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Immunological Responses in the Eyelid and Orbit

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Summary
Immunological responses in the eyelid and the orbit are reviewed:

(1) A local immune response is dependent on the presence of lymphoid tissue in an organ. Lymphoid tissue is found in the conjunctival fornices and in the lacrimal gland but not in the orbit. The eyelids also have lymphatic drainage into the local lymph nodes. A local immune response is found in the palpebral conjunctiva and in the lacrimal gland, measureable both as immunoglobulin or specific antibody levels in tears or as immunoglobulin producing cells within the tissue. No local immunity has been demonstrated in the orbit.

(2) The other type of immune response found in the eyelids, the lacrimal gland and the orbit is the involvement of these tissues in systemic diseases. Systemic diseases with an immunological basis, which affect the above mentioned tissues are: atopic diseases of the skin, autoimmune diseases, immunodeficiency diseases and lymphoproliferative diseases.

(3) Finally, it is possible that the extraocular muscles and the lacrimal gland have tissue specific antigens and therefore may be target tissues for organ specific autoimmune processes.

The initiation of an immune response to an infectious agent depends on the presence of lymphoid tissue at the site of infection. Both the conjunctiva and the lacrimal gland contain the necessary lymphoid elements for the initiation of an immune response.[1,2] The foreign agent must first be picked up by an antigen presenting cell and its antigens processed and presented to a T lymphocyte. The T lymphocytes are cytotoxic, destroying the foreign agent directly, or possess helper or suppressor potential. B lymphocytes can also recognise the antigen and if an appropriate T cell signal is also received the B cell will transform into a plasma cell which produces antibody [for details see Roitt *et al*[3]]. Until now it has been impossible to detect lymphoid tissue or lymphatic drainage to a lymph node in the orbit.

The immune system is meant to protect the host but sometimes harmful reactions are also observed due to overreaction or misrouting (hypersensitivity), lack or breakdown of tolerance to one's own antigens (autoimmunity) or breakdown in T-cell control (autoimmunity).

The involvement of the eyelids, the lacrimal gland and the orbit in beneficial and pathological immune responses is presented.

(1) Local Immune Response in Eyelids and Lacrimal Gland

The eyelids and the lacrimal gland participate in two types of immune response: the innate and the adaptive immunity. Apart from the mechanical removal of foreign particles by blinking, the skin of the eyelids and the conjunctiva are an effective barrier to most infectious agents and the lacrimal gland participates in this system by producing lysozyme and lactoferrin in tears. The resis-

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tance conferred by the innate immune system is not improved by repeated infection. In the adaptive immune response repeated infection confers resistance and the principle role is played by the lymphocytes. The palpebral conjunctiva and the lacrimal gland are considered part of the mucosa associated lymphoid tissue.[4] This secretory immune system serves as the principle line of defence against antigenic challenge at mucosal surfaces. The protective function is mediated primarily through secretory IgA (sIgA), which is the predominant antibody in external secretions.

The local immune response of the lacrimal gland and the palpebral conjunctiva is measurable as immunoglobulin levels in tears or as plaque forming cells in the tissues itself. In patients with herpes simplex keratitis, anti-herpes simplex virus (HSV) antibodies were detected in tears.[5,6] The production of these antibodies was shown to be local since they were found only during the active phase of the infection, they were of sIgA type which is not present in serum, they were not found in the tears of seropositive healthy controls without ocular disease and leakage of other serum proteins (albumin, transferrin or measles antibody) was not observed. Other examples of local production of immunoglobulins are found in patients with contact lens giant papillary conjunctivitis, where elevated levels of IgE and IgG were found in tears in comparison with both normal controls and contact lens wearers without symptoms.[7] Patients with vernal conjunctivitis were found to have elevated IgG levels in their tears, the antibody was shown to be specific for rye grass or ragweed.[8]

Attempts to induce local immunity in experimental animals by antigen instillation into the conjunctival sac were only successful when high doses of antigen and frequent application were employed or when lower doses were used in presensitised recipients.[9,10] Both humoral and cellular immunity were found, and a response was also observed in the regional lymph node.

The presence of lymphocytes in the interstitium of the lacrimal gland is probably the result of antigenic stimulation, since rats which have been reared germfree have 5 to 8 fold less plasma cells in their lacrimal glands than their conventionally reared sibs.[11] When these germ free rats were subsequently exposed for 4 weeks to a conventional environment, the number of plasma cells in their lacrimal gland was indistinguishable from that in conventionally raised rats. In humans, Damato *et al.*[12] have shown a tremendous heterogeneity in the presence of lymphocytes within the lacrimal gland. In 29 out of 99 lacrimal gland autopsy specimens (age range 7 to 93 years) no lymphocyte infiltrates were found at all.

(2) Systemic Immunological Diseases Affecting the Eyelids, the Lacrimal Gland and the Orbit

The eyelids are involved in allergic and autoimmune reactions which affect the skin: acute and chronic allergic conjunctivitis and blepharitis, vernal conjunctivitis, atopic eczema, pemphigus, pemphigoid, vitiligo, psoriasis, Stevens-Johnson syndrome, contact dermatitis and hereditary angioneurotic oedema. These diseases are discussed in detail elsewhere (White and Wright).

Other systemic immunological diseases which affect the eyelids, the lacrimal gland and/or the orbit: are lymphoproliferative diseases, Wegener's granulomatosus, sarcoidosis and myasthenia gravis.

Diseases such as Graves' ophthalmopathy and Sjögren's syndrome are certainly part of systemic autoimmune diseases but possibly also have an organ specific component and will therefore be presented separately.

Lymphoproliferative diseases

Lymphoid proliferations comprise 10 to 15 per cent of all space filling lesions of the orbit. Histopathologically the differentiation between some benign and malignant lesions may present a problem. The use of immunological techniques to determine cell surface markers has therefore become indispensable.[13,14,15] From our study it appeared that patients in the fourth or fifth decade of life with a history of pain, oedema, epiphora, double vision and ptosis, with a mass localised in the anterior part of the orbit, are more likely to have a benign lymphoproliferative process. A biopsy should always be taken and submitted for cytological analysis of imprint

smears, routine histology and immunohistochemistry to determine the monoclonal or polyclonal nature of the lymphocytes involved. Cell membrane marker analysis with monoclonal antibodies permits classification into T and B cells. T cells can be subdivided into helper cells and suppressor cells. Most orbital lymphomas are however, of B cell origin and these may be classified on the basis of the type of immunoglobulin light chain which they carry on their cell membrane. Polyclonal proliferations are characterised by the presence of T cells and two types of light chains on the B cells in the tumour.

In our patients with non Hodgkin lymphoma (NHL) of the orbit, systemic disease appeared to be rare. Jakobiec[16] associates well differentiated monoclonal lesions with a favourable prognosis and cytological irregularities with systemic spread.

It remains puzzling however, that isolated benign and malignant lymphoproliferative lesions are found in a tissue devoid of lymphoid tissue and lymphatic drainage. Experimentally, both the occurrence of pseudolymphomas and the lack of local immune response in the orbit have been described by Liu *et al*[17] in the following experiments. BCG or Ovalbumin (OA) were bound to Sepharose beads to immobilise the antigen. These beads were then injected into the right, respectively left, orbit of guinea pigs which had been systemically immunised with BCG 4 weeks previously. Granuloma formation was seen around the BCG-beads with multinucleated giant cells, epitheloid cells, lymphocytes, macrophages and focal necrosis, whereas only some minimal inflammatory changes were seen around the OA-beads with predominantly polymorphonuclear cells. These experiments show that an immune reaction is possible in the orbit but only because BCG-sensitised lymphoid cells recirculate and encounter the immobilised antigen within the orbital tissue. No local sensitisation occurs, within the 8 days of the experiment, as can be seen by the lack of a specific reaction towards OA-beads.

Although this experimental model offers a possible explanation for the development of pseudolymphomas in the orbit, clinically no sensitising agents have been found as yet. The development of lymphomas in the orbit is difficult to explain in the absence of systemic disease but could be attributed to the malignant mutation and subsequent uncontrolled growth of one lymphocyte involved in an inflammatory process.

Myasthenia gravis

Myasthenia gravis (MG) is a systemic disease, which may affect the ocular muscles first, resulting in diplopa and ptosis. Anti-acetylcholine (ACh)-receptor antibody is implicated in this disease[18] and has been shown to be pathogenic in mice.[19] Deposition of IgG and complement on the post-synaptic folds of the muscle results in increased ACh-receptor turnover and blockage of ACh binding. Garlepp *et al*[20] suggest that restricted ocular-MG and generalised -MG have different pathogenetic mechanisms. In ocular-MG anti-ACh receptor antibodies were found less frequently but anti-thyroid antibodies were more common than in generalised-MG, furthermore female predominance was not seen in ocular-MG.

Wegener's granulomatosus

Wegener's granulomatosus is a necrotising vasculitis of the arteries and veins. Half of the affected patients have ocular involvement, the orbit being the site of predilection.[21,22] The disease is thought to be immunologically mediated, by a cellular reaction, but no initiating agent is known.

Sarcoidosis

Sarcoidosis, a disease of unknown cause, is characterised by the formation of noncaseating granulomas. The granulomas are regarded as reactions to unidentified infectious agents or allergens. Characteristic of the patients with systemic disease is the decrease in delayed type hypersensitivity but this is not always true for patients with localised disease. Granulomas are found predominantly in the conjunctiva but also in the lacrimal gland.[23]

(3) Organ Specific Immunological Diseases Affecting the Lacrimal Gland and the Orbit

Graves' ophthalmopathy

The clinical findings in Graves' ophthalmopathy (Bleeker, this issue) are the consequence

of inflammation in the orbital tissues which leads to swelling of the extraocular muscles, the eyelids and the conjunctiva. Histological examination of the swollen muscles[24] shows extensive infiltration with lymphocytes, mast cells and plasma cells. The muscles are oedematous and between the fibres deposition of mucopolysaccharides, products of fibroblast activation, are seen. These findings and the close, but not absolute, association with a known autoimmune disease (thyrotoxicosis) suggests an autoimmune aetiology for this disease. Four different mechanisms for damage to orbital tissue have been proposed.

(1) Graves' ophthalmopathy may be initiated by the reaction of circulating antithyroglobulin autoantibodies or sensitised cells[25] with thyroid derived thyroglobulin or thyroglobulin-like antigens in orbital tissues giving rise to an immune complex initiated immune response.[26]
(2) Graves' ophthalmopathy may be initiated by autoantibodies to thyrotropin stimulating hormone (TSH)-like receptors in orbital tissues. The immune response may result in cell destruction or cell stimulation. In the latter case the antibody mimics the function of a hormone.[27,28]
(3) Orbital tissues and the thyroid have common antigens, therefore autoimmunity to thyroid antigens also effects the tissues of the orbit.[29]
(4) Finally, Graves' ophthalmopathy may be an organ specific disease, independent of thyroidal disease. Target antigens for the specific antibodies may be the extraocular muscles, the orbital connective tissue or possibly the lacrimal gland. Microscopically the extraocular muscles show two kinds of patterns: the 'fibrillenstruktur' which is also found in the peripheral musculature and the 'felderstruktur' which appears to be typical for extraocular muscles.[30] The latter could possibly be organ specific tissues, however, it is not certain that the difference in microscopical appearance is reflected as an antigenic difference between skeletal muscles and extraocular muscles. Antibodies to extraocular muscles have already been detected,[31,32,33] but not proven to be pathologic. Not all investigators agree on the restriction of this antigen to extraocular muscles only.[34] Some evidence has also been found for cellular immunity to orbital antigens[35] or eye muscles[36] in Graves' ophthalmopathy patients. Analysis of peripheral blood lymphocyte subsets does not support a systemic immunologic dysregulation,[37,38] therefore a local T cell disbalance (immune compartmentlisation) may play a role here.

Sjögren's syndrome

The lacrimal gland of patients with Sjögren, syndrome shows marked lymphocytic infiltration and there is also focal dilatation of the ducts and intraductal proliferation. The complications of the disease are due to deficiency of tears as a result of acini destruction by the inflammatory process. In biopsies taken from patients, membrane marker analysis of the inflammatory cells shows that there are clusters of B lymphocytes surrounded by scattered T lymphocytes.[39]

The pathogenesis of the disease remains uncertain but there seem to be some organ specific tissue antigens in the lacrimal gland as demonstrated by Liu *et al*[40] in rats. Injection of lacrimal gland extract in complete Freunds' adjuvant and with Pertussis vaccine resulted in an autoimmune dacryoadenitis. The response appeared to be specific since no lymphocyte infiltration was found in other organs. In another potential model for Sjögren's syndrome, the systemic nature of the disease is highlighted.[41] Mice which spontaneously develop an autoimmune connective tissue disease also develop lacrimal gland inflammatory infiltrates.

In conclusion, the immunological responses in eyelid and orbit have both host-protective and host-destructive effects and in that respect do not differ from responses elsewhere in the body. As may be expected local immunity is found only in the tissues which possess lymphoid tissue. The immunopathological effects observed are however, more marked than elsewhere in the body. This is probably mainly due to the particular anatomical features (Koornneef, this volume) and the high degree of specialisation of (peri-) orbital tissues.

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