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Mini-Review

A unified viral theory of autoimmunity

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ABSTRACT

Retroviruses and EBV have been championed by different schools of thought as inducers of autoimmunity. The present theory suggests ending this competition between schools: They are both right. The viruses synergize! Probably, they even form a hybrid genome.

KEYWORDS: autoimmune diseases, multiple sclerosis, retroviruses, Epstein Barr virus.

1. Introduction

Various viruses have long been suggested to be involved in multiple sclerosis (MS). Initially, the idea was that the viruses directly caused tissue damage. An alternative view, that the tissue damage is caused by the immune system itself has also been suggested. The present theory suggests that the viruses infect and immortalize cells of the immune system and that the immortalized cells in turn cause the damage. The mechanism may well apply to many other autoimmune diseases, too.

2. Theory

This theory postulates 3 things to happen:

1) During life, endogenous retroviruses present in the genome or any other retrovirus start up an infectious process in some individuals.
2) The replicating retroviruses integrate in an Epstein Barr Virus (EBV) genome and contribute by way of their enhancers to a new tropism: The recombinant viruses can now infect and/or express in T-cells.
3) The recombinant EBV-retrovirus by way of the EBNA antigens immortalizes effector T-cells, that would otherwise have a limited lifespan.

If the transformed cell happens to encode a T-cell receptor-protein binding to tissues in the individual, we have autoimmunity. If it binds to a pathogen or another structure, it may just strengthen immune protection and otherwise go unnoticed. This theory suggests an unwanted way to amplify and extend an immune response. It does not explain the initial presence of autoimmune reactivities.

In effect, the theory suggests that autoimmunity is a quasi-neoplastic condition of antigen-specific killer lymphocytes, such as T-cells, brought about by an EBV-retrovirus hybrid. The presumed T-cells are immortalized but retain differentiated functions. Presumably, in most cases the final transforming principles are the EBNA antigens, well known to transform B-lymphocytes [1, 2].

3. Activation of or infection with retroviruses

The sequencing of the human genome has revealed that the human genome contains in the order of 100 000 fragments of endogenous retroviruses. The majority are grossly defective but approximately 50 can encode a protein [3].

Complementation and recombination among endogenous retroviruses are well-known in animals [4], and sometimes give rise to infectious and disease-causing virus. The classical example is the AKR mice, which harbor infectious virus shortly after birth, and of which the majority eventually succumb to virally related leukemias [5]. Quite likely, the same mechanisms operate in humans.

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There is genetic evidence of synergy among human endogenous retroviruses in diseases such as MS and Rheumatoid Arthritis [6, 7], and evidence of replicating retroviruses in MS [8]. The author does not think that horizontal transmission between individuals by endogenous viruses occurs to any large extent. However, infection with horizontally transmitted retroviruses contributes to certain autoimmune diseases, such as hind leg paralysis in Lake Casitas mice [9], Visna-Maedi in sheep [10], and Human Tropical Spastic Paraparesis [11].

In a few instances, we believe to have identified endogenous viruses involved in individual autoimmune diseases. Among others is the identification of HERV-Fc1 on the X-chromosome in Multiple Sclerosis. Markers near this endogenous viral locus appears genetically strongly associated with the disease, and at least part of the viral genome is upregulated in active disease in T-cells and plasma, suggesting ongoing viral replication [6, 12]. Interestingly, the location of the endogenous virus on the X-chromosome means that any disease, in which it is important, and in which the gene for the virus acts as a genetically dominant feature, should be twice as common in females as in males, simply due the fact that females have two copies, and thus have twice the risk of obtaining a disease-causing allele. This gender-ratio is pretty much what is observed with the common form of Multiple Sclerosis. The ratio does not hold for the specific form of MS known as Primary Progressive MS, and indeed attempts to involve HERV-Fc1 in PPMS have failed [13]. However, a retroviral locus on another chromosome could act in a similar fashion in this subgroup of MS.

4. The retroviral enhancer gives EBV T-cell tropism

EBV contributes to the autoimmune disease Multiple Sclerosis [14, 15], and it may well contribute to others. MS in EBV-negative persons appears to be infrequent. Other Herpes viruses might in some instances work as substitutes.

It is well-known that EBV can infect and immortalize B-lymphocytes. Above 90 percent of humans harbor such immortalized cells in their bloodstream, evidence of a previous infection with EBV. It seems that the EBNA antigens are responsible for the immortalization. Their expression is also an easily detected marker of these immortalized cells. Moreover, it is also well known that the retroviral enhancer, after re-integration enhances the chromosomal surroundings [16]. The same thing could happen when it integrates in the EBV genome.

There could be other ways, in which retroviruses could change EBV cell tropism but this is the simplest and it is well known. In such situations, the enhancer after re-integration of the virus typically raises the expression of the surrounding chromosomal genes considerably. This phenomenon has been used to identify the involved oncogenes. Integration could also destroy a gene but then this gene would presumably have to be hemizygote or the other allele would take over.

There is a certain chance that the enhancement of the ability of EBV expression in T-cells occurs not in the EBV genome itself but in some cellular chromosomal region. In some ways, this would bring the mechanism even closer to what is known to happen in retrovirally induced leukemias. For this mechanism to work, it would probably have to happen in an early stage of lymphocyte development before molecular formation of the antigen-defining molecule, since the study of Babbe *et al*. discovered multiple lesion-associated T-receptor rearrangements in individual patients, [17, 18]. It seems that this mechanism would be numerically at a strong disadvantage. On the other hand, this mechanism might explain how auto-reactivities occur in grown persons, which is otherwise a conundrum. The author suggests leaving this possibility for later. If a thorough search for EBV-retrovirus hybrids proves negative, one could resurrect the idea.

Alternatively, one could imagine that the retroviruses provide a route into the T-cells. However, it appears that at least some EBV already can infect these cells by binding to CD21 [19]. Maybe, there are further restrictions of EBV post penetration in T-cells and the retroviruses help EBV overcome these restrictions.

It is not clear, if formation and retention of the presumed EBV-retrovirus hybrid occurs in the T-cell itself or in another cell type. In the latter case,

the EBV-retrovirus hybrid presumably infects the T-cell later.

5. The hybrid EBV-retroviruses transform T-cells

Notably, Haahr and colleagues have isolated lymphocyte strains from MS patients, which harbor and express EBNA antigens [14]. The cellular origin of these cell strains is uncertain. The expression of EBNA has been interpreted as an argument that they were of B-cell origin but in view of what is suggested here, they may be T-cells or any other form of antigen-specific killer lymphocyte. A thorough re-investigation of these cell strains for origin may be warranted. Have they rearranged T-receptors, or do they encode immuno-globulins? Could they be some other form of T-cell receptor driven, antigen-specific killer cells? Indeed, if the cells are antigen-specific killer cells, such as T-cells, these authors may have been isolating the disease-principle in MS long ago and later been led astray by their cells' EBV expression to assume they were B-cells. Scrutiny of any EBV genome in these cells for the presence of an integrated retroviral copy is needed. However, it may be that only some of the EBV genomes in a cell harbor the retrovirus but that they can transactivate other EBVs and that this is enough for the EBNA to work. So, the search for EBV genome(s) with integrated retroviruses must be exhaustive. It is not certain that the enhancement would cover the entire EBV genome, so the location of the retrovirus would also be important.

As mentioned, the presence of expanded clones of lymphocytes with rearranged T-cell receptor in MS lesions of such patients has been documented [17, 18]. In one example, 35 percent of lymphocytes associated with lesions had the same T-cell receptor code, and thus apparently were of clonal origin. Nonetheless, in each patient, several receptor specificities were detected associated with the lesions, so formation of these cells must be reasonably effective.

The very character of the common form of MS, with its ebbs and flows, suggest an ongoing battle inside the patient. It could be that the EBV-retrovirus hybrids reside in another cell compartment and only occasionally hit a cell with autoimmune specificity with ensuing tissue damage. It could be that immunity to virus(es) has the upper hand most of the time. Alternatively, in one sub-model, the viruses infect a primitive lymphocyte and antigen-specificities are formed later. However, the principle: synergy of retroviruses and EBV remains.

6. Conclusion

From established properties of endogenous retroviruses and EBV it appears that synergy of these viruses, for instance in a hybrid viral genome, could well be at the root of many autoimmune diseases. Moreover, this paper has indicated investigations, spawned by the theory, which could test it. Maybe, in focusing on synergy of retrovirus and EBV, we have opened a door to the understanding of the origins of these important diseases.

CONFLICT OF INTEREST STATEMENT

The author declares that there are no conflicting interests.

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