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Despite recent advances in understanding the immunopathogenesis of oral lichen planus (LP), the initial triggers of lesion formation and the essential pathogenic pathways are unknown. It is therefore not surprising that the clinical management of oral LP poses considerable difficulties to the dermatologist and the oral physician. A consensus meeting was held in France in March 2003 to discuss the most controversial aspects of oral LP. Part 1 of the meeting report focuses on (1) the relationship between oral LP and viral infection with special emphasis on hepatitis C virus (HCV), and (2) oral LP pathogenesis, in particular the immune mechanisms resulting in lymphocyte infiltration and keratinocyte apoptosis. Part 2 focuses on patient management and therapeutic approaches and includes discussion on malignant transformation of oral LP. (Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2005;100:40-51)

Oral lichen planus (LP) is a chronic inflammatory condition that affects the oral mucous membranes with a variety of clinical presentations, including reticular, papular, plaque-like, atrophic, and ulcerative lesions. Oral LP affects from 0.1% to about 4% of the population, it is a disease of the middle-aged, and is more common among women.1 Although in searching for “lichen planus” more than 4000 papers could be found in the MEDLINE database by the end of 2002, many aspects of the disease are far from clear.

The authors met in France between 9 and 15 March 2003 to produce a consensus document based on the most recent literature published in peer-reviewed international journals. Some aspects of LP to be discussed were previously decided by the panel and assigned to each participant according to her or his field of expertise. During the meeting a report was presented by the author and discussed by the panel. Selected articles published after March 2003 were included by the authors in the reference list.

The aspects of oral LP discussed and presented in the current 2-part review include viral infection and immunopathogenesis (Part 1) and clinical management and malignant potential (Part 2).2
discussed elsewhere. Among the exogenous factors, several infective agents including some viruses and *Helicobacter pylori* have recently been linked with oral LP but sometimes on the basis of equivocal data. The present paper is focused on viral agents.

**Herpes viruses**

Almost all the 8 recognized human herpesviruses may give rise to oral lesions and 4 (Herpes simplex 1 [HSV-1], Epstein-Barr virus [EBV], Cytomegalovirus [CMV], Herpes virus 6 [HHV-6]) have been implicated in oral LP.

DNA from HSV-1, CMV, and HHV-6 has occasionally been found within oral LP tissue, mainly in erosive lesions and in small series. However, there are no significant differences in the prevalence of both immunoglobulin (Ig)G and IgM antibodies to CMV or HHV-6 between oral LP patients and controls. The receptor for EBV (CD21) is up-regulated in oral LP and a significantly higher optmetric density of EBV anti-earlier antigen (EA) IgG positivity has been reported in oral LP compared with controls, despite no difference in the frequency of both EBV IgG and IgM for EA and nuclear antigen-1 (EBNA). Using a nested polymerase chain reaction (PCR), between 0% and 50% of oral LP samples are found to be EBV-DNA positive, but it is unclear if EBV may be involved in the pathogenesis or is secondary to the oral LP lesions.

**HIV**

A few cases have been reported of lichenoid lesions in patients with HIV infection, but most of them could be related to zidovudine or ketoconazole therapy.

**Human papillomavirus (HPV)**

Human papillomaviruses (HPV) are small epitheliotropic DNA viruses that can induce hyperplastic, papillomatous, and verrucous squamous cell lesions in the stratified squamous epithelia. Studies to detect different HPV types in various oral mucosal diseases have been limited or have involved a small number of samples (Table I). The results appear to be equivocal, ranging from 0% to 100% of positive detection rate. It is extremely difficult to compare such results because of the many differences in inclusion criteria, clinical features (erosive vs nonerosive lesions), sampling of material (biopsies or brushing), preparation methods (fresh, frozen, or fixed), geographic differences, and methods adopted. Since highly sensitive techniques such as PCR may cause false-positive reactions, positive results in the literature should be viewed with caution. In fact, detection of HPV-DNA does not prove a casual relationship, since its presence in the lesional tissue may be casual or result from the disease process or immunosuppressive therapy, as shown by a recent case report of HPV reactivation following treatment of penile erosive LP.

**Hepatitis viruses**

The frequent association of LP with chronic liver disease (CLD) is well documented, at least in Mediterranean patients with oral LP, whereas prospective studies of Scandinavian and British oral LP patients have failed to show any significant correlation with liver diseases. The risk of chronic liver disorders in LP patients appears to be independent of age, sex, and alcohol consumption, or a positive hepatitis B surface antigen (HBsAg) reaction.
are also few reports of mainly skin lichenoid eruptions following administration of different hepatitis B virus (HBV) vaccines. Nevertheless, most patients with LP and CLD are not HBV-infected and the recently discovered viruses, hepatitis G virus and transfusion-transmitted virus, are not often associated with LP. In addition, various hepatic conditions such as Wilson’s disease, haemochromatosis, primary sclerosing cholangitis, and alpha-1-antitrypsin deficiency have rarely been related to LP, and the association of LP with primary biliary cirrhosis is mostly due to the administration of penicillamine treatment.

**Hepatitis C virus**

Since the first report in 1991, more than 80 papers worldwide have suggested an association between LP and hepatitis C virus (HCV) infection, among them numerous controlled studies (Table II). HCV-associated hepatic disease may precede LP onset or may be diagnosed together with it. To date, 36 studies have analyzed the prevalence of HCV infection among LP patients. In a recent systematic review including controlled studies, the proportion of HCV-positive subjects was higher in the LP group compared with controls in 20 of the 25 studies. The odds ratio (OR) of the pooled data from all studies was 4.80 (95% Confidence Interval [CI]: 3.25-7.09), showing a statistically significant difference in the proportion of HCV seropositive subjects among LP patients, compared with controls. When OR was calculated for oral LP patients only, it did not change substantially, whereas increased considerably in the studies from the Mediterranean.

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**Table II. Prevalence of hepatitis C virus infection in patients affected by lichen planus**

<table>
<thead>
<tr>
<th>Country</th>
<th>Reference</th>
<th>Study group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>LP</td>
<td>HCV+</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(n)</td>
<td>(%)</td>
</tr>
<tr>
<td>Brasil</td>
<td>Issa et al 1999</td>
<td>34*</td>
<td>5.9</td>
</tr>
<tr>
<td></td>
<td>Figueiredo et al 2002</td>
<td>68**</td>
<td>8.8</td>
</tr>
<tr>
<td>Egypt</td>
<td>Ibrahim et al 1999</td>
<td>43</td>
<td>20.9</td>
</tr>
<tr>
<td>France</td>
<td>Cribier et al 1994</td>
<td>52</td>
<td>3.8</td>
</tr>
<tr>
<td></td>
<td>Dupin et al 1997</td>
<td>102**</td>
<td>4.9</td>
</tr>
<tr>
<td>Germany</td>
<td>Imhof et al 1997</td>
<td>83</td>
<td>16</td>
</tr>
<tr>
<td>Italy</td>
<td>Rebora 1994</td>
<td>56</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>Carrozzo et al 1996</td>
<td>70**</td>
<td>27.1</td>
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<tr>
<td></td>
<td>Serpico et al 1997</td>
<td>100**</td>
<td>32</td>
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<tr>
<td></td>
<td>Migonmna et al 1998</td>
<td>263**</td>
<td>28.8</td>
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<tr>
<td>Japan</td>
<td>Tanei et al 1995</td>
<td>45</td>
<td>37.8</td>
</tr>
<tr>
<td>Nepal</td>
<td>Garg et al 2002</td>
<td>86^1</td>
<td>0</td>
</tr>
<tr>
<td>Nigeria</td>
<td>Daramola et al 2002</td>
<td>57</td>
<td>15.8</td>
</tr>
<tr>
<td>Spain</td>
<td>Gimenez-Arnau et al 1995</td>
<td>25</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td>Sanchez-Perez et al 1996</td>
<td>78</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Bagan et al 1998</td>
<td>100**</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>Gimenez-Garcia et al 2003</td>
<td>101</td>
<td>8.9</td>
</tr>
<tr>
<td>Turkey</td>
<td>Ilter et al 1998</td>
<td>72</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Kirtak et al 2000</td>
<td>73</td>
<td>6.8</td>
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<tr>
<td></td>
<td>Erk et al 2001</td>
<td>54^4</td>
<td>12.9</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>Ingafou et al 1998</td>
<td>55**</td>
<td>0</td>
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<td></td>
<td>Tucker et al 1999</td>
<td>45</td>
<td>0</td>
</tr>
<tr>
<td>United States of America</td>
<td>Bellman et al 1995</td>
<td>30</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>Chuang et al 1999</td>
<td>22</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>Beaird et al 2001</td>
<td>24</td>
<td>17</td>
</tr>
</tbody>
</table>

NA, not available.

*27% of the patients had oral lesions.

**100% had oral lesions.

***Prevalence data taken from the general population of São Paulo.

^1only 19 patients were tested.

^254.3% had cutaneous lesions, 23.9% had mucocutaneous lesions and 21.9% had oral lesions.

^3No significant difference with the control groups.

^458.9% had cutaneous lesions, 40.7% had mucocutaneous lesions and 20.4% had mucosal oral, genital lesions.

^5Different significant with the control groups.
basin and halved in studies from Northern Europe, becoming not significant. However, in studies from countries with highest HCV prevalence (Egypt and Nigeria), there were negative or not significant associations, suggesting that any LP-HCV association cannot be explained on the basis of high prevalence in the general population only. In addition, the few studies investigating the frequency of LP among HCV-positive subjects showed prevalences generally higher than expected (from 1.6% to 20%), independently from geographical origin. Interestingly, geographic heterogeneity in the prevalence of HCV infection was also found in patients with other HCV-related extrahepatic conditions, such as serum autoantibodies, porphyria cutanea tarda and lymphoma, possibly suggesting genetic differences among the populations studied. Indeed, HCV-related oral LP appears associated mainly with the HLA-DR6 allele in Italy and this could partially explain the peculiar geographic heterogeneity in the association between HCV and LP.

The putative pathogenetic link between LP and HCV is still under investigation but molecular mimicry between the virus and host epitopes is unlikely as well as viral factors such as genotype or viral load. The histological features of lesional tissue from HCV-positive or HCV-negative patients showed no substantial differences. The presence of HCV in oral LP lesional tissue has been object of several investigations (Table III). Both in situ hybridization and extractive PCR techniques revealed the presence of replicative intermediate HCV-RNA in LP specimens. Positive and negative strands were detected by PCR in 83% to 93% and 21% to 33% of oral LP tissue specimens, respectively. In addition, sequence analysis suggested a possible compartmentalization of HCV in the oral mucosa, although HCV may not cause direct damage to epithelial cells in oral LP lesions, since it was also found in normal mucosa. Two studies failed to detect HCV antigens in either frozen or formalin-fixed sections of cutaneous LP using various immunohistochemical techniques.

The lympho-mononuclear infiltrate typically found in oral lichen lesions suggests that the progressive destruction of the oral mucosa lining is due to local immune aggression. A recent study showed that HCV-specific CD4+ and/or CD8+ T lymphocytes can be found in the oral mucosa of patients with chronic hepatitis C and LP. CD4+ polyclonal T-cell lines were generated more efficiently from lichen-infiltrating lympho-mononuclear cells than from peripheral blood mononuclear cells from the same patients, suggesting a higher frequency of HCV-specific T cells in the oral compartment. T-cell clones present in the oral mucosa showed a different TCR-Vβ chain usage than those circulating in the peripheral blood, suggesting a specific compartmentalization at the site of the LP lesions. Furthermore, HCV-specific CD8+ T cells were present with higher frequency in mucosa tissue than in the blood and produced gamma interferon upon peptide stimulation. In view of the already mentioned demonstration of both forms of HCV-RNA in LP lesions, these results strongly suggest that HCV-specific T cells may play a role in the pathogenesis of oral LP; oral cell damage being the possible result of a direct immune aggression of epithelial cells expressing HCV antigens, possibly sustained by a cytokine environment favorable to trigger and maintain the lichenoid reactions.

**IMMUNOPATHOGENESIS OF ORAL LP**

A large body of evidence supports a role for immune dysregulation in the pathogenesis of oral LP, specifically involving the cellular arm of the immune system. The inflammatory infiltrate consists primarily of T cells and macrophages. Plasma cells are rarely seen and immune deposits are not characteristic.

**CD8+ T cells**

In oral LP, the majority of T cells within the epithelium and adjacent to damaged basal keratinocytes are activated CD8+ lymphocytes, while CD8+ T cells colocalize with apoptotic keratinocytes in oral LP lesions. T-cell lines and clones isolated from lichen planus lesions are more cytotoxic against autologous lesional keratinocytes than T-cell lines and clones from clinically normal skin of LP patients. The majority of cytotoxic clones from LP lesions are CD8+ and the majority of noncytotoxic clones are CD4+. The cytotoxic activity of CD8+ lesional T-cell clones is partially inhibited by anti-MHC class I monoclonal antibody. These data suggest that CD8+ lesional T cells may be activated, at least in part, by an antigen associated with MHC class I on basal keratinocytes and that activated CD8+ cytotoxic T cells may trigger keratinocyte apoptosis in oral LP (Fig 1). The nature of the antigen is uncertain.

**CD4+ T cells**

While the majority of intraepithelial lymphocytes in oral LP are CD8+, most lymphocytes in the lamina propria are CD4+. T-cell clones with helper activity and CD4+ T-cell clones that lack cytotoxic activity can be isolated from oral and cutaneous LP lesions, respectively. There are increased numbers of Langerhans cells (LCs) in oral LP lesions with up-regulated MHC class II expression. Keratinocytes in oral LP also express MHC class II antigens. Hence, CD4+ T cells may be activated, at least in part,
CD4+ T-cell activation and subsequent clonal expansion may underlie restricted T-cell receptor Vβ gene expression (especially Vβ22 and Vβ23) by infiltrating T cells in oral LP. High levels of antigen expression, CD40 and CD80 coexpression and interleukin (IL)-12 secretion by MHC class II antigen-presenting cells (APCs) in oral LP may promote a T helper-1 (Th1) CD4+ T-cell response with IL-2 and interferon-gamma (IFN-gamma) secretion. In support of this, recent studies identified IFN-gamma expression by T cells adjacent to basal keratinocytes in oral LP and IFN-gamma production and secretion by oral LP lesional T cells in vitro. Furthermore, both epidermal LCs and keratinocytes are capable of producing IL-12. Together, these data suggest that LCs or keratinocytes in oral LP present antigen associated with MHC class II to CD4+ helper T cells that are stimulated to secrete the Th1 cytokines IL-2 and IFN-gamma. CD8+ cytotoxic T cells may then be activated by the combination of (1) antigen associated with MHC class I on basal keratinocytes and (2) Th1 CD4+ T-cell–derived IL-2 and IFN-gamma. Activated CD8+ cytotoxic T cells then trigger basal keratinocyte apoptosis (Fig 1). Local production of IFN-gamma may maintain keratinocyte MHC class II expression, thereby contributing to oral LP chronicity.

Mast cells

Mast cell density is also increased in oral LP and approximately 60% of mast cells are degranulated compared with 20% in normal mucosa. Mast cell degranulation in oral LP releases a range of pro-inflammatory mediators such as tumor necrosis factor-alpha (TNF-alpha), chymase and tryptase. In oral LP, TNF-alpha may up-regulate endothelial cell adhesion molecule (CD62E, CD54, and CD106) expression that is required for lymphocyte adhesion to the luminal surface of blood vessels and subsequent extravasation.

**Table III. Hepatitis C virus (HCV) detection in lichen planus lesion I tissue**

<table>
<thead>
<tr>
<th>Country</th>
<th>Reference</th>
<th>Patients with oral lesions</th>
<th>Detection of HCV in specimens of lichen planus %</th>
<th>Technique</th>
<th>HCV antigens</th>
<th>Genomic stand n (%)</th>
<th>Negative strand n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Italy</td>
<td>Sansonno et al. 199559</td>
<td>NA</td>
<td>0/7 (0)*</td>
<td>IP</td>
<td>c22, c23, c100-3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mangia et al. 199060</td>
<td>0/19</td>
<td>0/19 (0)</td>
<td>PCR</td>
<td>-</td>
<td></td>
<td>10 (83.3)</td>
<td>4 (33.3)</td>
</tr>
<tr>
<td>Carrozzi et al. 200261</td>
<td>12/12</td>
<td>10/12 (83.3)</td>
<td>PCR, SA, PhA</td>
<td>-</td>
<td></td>
<td>3 (75)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pilli et al. 200262</td>
<td>4/4</td>
<td>3/4 (75)</td>
<td>PCR</td>
<td>-</td>
<td></td>
<td>13 (93)</td>
<td>3 (21.4)</td>
</tr>
<tr>
<td>Nagao et al. 200063</td>
<td>14/14</td>
<td>13/14 (93)</td>
<td>PCR, SA</td>
<td>-</td>
<td></td>
<td>3 (100)</td>
<td>3 (100)</td>
</tr>
<tr>
<td>Kurokawa et al. 200364</td>
<td>2/3</td>
<td>3/3 (100)</td>
<td>PCR</td>
<td>-</td>
<td></td>
<td>5 (100)</td>
<td>5 (100)</td>
</tr>
<tr>
<td>Spain</td>
<td>Arrieta et al. 200065</td>
<td>23/23</td>
<td>23/23 (100)</td>
<td>ISH</td>
<td></td>
<td>23 (100)</td>
<td>23 (100)</td>
</tr>
<tr>
<td>Lazarro et al. 200266</td>
<td>0/5</td>
<td>5/5 (100)</td>
<td>ISH, IP</td>
<td>core</td>
<td></td>
<td>5 (100)</td>
<td>5 (100)</td>
</tr>
<tr>
<td>Turkey</td>
<td>Erkek et al. 200167</td>
<td>4/5</td>
<td>4/5 (100)</td>
<td>PCR</td>
<td></td>
<td>5 (100)</td>
<td>NA</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>Roy et al. 200068</td>
<td>27/27*</td>
<td>0/27 (0)</td>
<td>PCR</td>
<td></td>
<td>0 (0)</td>
<td>NA</td>
</tr>
<tr>
<td>United State of America</td>
<td>Boyd et al. 199869</td>
<td>NA</td>
<td>0/25 (0)**</td>
<td>IP</td>
<td>NA</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

NA, not available; IP, Immunoperoxidase; PCR, polimerase chain reactions; ISH, in situ hybridization; SA, sequence analysis; PhA, phylogenetic analysis.

*All the patients were HCV seronegative.

**All but 2 of the patients were HCV seronegative.

Chemokines

Recent studies of cutaneous lichen planus identified basal keratinocyte expression of the CC chemokine MCP-1 and two CXC chemokines MIG and IL-10. IL-8, MCP-1, and GRO gamma were expressed by IL-1–stimulated human oral keratinocytes in vitro, while oral keratinocytes from oral LP patients secreted cytokines that up-regulated mononuclear cell adhesion molecule expression and transendothelial cell migration in vitro.
secrete chemokines attracting lymphocytes and other immune cells into the developing oral LP lesion (Fig 1).131,132

Various data implicate a role for T-cell-secreted regulation-upon-activation, normal T expressed and secreted (RANTES) in the pathogenesis of oral LP. T cells from oral LP express RANTES in situ.133 In vitro, oral LP lesional T cells express mRNA for RANTES and TNF-alpha stimulation up-regulates T-cell RANTES secretion.121 Mast cells express the CCR1 RANTES receptor in oral LP in situ.133 An unidentified factor in oral LP lesional T-cell supernatant, up-regulates human mast cell line (HMC-1) CCR1 mRNA expression in vitro.133 Oral LP lesional T-cell supernatant stimulates HMC-1 migration in vitro, while this effect is partially blocked by anti-RANTES antibody.133 The same supernatant stimulates HMC-1 degranulation in vitro with release of TNF-alpha and histamine. This effect is also blocked by anti-RANTES antibody.121

Hence, RANTES secreted by oral LP lesional T cells may attract mast cells into the developing oral LP lesion and subsequently stimulate mast cell degranulation. Degranulating mast cells release TNF-alpha, which up-regulates T-cell RANTES secretion. Such a cyclical mechanism may promote disease chronicity. Furthermore, RANTES induces expression of PI 3-kinase, which is involved in signal transduction for both chemotaxis and mitogen-activated protein kinase activation. PI 3-kinase activates Akt/protein kinase B that is an important component of the cell’s pro-survival machinery.134 Both T cells and mast cells express CCR1 in oral LP.133 Hence, in addition to stimulating mast-cell chemotaxis and degranulation, RANTES secreted by lesional T cells may also prolong the survival of inflammatory cells in oral LP and thereby contribute to disease chronicity.

Antigen identity

Antigens presented by MHC class II are processed through an endosomal cellular pathway. In contrast, antigens presented by MHC class I are processed through a cytosolic cellular pathway. Hence, the putative antigen presented by MHC class II to CD4+ helper T cells in oral LP may differ from that presented by MHC class I to CD8+ cytotoxic T cells (Fig 1). Alternatively, a single antigen may gain access to both the endosomal and cytosolic cellular pathways of antigen presentation. For example, some viruses encode proteins that are available for cytosolic processing and expression in association with MHC class I. These viral proteins are also present on the plasma membrane and therefore available for endosomal processing and expression in association with MHC class II.135 Whether 1 antigen or 2 different antigens are involved in the pathogenesis of oral LP, it is likely that antigen presentation to both CD8+ and CD4+ T cells is required to generate CD8+ cytotoxic T-cell activity (Fig 1).

The antigen may be a self-peptide, thus defining LP as a true autoimmune disease. The role of autoimmunity in disease pathogenesis is supported by many autoimmune features of oral LP including disease chronicity, adult onset, female predilection, association with other autoimmune diseases, occasional tissue type associations, depressed immune suppressor activity in oral LP patients, and the presence of autotoxic T-cell clones in lichen planus lesions.105,136,137 Keratinocytes in oral LP show up-regulated expression of heat shock protein (HSP),138-140 while oral LP lesional T cells proliferate in response to HSP in vitro.139 Keratinocyte HSP expression in oral LP may be an epiphenomenon associated with preexisting inflammation. Alternatively, keratinocyte HSP expression may be a common final pathway linking a variety of exogenous agents (systemic drugs, contact allergens, mechanical trauma, bacterial or viral infection) in disease pathogenesis. In this context, HSP expressed by oral keratinocytes may be autoantigenic. Susceptibility to oral LP may result from dysregulated HSP gene expression by stressed oral keratinocytes or from an inability to suppress an immune response following self-HSP recognition.

Antigen location

LP has a well-defined clinical distribution and there is a clear demarcation between lesional and nonlesional tissue. A possible explanation for this pattern of presentation is that keratinocytes express the LP antigen, but only at the lesion site. In other words, the clinical distribution of lichen planus is determined by the distribution of the antigen. Hence, an early event in LP lesion formation may be keratinocyte antigen expression or unmasking at the future lesion site induced by systemic drugs (lichenoid drug reaction), contact allergens in dental restorative materials or toothpastes (contact hypersensitivity reaction), mechanical trauma (Koebner phenomenon), bacterial or viral infection, or an unidentified agent. Following altered keratinocyte antigen expression, antigen-specific CD4+ and CD8+ T cells may be either (1) on routine surveillance in the epithelium and encounter the keratinocyte antigen by chance (“chance encounter” hypothesis) or (2) attracted to the epithelium by keratinocyte-derived chemokines (“directed migration” hypothesis). The “chance encounter” hypothesis is supported by findings of CD8+ T cells in normal human epidermis141,142 and basal cell degeneration in the absence of a dense inflammatory infiltrate in LP lesions.143 Conversely, the “directed
Migration hypothesis is supported by findings of constitutive chemokine receptor expression by naive T cells and a dermal T-cell infiltrate prior to the appearance of intraepithelial lymphocytes and epithelial damage in LP lesions. In this context, keratinocyte antigen expression and chemokine production are primary events in oral LP lesion formation, followed by keratinocyte apoptosis triggered by antigen-specific CD8+ cytotoxic T cells (Fig 1).

**Keratinocytolysis**

The mechanisms used by CD8+ cytotoxic T cells to trigger keratinocyte apoptosis in oral LP are unknown but possible mechanisms include (1) T-cell-secreted TNF-alpha binding TNF-alpha receptor 1 (TNF R1) on the keratinocyte surface, (2) T-cell surface CD95L (FasL) binding CD95 (Fas) on the keratinocyte surface, or (3) T-cell-secreted granzyme B entering the keratinocyte via perforin-induced membrane pores. All may activate the caspase cascade resulting in keratinocyte apoptosis (Fig 1). Serum TNF-alpha is elevated in oral LP patients while lesional T cells contain mRNA for TNF-alpha and secrete TNF-alpha in vitro. TNF-alpha is expressed by basal keratinocytes and by T cells throughout the subepithelial infiltrate in oral LP. The TNF-alpha receptor TNF R1 is expressed by basal and suprabasal epithelial cells in oral LP lesions. It is tempting to speculate that basal keratinocyte TNF-alpha expression in oral LP may be due to T-cell-secreted TNF-alpha binding epithelial TNF-alpha receptors. Hence, CD8+ cytotoxic T cells may secrete TNF-alpha that triggers keratinocyte apoptosis via TNF R1, although roles for granzyme B and Fas cannot be excluded at this stage.

**ORAL LP AND GRAFT VERSUS HOST DISEASE**

Graft-versus-host disease (GVHD) is a common serious complication following allogeneic hematopoietic stem cell transplantation (HSCT), and is a major cause of HSCT-related mortality. Acute GVHD occurs within the first 100 days of transplantation and comprises dermatitis, enteritis, and...
hepatitis with immunosuppression and cachexia. Chronic GVHD develops after day 100 and comprises an autoimmune-like syndrome comparable to ulcerative colitis, primary biliary cirrhosis, Sjögren’s syndrome, rheumatoid arthritis, and lupus-like disease with glomerulonephritis. The skin is a primary target in chronic GVHD and exhibits either a lichenoid eruption or sclerodermatous changes. Oral involvement occurs in 33% to 75% of patients with acute GVHD and up to 80% of patients with chronic GVHD. Oral mucosal GVHD resembles oral LP both clinically and histologically. As with oral LP, squamous cell carcinoma (SCC) may develop in oral and cutaneous chronic GVHD.

Most patients who undergo allogeneic HSCT receive stem cells from MHC-identical donors. In these patients, GVHD is initiated by donor T cells that recognize a subset of host peptides called minor histocompatibility antigens (miHAs). Although the antigen specificity of LP and mucocutaneous GVHD is probably distinct, it is likely that they share similar immunological effector mechanisms resulting in T-cell infiltration, epithelial basement membrane disruption, basal keratinocyte apoptosis, and clinical disease. Hence, research findings in one disease may give clues to the pathophysiology of the other. The role of TNF-alpha as a major effector molecule in GVHD has provided many important clues to the pathophysiology of the other. The role of TNF-alpha in GVHD has been confirmed in a number of experimental systems. Importantly, neutralizing anti-TNF-alpha antibodies have been shown to alleviate cutaneous and intestinal GVHD in both mice and humans. Blockade of the CD40-CD154 costimulatory pathway prevented GVHD following allogeneic HSCT. The role of the Fas apoptotic pathway in cutaneous GVHD is less clear. In one study, the transfer of cells lacking Fas-L (CD95L) reduced the severity of murine cutaneous GVHD. In another study, recipient mice deficient in Fas (CD95) showed increased severity of cutaneous GVHD. An MMP inhibitor was shown recently to alleviate GVHD pathology in the liver, intestine, and hematopoietic tissues and reduce weight loss and mortality in murine GVHD.

To further elucidate the cellular and molecular mechanisms of lichenoid cutaneous pathology, a recent study correlated detailed histopathology with global gene expression in a murine model of cutaneous GVHD. Cutaneous GVHD was induced by MHC-matched allogeneic HSCT, and ear skin was examined at days 7, 14, 21, and 40 posttransplantation. On day 7 post-HSCT, the skin appeared relatively normal with the only pathological changes consisting of rare dermal vessels cuffed by occasional lymphocytes and dermal mast cells containing clear cytoplasmic vacuoles indicating degranulation. By day 14, lymphocytes were diffusely present within the dermis and focally within the epidermal layer in association with early keratinocyte apoptosis. Gene expression patterns were consistent with early infiltration and activation of CD8+ T and mast cells, followed by CD4+ T, natural killer (NK), and myeloid cells. The sequential infiltration and activation of effector cells was accompanied by up-regulated expression of many chemokines and their receptors (CXCL1, 2, 9, 10; CCL2, 5, 6, 7, 8, 9, 11, 19; CCR1, CCR5), adhesion molecules (ICAM-1, CD18, Ly69, PSGL-1, VCAM-1), molecules involved in antigen processing and presentation (TAP1 and 2, MHC class I and II, CD80), regulators of apoptosis (granzyme B, caspase 7, Bak1, Bax, and Bcl2), and interferon-inducible genes (STAT1, IRF-1, IIGP, GTP, IgTP, Ifi202A). On day 14 and thereafter, the epidermal thickness exceeded twice that observed on day 7, and the superficial epidermis exhibited marked hypergranulosis. These observations correlated with up-regulated expression of keratins 5 and 6 (markers of keratinocyte proliferation) and small proline-rich proteins 2E and 1B (markers of keratinocyte differentiation). By days 21 and 40 post-HSCT, there were multiple foci of epidermal apoptosis and the entire dermal thickness was more than twice that observed on days 7 and 14. The latter observation was associated with up-regulated expression of IL-1β and TGF-β1 that stimulate fibroblast proliferation and matrix synthesis. Many acute phase proteins were up-regulated early in murine cutaneous GVHD including serum amyloid A2 (SAA2), SAA3, serpins a3g and a3n, secretory leukocyte protease inhibitor, and metallothioneins 1 and 2. These intriguing gene expression findings in murine cutaneous GVHD are currently under investigation in oral LP.

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