Lymphocyte subsets and ocular inflammation: future prospects for immune deviation therapy?

In the early 1960s the cells of the immune system were simply divided into the B cells and the T cells. B cells were responsible for antibody production whereas T cells produced a wide variety of soluble factors designated as lymphokines. Subdivision of T cells became possible with the development of the technique to produce monoclonal antibodies against a wide variety of proteins including cell surface components. This led to a classification of T cells based on the presence of the so called markers CD4 or CD8. Analysis of these two types of T cells resulted in a functional separation of T cell populations into CD4 positive T cells providing a helper function for the differentiation of antibody producing B cells and CD8 positive T cells which were shown to kill target cells and thus were named cytotoxic T cells. Recently it has become clear, however, that such a strict functional division is not valid anymore and that certain properties of CD4 and CD8 T cells show an overlap. CD4 cells interact with antigen presenting cells via MHC class II (HLA-DR) molecules, whereas CD8 cells recognise antigen in the context of MHC class I (HLA-A, B, or C).1

It soon appeared that the membrane markers were not sufficient to characterise the various functions of T cells, and a further breakthrough came from the functional and molecular characterisation of the many lymphokines produced by these cells. In the late 1980s Mosman and Coffman2 presented a division of the T helper cells into Th1 and Th2 populations, depending upon their lymphokine (cytokine) production profile. The balance between a Th1 or a Th2 response is of great importance in the outcome of the immune defence mechanisms employed to combat infectious disease, and may also influence the occurrence of allergic (conjunctivitis) or autoimmune disease.3 This has been nicely illustrated in a mouse model of leishmaniasis whereby mouse strains that react to this infection with a Th2 type response succumb, whereas animals showing a Th1 reactivity survive.

Deviation of the Th2 response in these mouse strains to a Th1 response leads to protection against the Leishmania parasite.

A large body of evidence now shows that a Th1 response is primarily responsible for a delayed type hypersensitivity response and is characterised by a high production of interferon γ and IL-2 and a low or absent release of IL-4 (see Table 1). The Th2 cells, on the other hand, produce large amounts of IL-4 and IL-5 and play a key role in humoral immunity including the IgE response. The cytokines produced by the Th2 cells have a deactivating effect on macrophages and thus counteract the tissue destruction which is characteristic of the Th1 response. An exaggerated Th2 response is associated with allergic disease and immunoglobulin mediated autoimmune, whereas a Th1 response is held responsible for contact hypersensitivity and certain autoimmune diseases such as rheumatoid arthritis. It has been speculated that several organ specific autoimmune diseases are caused by interferon γ producing Th1 cells. These findings have led to new approaches for the immunotherapy of inflammatory autoimmune disease which are based on a deviation of the harmful Th1 response towards an immunosuppressive Th2 response.

Our knowledge concerning the factors that regulate the balance between Th1/Th2 is rapidly expanding. Th2 cell proliferation is inhibited by interferon γ and Th1 cell proliferation is suppressed by IL-4. Other cytokines that play a regulatory role are IL-10 and IL-12 which are both produced by antigen presenting cells. IL-10 supports the Th2 response and IL-12 the Th1 response. The microenvironment may dictate whether an antigen presenting cell produces IL-10 or IL-12 thus leading to either a Th1 or a Th2 response. Administration of antigens via the mucosal immune system is thought to induce a Th2 response and so called oral tolerisation strategies are currently being explored to treat a number of putative autoimmune diseases.

Lymphocyte subsets and ocular inflammation

Table 1  Properties of the Th1 and Th2 immune response

<table>
<thead>
<tr>
<th>Characteristic cytokine</th>
<th>Th1</th>
<th>Th2</th>
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<tbody>
<tr>
<td>Interferon γ</td>
<td>IL-4</td>
<td></td>
</tr>
<tr>
<td>IL-12</td>
<td>IL-5</td>
<td></td>
</tr>
<tr>
<td>IL-2</td>
<td>IL-6</td>
<td></td>
</tr>
<tr>
<td>TNF α/β</td>
<td>IL-10</td>
<td></td>
</tr>
<tr>
<td>Action</td>
<td>Delayed type hypersensitivity</td>
<td>Immediate type hypersensitivity</td>
</tr>
<tr>
<td></td>
<td>Complement binding antibodies</td>
<td>Non-complement binding antibodies</td>
</tr>
<tr>
<td>Beneficial effect</td>
<td>Intracellular organisms (leprosy, Leishmaniasis, Toxoplasma)</td>
<td>Suppression autoimmunity (arthritis, uveitis?)</td>
</tr>
<tr>
<td>Harmful effect</td>
<td>Autoimmune disease</td>
<td>Allergic disease (asthma, allergic conjunctivitis)</td>
</tr>
<tr>
<td></td>
<td>Intraocular inflammation</td>
<td>Intracellular organisms</td>
</tr>
</tbody>
</table>

From healthy donors. By analysing the cytokine production profile they showed that these cells were high producers of interferon γ and IL-2, but did not release IL-4, which allowed them to draw the conclusion that these cells belonged to the Th1 type of T lymphocytes. Of interest is their observation that the generated cytotoxic T cell lines all carried the CD4 marker, which was originally not considered to be associated with target killing properties. Since CD4 cells can only recognise antigen when it is presented to them via HLA class II molecules this may explain the strong association observed between HLA-DR4 and VKH.

Ultimate proof of the role of the Th1 type autoimmune reactivity against melanocytes in VKH and, possibly other uveitis entities, will come from the analysis of the specificity and phenotype of T cells obtained from the inflamed ocular tissue or its surrounding media, an approach that is currently being undertaken in ocular toxoplasmosis. If this also supports a major role for interferon γ producing Th1 cells, further therapeutic strategies may be developed to deviate this response to a more benign interleukin 4 producing Th2 phenotype.

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