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PLENARY ABSTRACT

The Current Understanding of the Aetiology of Oral Lichen Planus

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Overview

Oral lichen planus (OLP) is a relatively common chronic inflammatory disease of the oral mucosa affecting between 1-2% of the population. Clinically, it results in reticular white lesions that are usually bilaterally distributed on the oral mucosa. These lesions may be associated with areas of mucosal erosion and ulceration. Although the cause of OLP is not known, it is characterised by chronic, cell mediated, autoimmune damage to basal keratinocytes in the oral mucosa that are recognised as being antigenically foreign or altered. In most cases, however, the identity of the target antigen remains unknown. It is likely that cytokines released by the affected keratinocytes, and the associated inflammatory infiltrate, play a key role in the selective recruitment of the T-cell dominated infiltrate that characterises OLP, through their ability to induce adhesion molecule expression as well as further cytokine and chemokine release. In susceptible individuals, chronic presentation of antigen by basal keratinocytes may perpetuate the condition.

Cell Mediated Auto-immune Damage To Basal Keratinocytes

Histologically, OLP is characterised by a sub-epithelial band like infiltrate of T-cells (Walsh *et al*., 1990), disruption of the epithelial basement membrane and cell mediated autoimmune damage to basal keratinocytes. The keratinocytes may become the target of damage because they express foreign or altered self-antigen on their surface (Walsh et al., 1990). Evidence to support this hypothesis comes from graft-v-host disease where grafted T-cells may target oral mucosal keratinocytes, that are regarded as antigenically foreign, giving rise to lesions difficult to distinguish from OLP (Lodi *et al*., 2005, Thornhill, 2001).

Target Antigens

In idiopathic OLP, however, the nature of the auto-antigens targeted by T-cells is not known. To try and identify the nature of the antigens, T-cell receptor gene expression studies have been carried out on lesional T-cells. However, these studies have shown that OLP is unlikely to be caused by a single antigen (Thomas *et al*., 1997). More likely, it is the common outcome of a limited range of extrinsic antigens, altered self antigens or possibly a superantigen. Extrinsic antigens could come from a number of sources including food, bacterial flora and dental materials. Self antigens could be altered to appear foreign by haptenisation with other molecules. This probably explains the ability of some medicines and dental materials to induce lichenoid lesions in susceptible individuals (Scully *et al*., 1998). In amalgam induced lichenoid lesions, small molecular weight corrosion products and mercury salts that readily cross the epithelium probably act as haptens to alter the antigenicity of epithelial self-antigens (Thornhill, 2001). In hepatitis C related OLP, viral antigens expressed on the surface of oral keratinocytes could be the target of cytotoxic damage by T-cells (Lodi *et al*., 2005).

Whatever the source of the responsible antigen, it is likely that it will first be taken up by Langerhan's cells in the epithelium. Under the influence of tumour necrosis factor (TNF), released by surrounding keratinocytes or the inflammatory infiltrate, these Langerhan's cells will be induced to migrate to draining lymph nodes. Although, the number of Langerhan's cells present in the epithelium in OLP appears to be no greater than in normal oral mucosa, they are in a higher state of activation and the rate of trafficking between the oral mucosa and lymphoid tissue appears to be increased (Lodi *et al*., 2005, Thornhill, 2001). In the draining lymphoid tissue they present antigen to T-cells. Those that recognise the antigen will become activated and preferentially re-circulate through the oral mucosa (Walton et al., 1998).

The Role Of Cytokines, Chemokines And Adhesion Molecules

TNF, interferon-γ (IFN) and other cytokines (Lodi *et al*., 2005, Thornhill, 2001) released by the inflammatory infiltrate in OLP play an important role in recruiting these lymphocytes from the circulation to form the characteristic band-like sub-epithelial infiltrate. TNF and IFN induce the expression of addressin type adhesion molecules such as E-selectin and MadCAM-1 on the lining or blood vessels in the affected oral mucosa. This results in the selective recruitment of activated skin (CLA+) and gut ($\alpha_4\beta_7$+) homing lymphocytes into the inflammatory infiltrate of OLP (Brown et al., 1999, Walton *et al*., 1998). Both CLA+ and $\alpha_4\beta_7$+ T-cells are present in much higher numbers in the infiltrate than in peripheral blood. TNF and IFN also induce VCAM-1 expression and increased ICAM-1 expression on the endothelial lining of local blood vessels. The expression of both these adhesion molecules is necessary to facilitate the transmigration of adherent lymphocytes across the vessel wall and into the connective tissue (Thornhill, 2001).

Once they have left the blood vessels the directed migration of lymphocytes towards the epithelium is likely to be under the control of chemokines released by the epithelial cells. Oral keratinocytes are capable of secreting the T-cell specific chemokines RANTES and MCP-1 (Thornhill, 2001) and in OLP these are secreted in preference to the neutrophil specific chemokine IL-8. Together, these will serve to recruit the sub-epithelial band like infiltrate of T-cells that typifies OLP.

TNF and IFN also induce keratinocyte expression of ICAM-1 in OLP (Thornhill, 2001). This allows T-cells to adhere to the keratinocytes (Little *et al*., 2001) and facilitate intra-epithelial lymphocyte invasion. ICAM-1 expression may also support keratinocyte antigen presentation to T-cells and the killing of keratinocytes by cytotoxic T-cells and NK cells. Chronic antigen presentation by keratinocytes is likely to be responsible for perpetuation of OLP lesions.

The majority of intraepithelial T-cells and T-cells co-localising with basal keratinocytes in OLP are CD8+ while most T-cells in the connective tissue are CD4+. It is possible, therefore, that Langerhans cells and basal keratinocytes present antigen in the context of MHC class II to CD4+ helper T-cells that then secrete Th1 cytokines such as IL-2 and IFN. This in turn may help to activate cytotoxic CD8+ T-cells that recognise self or altered-self antigen on the surface of basal keratinocytes in the context of MHC class I and induce apoptosis.

T-cell Damage to Basal Keratinocytes

Antigen presentation by basal keratinocytes in association with ICAM-1 will result in keratinocytes being targeted for cell mediated immune destruction (Sugerman *et al*., 2000). Such damage is thought to be fundamental to OLP. Evidence for this comes from studies that have shown increased apoptosis of basal keratinocytes in OLP (Bloor *et al*., 1999). This damage is greatest in basal keratinocytes closely associated with areas of heavy inflammatory cell infiltrate, destruction of the basement membrane or T-cell invasion of the epithelium.

There are two mechanisms by which cytotoxic CD8+ T-cells could induce apoptosis in basal keratinocytes. The first involves cross linking of the keratinocyte cell surface molecule Fas by its ligand Fas-L expressed by cytotoxic T-cells and NK cells. In the second, the T-cell releases perforin that polymerises in the target cell membrane to form holes through which the T-cell secretes the enzyme granzyme B to breakdown intra-cellular proteins. At present it is not clear which process is responsible for basal cell damage in OLP and there is some evidence for both. Further evidence to support the cell mediated autoimmune damage of keratinocytes in OLP has been provided by the isolation of auto-reactive cytotoxic T-cell clones from lichenoid tissue, that exhibited cytotoxic activity for autologous keratinocytes (Sugerman *et al*., 2000).

TNF may also promote apoptosis in OLP. It induces differentiation and activation of cytotoxic T-cells, lymphokine activated killer cells and NK cells (Lodi *et al*., 2005, Thornhill, 2001). It is also anti-proliferative to keratinocytes and cytotoxic to them at high concentrations. Moreover, when released directly onto the surface of target cells by adherent cytotoxic T-cells, it may directly induce apoptosis or further enhance Fas/Fas-L mediated apoptosis.

Initiating Events And Individual Susceptibility To Lichen Planus

Currently, we know little about how OLP is initiated. Most studies of OLP have been restricted to looking at the established lesion and we know very little about the initiating events. However, knowledge of the antigenic role played by mercury salts in oral lichenoid reactions to amalgam, has allowed some work to be done looking at this. At sub-toxic concentrations $HgCl_2$ induces ICAM-1 expression by normal oral keratinocytes *in vitro* and increased binding of T-cells. In addition, $HgCl_2$ directly stimulated TNF production (Little *et al*., 2001). TNF production by oral keratinocytes is likely to set in motion Langerhan's cell migration, the release of chemokines such as RANTES and the expression of the vascular adhesion molecules etc necessary to recruit T-cells. It is possible that other antigens can also stimulate such changes. Whether this initial reaction progresses to the development of OLP, or switches off, probably depends on a

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number of factors. These include: the nature of the antigen, the ability of the individual to present the antigen (i.e. their HLA type), the presence of T-cells capable of recognising the antigen (T-cell receptor repertoire) and possibly the inheritance of a profile of cytokine and other gene polymorphisms that promote, rather than suppress, a cell mediated response to the antigen.

A growing body of evidence points to OLP being a chronic, cell mediated autoimmune disease process targeted against basal keratinocytes of the oral mucosa in susceptible individuals. As our understanding of the details of this process improves it will hopefully lead us to the development of more specific and effective therapies for this condition and greater knowledge of how the immune system functions in the oral mucosa both in health and disease.

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