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RESEARCH ARTICLE

Viruses and Autoimmunity

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AIM and SCOPE

Here, I present some ideas about a viral involvement in Multiple Sclerosis and the other about 80 human autoimmune diseases.

ABSTRACT

Two types of viruses seem to be involved in MS. First, retroviruses mostly in the form of endogenous retroviruses, recruited from the repertoire present in the human chromosomes. Secondly, a Herpesvirus, normally Epstein-Barr Virus. The retrovirus contributes an enhancer, which makes it possible for a virus to grow in T-cells. The EBV provides it's EBNA proteins, which transform lymphocytes. The result is a transformed, quasi-neoplastic T-cell clone with a "wild" specificity.

Most, if not all, animals have endogenous viruses i.e., copies of parts of or complete retro-viral genomes in their chromosomes. Man, for example, has in the order of 100 000 bits and pieces of retrovirus, distributed on all chromosomes. Most of these bits are grossly defective but in man about 50 can encode a protein. There is evidence several coding endogenous viruses can recombine and start an infection. I believe these coding endogenous viruses contribute to human disease. Indeed, I speculate, they are the most important limitation on size and longevity of the members of a species: both these parameters are roughly proportional to the chance of making a replicating virus. In the following I will try to argue for the importance of coding endogenous viruses.

If the presence of retroviral sequences does not lead to replicating virus the situation is mostly fine However, as soon as a virus starts replicating in an individual, the mutational level in the animal increases dramatically, by way of insertion of viral genomes at unusual places, and the animal in part loses control of its genome. This is known to result in cancer, and I believe in autoimmune disease.

Sometimes the situation can be worse. Occasionally, acquisition of a new endogenous sequence elicits species-threatening scenarios. This may be the case with Australian Koala Bear (1). It may also lead to sub-speciation, as seems to be the case with the American Mule deer (2).

Replication may be brought about by recombination between endogenous loci that are competent for different functions i.e., encodes different parts of the 3 or 4 gene in the viral genome. This seems to happen efficiently in some host individuals. It is true, that the genome of an animal species contains retroviralBsequence from many origins but is seems that the encoded viral proteins often work well together. At first by complementation, later by recombination. The latter probably requires co-packaging of different viral RNAs in the same virion. Replication at first simply increases the viral load 10 to 100-fold. See for instance the level of murine leukemia virus core protein in blood as it develops in the first week and months of life in AKR mice (3). We do not know for sure if the initial low level of core protein represents infectious virus, but later AKR mice are full of infectious virus. Later, most of the AKR mice will succumb to leukemia (4). It has been clearly shown that these leukemias are initiated by integration of retroviruses in or near growth-promoting genes, the so-called oncogenes. The reason seems to be that the endogenous viruses carry efficient gene-up-regulating sequences, known as enhancers, in their genome. These enhancers primarily serve to ensure viral replication but have the added effect of deregulating the host genome around the site of integration.

Syncytium formation is another mechanism by which retrovirus can cause cytopathogenicity. In fact, syncytia in a particularly sensitive cell line constituted an early plaque-assay for mouse retrovirus (6). If a cell becomes productively infected, then a budding virus can infect another cell while still part of the first, thus forming a cytoplasmic bridge. This situation often leads to formation of a syncytium. I think, this in part, is what happens in the blood vessels during diabetes and other autoimmune diseases, making the vessel wall thick and inflexible, which again leads to high orthostatic blood pressure. This could also be the mechanism behind both the retinopathy and the nephropathy. If I am right that these are independent results of the retrovirus replication, attempts to control these conditions via better blood sugar control in diabetes will prove insufficient. Syncytium formation is by far the most frequent consequence of retrovirus infection of neighboring cells, and it is nonrandom, in contrast to the genomic consequences of retrovirus infection. In fact, at a late stage, it might include most cells in a vessel-system. In a few situations, syncytium formation may have a positive role for the species. The most well-known example is the formation of syncytial trophoblasts in placenta (7). Specific endogenous retrovirus genes have been identified as relevant for the formation of this cell layer. Curiously, while the formation of the syncytium cell-layer is common to many mammalian species, the contributing viruses do not seem to be common. So, there must have been a selective convergent evolution behind the formation of these cells.

Many recent reviews impinge upon the role of endogenous viruses in cancer and therefore this topic will not be discussed here (8,9). Instead, I will discuss

the possible role of endogenous retroviruses and Herpes viruses in autoimmune diseases.

In my take, autoimmune diseases are quasi-neoplastic conditions of killer T-cells directed towards an antigen on a particular cell type. Somehow, the killer T-cell clones can outlast their normal lifespan and their longevity is either infinite or at least much longer than normal. How could this be brought about? My belief is that two quite different kinds of viruses cooperate to bring about the longevity of the T-cell clones. First, some autoimmune diseases appear associated with endogenous retroviruses. Specifically, we have shown that three autoimmune diseases are associated with such viruses, namely type 1 diabetes, rheumatoid arthritis, and multiple sclerosis (8,9). It is not clear that all autoimmune diseases display this association; it has not been investigated; it could still be that most autoimmune diseases do not. However, many autoimmune diseases are associated with each other, suggesting that they have a common origin, and since for a few diseases we have firm evidence of a retro-viral involvement, we will for now assume that the other diseases are associated with retroviruses, too. This is simplification, not proof, and I am willing to repeal the statement if serious arguments to the contrary arise. Next, in the mentioned diseases it appears that development of problems is associated with replicating virus. In other words: the scattering of the viral genome. It seems that hybrid retroviruses are involved with cores from the rich beta-retrovirus complement in humans, while the envelope protein originates from gamma-type viruses. It is not uncommon for different types of retroviruses to form hybrids. Another example is the Mason-Pfizer Monkey Virus of Macaques (10). In Multiple Sclerosis we have found that a gamma-type retrovirus on the X-chromosome, HERV-Fc1, participates. This is highly significant in that presence of a dominant gene on the X-chromosome leads to the disease being twice as common in women as men. Such a bias for women is present in many autoimmune diseases. It will be remarkably interesting to see if this virus contributes to other autoimmune diseases. Many retroviruses carry an enhancer allowing for the expression of associated genes in T-lymphocytes. We expect this to be an important feature in the development of transformed T-cells in the autoimmune diseases.

Secondly, an entirely different class of viruses, the Herpes viruses, also seems to play a role in autoimmune disease. This is particularly clear for the Epstein-Barr Virus in Multiple Sclerosis (11). EBV has the peculiar property (the EBNA1 gene) that it can immortalize B-lymphocytes. We speculate that it with the help of the retrovirus enhancer can immortalize T-cells, too. EBV is transmitted horizontally, and above 90 percent of adult have been infected as evidenced by immortalized EBNA-positive B-lymphocytes persistent in the blood.
In children, EBV infection normally produces few or no symptoms, but EBV gives rise to at least two serious human illnesses: Burkett's Lymphoma and Infectious Mononucleosis. The common, EBV-associated, form of Burkett's Lymphoma, is a B-cell lymphoma typically occurring in infants living in Malaria infested area of Africa, South America, and New Guinea. It is believed that the malaria works as an immunosuppressant. With modern treatment most patients survive. Infectious Mononucleosis is typically a disease of young adults. It involves fever, sore throat and swollen glands, tiredness, and headache. Fatigue may last for months. Most cases are caused by EBV but a minority of cases by Cytomegalovirus (CMV). In addition, EBV is associated with several rare lymphoproliferative diseases, in some cases full-blown cancers. As I suggested above, a retroviral enhancer may facilitate the expression of EBV in T-cells giving rise to T-cell proliferation. It is not clear if the retrovirus infects EBV-DNA and the hybrid virus then infects T-cells, or some T-cells already contain EBV-DNA, but the virus is inactive, until it acquires a retrovirus enhancer. This would then lead to autoimmune conditions depending on the T-receptor specificity of the transformed T-cell. Alternatively, the EBV-retrovirus hybrid could transform a primitive T-cell, from without or from within, and many T-receptor specificities would develop from that cell later.

There are many unsolved problems with the involvement of retrovirus and Herpesvirus in autoimmune disease but also experimental data for it (11,12,13). My hope is that the thoughts presented here may inspire scientists to explore experimentally the possibilities laid forward.

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