication of these viruses from infected person mostly impossible [5-7]. The molecular mechanisms that allow the viral genome to remain in a latent state and those leading to the exit from latency and triggering the lytic cycle of viral replication are yet to be clarified, although some viral genes have been identified that are responsible for this alternative [8-10].

In details HSV 1 and 2 (Herpes Simplex Virus 1 and 2) hit epithelial cells and establish latent infection in the neurons. Cold sores associated with oropharyngeal lesions are due to HSV type 1 with recurrent episodes and even rare encephalitis [11].

The genital mucosa is mostly implicated by HSV type 2. The VZV (Varicella Zoster Virus) is responsible for the chickenpox, disease with primary rash and then latent infection in nerve cells that causes shingles after reactivation (herpes zoster) [12]. Finally Epstein-Barr virus infection is reported as a pathogen in viral oncology [13,14].

The family of Polyomaviridae includes SV40, JC Virus and BK Virus. They infect human beings and establish body latency. During childhood it happens the primary infection with no symptoms and then the Polyomavirus becomes latent. In the world the adult population is positive in healthy conditions even at 80-100% for these viruses. JCV is latent mainly in renal tissue, also in lymphocytes and BK Virus (BKV) and SV40 in bone marrow, lung, intestine and in the brain [15-17]. When the immune system of the host undergoes stages of immunosuppression for various reasons the Polyomavirus can reactivate its replication and cause disease. JCV can cause a demyelination disease of the CNS (central nervous system) in immunocompromised host: the PML (progressive multifocal leukoencephalopathy) has a fatal outcome [18,19], while BKV causes nephropathy and hemorrhagic cystitis in humans [20,21].

From the Flaviviridae family the HCV (Hepatitis C Virus) infects primarily people by contaminated blood. The infection can cause mild hepatitis, it can remain stable with diverse severity and various symptoms.

It may become chronic in approximately 85% of cases, with liver damage after 10-30 years of infection till liver cirrhosis or it may evolve in hepatocellular carcinoma [22,23]. Nevertheless a strong immune response, humoral and cellular, against HCV, the virus is not cleared by the body of the patient for its genetic variation used as survival strategy by the viral genome. After primary infection the predominant viral population is leading to the appearance of one or more viral strains that, as a result of genetic modification, have obtained an "advantage" in terms of survival over the length of time. That is the main reason, from a genetic perspective, why there is a high rate of chronic infection for the heterogenicity of HCV gene expression and phenotypic mutation and of the possible re-infection with viral strains of different genotype, of the not satisfactory efficacy of the therapies and also of the difficulty of preparing vaccines. Of course the hepatitis B associated cancer [24] is prevented by the hepatitis B virus vaccine [25].

In fact the rate of viral genomic variation takes place in a very short period of time, while the rate of human genomic variation amounted to only 2% during the 8000000 year evolution to man from the state of monkey in comparison to the same amount of viral genomic mutations during just 5 days of replicative activity.

A high mutation rate is present mostly in RNA viruses which have a less complex genome. The influenza virus is a typical example [26].

The type A influenza viruses, circulating in animals and humans, are distinguishing among themselves according to hemagglutinin (HE) and neuraminidase (NE) glycoproteins of the external surface: there are 16 subtypes of HE and 9 subtypes of NE, with 144 possible combinations [27-30]. These viruses tend strongly to mutate and this genetic variability is divided into antigenic shift, with creation of new subtypes, which is responsible for large epidemic and pan-epidemics, and antigenic drift with minor changes, associated with sporadic cases or small outbreaks, according to Patrick Forterre, Pasteur Institute, Paris [31-33]. This short communication takes care of the recent paper on origin of the HIV [34-35] and evolutionary history of the viruses [36,37], where the human papilloma viruses were mentioned for further update [38-40] as well as the role of KSHV in the pathogenesis of Kaposi's sarcoma [41,42].

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