

Rubella and autoimmunity

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Molecular mimicry has been proposed as a pathogenic mechanism for autoimmune disease. The hypothesis is based on the epidemiological, clinical, and experimental studies and in evidence finding an association between infectious agents and autoimmune disease, observing cross-reactivity of immune agents with host antigens and microbial determinants.¹

Recent studies have revealed that carbohydrate mimicry of bacterial lipo-oligosaccharide by the human ganglioside is an important cause of Guillain-Barré syndrome, for example. This new concept that carbohydrate mimicry can cause an autoimmune disease provides a clue of the pathogenesis of immune-mediated diseases.¹

Molecular mimicry is based on a structural similarity between a pathogen or metabolite and self-structure. The similarity could be expressed as shared amino acid sequences or as a similar conformational structure between a pathogen and self-antigen.² The strongest association of viruses and type 1 diabetes (T1D) involves enterovirus species, of which some strains have the ability to induce or accelerate autoimmune disease in animal models.

Several hypotheses regarding the mechanism to explain how viruses affect islet autoimmunity and beta-cell destruction were proposed.³ Viral infection may serve as an accelerating factor that, superimposed onto advanced insulinitis, leads to rapid culmination into hyperglycemia. Rubella virus is a possible environmental agent which may be involved in the triggering of autoimmunity to pancreatic islet cells, leading to T1D. Autoantibody responses were found in 239 10-year-old girls who received live attenuated rubella vaccine, of whom 61 (26%) had no pre-existing rubella immunity.⁴ Infection can promote the expression of human endogenous retroviruses by molecular mimicry or by functional mimicry.⁵ There are additional mechanisms which may control the expression of human endogenous retroviruses, such as the epigenetic status of the genome.⁶

T1D develops during months to years, in which islet autoimmunity destroys the insulin-producing beta cells of the pancreas. This period is marked by the presence of antibodies

to insulin, glutamic acid decarboxylase, and tyrosine phosphatase IA-2, as well as by islet-reactive T cells, but how islet autoimmunity is initiated and accelerated is not well defined. The incidence of T1D in many countries has risen rapidly over the past 30–50 years, mainly among the young population. The hypothesis explains that it is an increased environmental pressure on susceptibility genotypes.

A rapid rise in the prevalence of virus infection could perhaps explain this phenomenon by increasing the frequency of diabetogenic infections. The following criteria have been proposed for disease causality:

- Temporal relationship: exposure precedes disease – the only absolutely essential criterion.
- Statistical strength of association: the higher the more convincing.
- Dose-response relationship: increasing exposure increases risk.
- Consistency: replication of results by different methods or in different populations.
- Plausibility: how well the data agree with current concepts of pathological mechanisms.
- Consideration and/or rejection of other alternative explanations.
- Experiments: can the findings be replicated experimentally?
- Specificity: the weakest criterion. Lack of dose specificity does not negate causality, but, if present, strengthens the claim.
- Coherence: is the association compatible with the existing body of knowledge?

Rubella fulfils the criteria for causality of T1D, with statistically strong temporal association that is consistent, plausible, and specific. Despite strong data and the association between T1D-susceptibility and HLA the mechanism of rubella-associated T1D remains unresolved and rubella vaccination is clearly not the answer to prevention of T1D.⁷

Rubella virus infection during pregnancy is known to spread to the fetus in the majority of seronegative mothers. If the infection occurs during the first trimester of pregnancy, there is high risk of serious organ damage in the fetus. A

variety of clinical abnormalities is seen in congenital rubella syndrome, including endocrine diseases such as Addison's disease, growth hormone deficiency, and increased frequency of diabetes.⁸

In the case of viral triggering of autoimmune T1D, certain viruses (retrovirus in NOD mice, rubella virus in hamsters and humans) may alter a normally existing beta cell antigen into immunogenic form or might induce a new antigen, leading to beta cell-specific autoimmune insulin dependent diabetes mellitus. In addition, other viruses could generate antigen-specific T effectors cells which may cross-react with a beta cell-specific autoantigen.⁹

Another issue raised up in the last years is whether vaccination can induce autoimmunity. Autoimmune reactions to vaccinations may rarely be induced in predisposed individuals by molecular mimicry or bystander activation mechanisms. Vaccine-associated autoimmune reactions include Guillain-Barré syndrome after 1976 swine influenza vaccine and immune thrombocytopenic purpura after measles/mumps/ rubella vaccine.¹⁰⁻¹³

Vaccines can cause adverse events, and most of the side effects are mild and transient; however, reactions such as hypersensitivity, induction of infection, and autoimmunity do occur. The rarity and subacute presentation of post-vaccination autoimmune phenomena means that ascertaining causality between these events can be difficult. Moreover, the latency period between vaccination and autoimmunity ranges from days to years.¹²

Experimental animal model, in which the causal relation between vaccines and autoimmune findings has been examined: in healthy puppies immunized with commonly given vaccines, a variety of autoantibodies have been documented, but no autoimmune illness was found. The findings could also represent a polyclonal activation (adjuvant reaction).

The mechanisms of autoimmune reactions following immunization have not been elucidated. As mentioned above, one of the possibilities is molecular mimicry, when a structural similarity exists between some viral antigen and self-antigen.¹¹ Various environmental factors in the pathogenesis of immune mediated diseases are well established, of which factors entailing an immune adjuvant activity, such as infectious agents, silicone, aluminum salts, and others were associated with defined and non-defined immune mediated diseases, both in animal models and in humans. In recent years a syndrome entitled ASIA (Autoimmune Syndrome Induced by Adjuvants), comprising four conditions (siliconosis, the Gulf war syndrome, macrophagic myofasciitis syndrome, and post-vaccination phenomena), has been linked with previous exposure to an adjuvant.¹⁴ Further epidemiological studies are needed to obtain more data for the issues raised above.

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