Prevention of lymphocytic thyroiditis and insulinitis in diabetes-prone BB rats by the depletion of macrophages

Dear Sir,

The article by Yoon's group [1] on the prevention of autoimmunity in the BB rat by administration of silica was a useful confirmation and extension of the studies by Oschilewski et al. [2] in the BB rat using silica and electron-microscopy.

However, the authors did not take the opportunity to discuss the critical question of whether thyroiditis and insulinitis are initiated through antigen presented conventionally or "aberrantly" in conjunction with class II molecules expressed on the endocrine cells themselves [3]. The prevention of the autoimmune response by the inactivation of conventional antigen presenting cells might suggest that "aberrant" presentation of endocrine cell immunogens was unimportant in the initiation of autoimmunity.

In their Summary and in their Discussion, the authors assume that the initiating steps taken by macrophages are aimed at autoantigens. With this group's recent work on cytomegalovirus [4] and other evidence to suggest that so-called autoimmunity may in fact be a response to foreign antigen [5, 6], one wonders why it is necessary to so restrict the nature of the primary immunogen.

Yours faithfully,
T.J. Wilkin

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The initial step in the development of organ specific autoimmune disease in BB rats

Dear Sir,

We appreciate Dr. Wilkin's valuable comments on our paper [1]. Due to the space limitation of a short communication, we did not discuss in detail the involved possible hypothesis and mechanism that Dr. Wilkin pointed out. I would like to discuss two main points related to the initial step in the development of organ specific autoimmune disease in BB rats on the basis of Dr. Wilkin's comments.

First comment on the critical question of whether thyroiditis and insulinitis are initiated through "antigen presented conventionally" or "aberrantly expressed class II molecules on endocrine cells":

The aberrant expression of Ia antigen on endocrine cells has been implicated in the pathogenesis of autoimmune endocrine disorders including Type 1 (insulin-dependent) diabetes. This is an attractive hypothesis since Ia antigen expressed on the target cell surface may initiate an immune response against self without help of other antigens. However, there has been no definite proof that aberrant expression of Ia antigen on BB rat B cells precedes inflammatory infiltrates [2, 3]. In fact, recent electron microscopic examination disclosed that most Ia+ cells in pancreatic islets are nonendocrine mononuclear cells [4].

Recently, we have carefully re-evaluated this hypothesis using silica-treated BB rats. A total of 26 diabetes-prone BB rats, divided into two groups (13 animals per group), were used for this study. We injected silica, at a dose of 100 mg/kg body weight, i.p. every 10 days from the age of 40 to 80 days into the animals in Group I. The animals in Group II did not receive silica and were used as controls. The Group II animals were killed at the age of 85 days and the frozen pancreatic sections were stained with MRC-OX-6 antibody by indirect immunofluorescent techniques. Numerous Ia+ mononuclear cells were found in the islets (148 ± 127 cells/islet section). When the serial sections were fixed with cold acetone and stained with either fluorescein or rhodamin-labelled anti-insulin antibody, none of the Ia+ cells were stained indicating that Ia+ cells were not insulin-containing B cells. The Group I animals were also killed at the age of 90 days and the frozen pancreatic sections were stained with MRC-OX-6 antibody as described above. Ia+ cells were rarely found in the islet (0.23 ± 0.42 cells/islet section). When the serial sections were fixed with cold acetone and stained with fluorescein or rhodamin-labeled anti-insulin antibody, none of the Ia+ cells were stained but most of Ia negative cells were strongly stained in the islets, indicating that islet cells preserved by treatment with silica did not express Ia antigens. Our experimental data do not support the hypothesis that aberrant Ia antigen expression on the B cells initiates autoimmunity. In contrast, Ia antigen expression in islet cells from diabetic-prone BB rats could be due to the presence of macrophages and/or lymphocytes.

Our experimental data are supported by the recent report from Kabet et al. [5]. They showed that, during the initial phase of thyroiditis in BB rat, the number of thyroid dendritic cells increased and, throughout the process of autosensitisation, thyrocytes stayed negative for Class II MHC determinants. These data revealed that Class II antigen expression on thyrocytes is not prerequisite for the development of thyroiditis in the BB rat [5]. Of course, it is quite possible that expression of Class II molecules on target cells, possibly by the influence of secretory products of lymphocytes and/or macrophages, would contribute to the amplification of the immune response. However, "aberrant" expression of Class II molecules on endocrine cells is unlikely to be the initiating event of autoimmune diabetes in BB rats.

Second comment on the restriction of the nature of the primary immunogen in the initiation of organ specific autoimmune disease in BB rat:

One of our hypotheses reported in our previous paper is that presentation of autoantigens on the target cells by antigen-presenting cells would be the initial step in the development of organ-specific autoimmune disease in BB rats. However, we do not exclude other possibilities. Our speculation on the presentation of autoantigen on the target cells by antigen-presenting cells comes from experimental results showing that (a) the major population of infiltrated cells during the initial stage of insulinitis is macrophage [6] and (b) the depletion of macrophages results in the inhibition of the autoimmune process in BB rats and NOD mice [1, 7, 8]. The possibility for the presence of autoantigen or foreign antigen and the possible role of the antigen in the initiation of organ-specific autoimmune disease in BB rats have been described in our recent publications [6, 8].

Yours sincerely,
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