

Theory on the involvement of retroviruses and EBV in autoimmunity

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Abstract

There is a striking likeness between an old model for the action of mobile genetic elements in Maize and recent observations on endogenous retroviruses in human Multiple Sclerosis. Nexø discussed this and other developments in his recent theory on autoimmunity. Specifically, in analogy to the *onc* genes the author suggest that insertion of a retrovirus activates a so-called *aut* gene. This *aut* gene may well be an EBV genome.

Text

Human endogenous viruses are retroviral sequences embedded in the human chromosomes. They are presumably remnants of past infections that managed to reach the germline in the ancestors. The sequencing of the human genome and later analyses have revealed in the order of 100,000 such retroviral sequences, distributed on all chromosomes. Most of them are grossly defective, representing only fragments of retroviruses but approximately fifty can encode a protein. Very few, if any are complete and could in principle start a new infection on their own. However, retroviruses are very good at complementing each other or recombining, so sets of endogenous retroviruses might collaborate to reach replication.

Nexø has recently suggested that autoimmunity is quasi-malignant process, in which a set of endogenous retroviruses by insertion mutagenesis near a putative *aut* gene transform one or more clones of T-lymphocytes [1] and cause autoimmunity. He proposed the theory after detection of genetic association of markers near two endogenous viruses with disease in Scandinavians, and of synergy of these markers in the causation of Multiple Sclerosis, as well as of several indirect observations [2-5]. It is worth mentioning that while presence of retrovirus particles does not signify causality, genetic association does, not necessarily of the closest gene, but of some gene in the immediate vicinity of the marker. When we are studying linkage disequilibrium (as in the present case), the limit of the distance is very likely less than 50 kb and more likely about 10 kb. This is very close. Since we also have shown synergy between the two markers close to endogenous retroviruses, we are confident that the viral genes interact in the disease. We have made similar but less extensive observations on Type-1 Diabetes and Rheumatoid Arthritis. It is not presence or absence of the viral genes that differentiate people. As far as we know all humans share the viruses. Rather, it is a difference in epigenetic suppression. Azacytidine, a drug that inhibits DNA-methylation is a powerful inducer of HERV-Fc1 [6], one of the retroviruses implicated in MS.

The theory combines two previous viewpoints: That autoimmunity is a disease of the immune system, and that it is a viral disease: It is both. The strife between these two schools of thought is thus laid to rest. The specific viruses implicated in MS in Scandinavians seem to be HERV-Fc1 on the X chromosome and HERV-K13 on chromosome 19. Scandinavians have a very high risk of MS. Possibly; other endogenous retroviruses could play a role in other ethnicities.

There is a remarkable likeness between this theory and the observations, and the ideas suggested 70 years ago by Barbara McClintock on the action of mobile genetic elements in Maize [7]. She observed that two genetic elements, now called transposons interacted, and that the interaction

resulted in the spawning of copies to new places in the genome. *Mutatis mutandis*, this is also, what the author suggests. The scientific community ostracized Barbara McClintock for 20 years for her radical ideas about moving genes but she was later vindicated. The author hopes that it will not be so long before we see proof or disproof of his ideas.

The assumption of the existence of *aut* genes is an analogy to the *onc* genes, which activate by insertion of retroviruses in animal leukemias [8,9]. The nature of the putative *aut* gene(s) is unknown. However, I am particularly attracted to the notion that it is Epstein Barr Virus or another Herpes virus. There is good epidemiological evidence that EBV contributes to MS [10,11]. It seems that MS is rare in people without EBV [9,10]. We have long known that EBV can immortalize B-lymphocytes. The EBV genome could also be present in T-cells but unable to express the EBNA-antigen, which is the hallmark of B-lymphocyte transformation. Insertion of the retrovirus with its T-cell enhancer in the EBV genome might then allow for expression, activate EBNA in T-cells, and cause T-cell immortalization. Alternatively, the retrovirus(es) may infect B-cells and its enhancer transform an EBV genome to T-cell tropism, and the modified EBV virus then infects T-cells. If the author is right, autoimmune T-clones express EBNA, and vaccination against EBV might eradicate autoimmune diseases [10]. However, it is conceivable that other Herpes viruses could play a similar role.

A murkier problem is why different sets of retroviruses are associated with different autoimmune diseases, assuming the same kind of lymphocyte is acting in different diseases. Maybe this represents a temporal coincidence. We know that these diseases occur at different age-ranges in humans, most likely reflecting the formation of the initial autoimmune cells at different age. At the same time, different sets of retroviruses may be active at different ages in susceptible individuals.

Conflicts of Interest

The author declares to have no competing interests.

Ethical Statement

This study did not involve investigation of humans or animals. In the previous work of the author all procedures performed involving human participants were in accordance with the ethical standards of the regional research committee (Midjysk Science-Ethical Committee, Denmark) and with the 1964 Helsinki declaration and its later amendments.

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