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CHRONIC INFLAMMATION: AN IMPORTANT FACTOR IN THE PATHOGENESIS OF ORAL CANCER

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Abstract
Chronic inflammation is recognized as a risk factor for many human cancers. Examples include inflammatory bowel diseases giving rise to colic adenocarcinoma, chronic gastritis with later adenocarcinoma and gastric lymphoma, chronic reflux of gastric acid and esophageal adenocarcinoma, and chronic cholecystitis and cholangiocarcinoma. Recent molecular studies on the relationship between solid malignancies and the surrounding stroma indicate that the chronic inflammatory process ***per se*** provides a cytokine-based microenvironment which is able to influence cell survival, growth, proliferation, differentiation, and movement. This stromal activated "soil" is considered to predispose and contribute to cancer initiation, progression, invasion, and metastasis. In the oral cavity some types of chronic inflammation have been clinically associated with the development of malignancy (e.g., oral squamous cell carcinoma [OSCC]), and molecular studies have recently investigated some of the components of the complex cascade of cellular and humoral factors of local chronic inflammatory processes which may potentially lead to carcinogenesis.

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Inflammation and cancer: historical overview

The association between chronic inflammation with a variety of epithelial malignancies has been recognized since the observation of Virchow,[1] who attributed tumor formation to chronic irritation in the 19th century. Examples of inflammatory processes linked with an increased cancer risk include inflammatory bowel diseases and colorectal adenocarcinoma, atrophic gastritis and gastric cancer, cholangiocarcinoma related to chronic cholecystitis, and esophageal carcinoma following reflux esophagitis.[2-4] As the concept of inflammation involves reaction to microbial agents, cancers caused by chronic infection, causing chronic inflammation, can be added to this list of examples. These infectious agents include *Helicobacter pylori* (chronic gastritis linked with adenocarcinoma of stomach and B-cell lymphoma), Epstein-Barr virus (non-Hodgkin lymphoma, Hodgkin lymphoma, nasopharyngeal carcinoma, and natural killer-T cell lymphoma), human papillomavirus (anogenital carcinoma and perhaps oropharyngeal carcinoma), hepatitis B or C virus (hepatocellular carcinoma), human herpesvirus 8 (Kaposi sarcoma), and schistosoma haematobium (squamous carcinoma of urinary bladder).[5,6]

The issue has been highly controversial as the infiltration of leukocytes in and around neoplastic tissue has been traditionally viewed as exerting an anti-tumor effect.[5] The concept of antineoplastic immunosurveillance as an important component of the immune system is supported by several data including the presence of functionally active human tumor antigen-specific T cells in patients with cancer, the correlation of T-cell infiltration of several human tumors with disease outcome,[7]

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the increased risk of certain malignancies in immunosuppressed individuals,[8-10] and the recent development of immunotherapeutic modalities (cancer vaccine) for some malignancies (e.g., malignant melanoma).[11] However, there is now substantial evidence to suggest the inflammatory cells and cytokines found in peritumoral stroma are more likely to contribute to tumor development, progression and metastasis than to mount an effective host anti-tumor response.[4] In brief, if genetic damage is the "match that lights the fire" of cancer, some types of inflammation may provide the "fuel that feeds the flames."[4] It is interesting to note these concepts were originally proposed at the end of the 19th century, when the biological and molecular bases of cancer were almost completely unknown.[4,12] Molecular medicine has now provided evidence that such a notion is indeed possible.

The new model of neoplasia and the "seed and soil" theory

Oncological research has generally focused upon the genetic changes that occur in cells as they progress from normal to malignant phenotype;[13] however, during the last few years a new picture has been emerging: throughout the entire process of cancer etiology, progression and metastasis, the microenvironment of the local host tissue can be an active participant.[14] Cancer and the surrounding inflammatory infiltrate can be "friends" rather than "foes." Neoplasia can be considered the expression of a "pathological imbalance of tissue-cell societies"[14] where the tumor cells interact with the surrounding microenvironment. This microenvironment consists of an insoluble extracellular matrix, a stroma composed of fibroblasts, vascular and local immune cells, and a milieu of cytokines and growth factors,[15] and is now known to influence many cell processes of tumor onset and progression, such as gene expression, growth, death, differentiation, migration, and invasion.[15]

This concept of cellular function being influenced by local surroundings applies to the process of metastasization. For many decades metastatic dissemination was thought to be the outcome of mechanical factors resulting from the anatomical structure of the lymphatic and vascular systems.[16] Recent clinical observations of cancer patients and studies in rodent models have revealed the pattern of metastases to specific organs may be independent of vascular anatomy, rate of blood flow, and the number of tumor cells delivered to each organ. These observations supported a theory introduced in 1889 by Paget,[12] who published the seminal "seed and soil" hypothesis explaining the non-random pattern of metastasis. He suggested certain tumor cells (equated to the "seed") have specific affinity for the milieu of certain organs (equated to the "soil") and concluded metastases formed only when the seed and soil were compatible.[17] It is now evident metastases can only develop in specific organs, each with a different and unique biological microenvironment. Endothelial cells in the vasculature of different organs express different cell-surface receptors and growth factors that influence the phenotype of metastases that develop locally.[18,19] The outcome of metastasis depends on multiple interactions ("cross-talk") of metastasizing cells with homeostatic mechanisms, including specific binding to endothelial cells and responses to local growth factors.[17] These findings support the role of inflammatory peritumoral microenvironment, stromal factors, and cellular cross-talking in being important elements of neoplasia pathogenesis and development.

Cellular microenvironment in physiology and pathogenesis of cancer

It is known that the cellular function within organs is determined by reciprocal communication between the cells in the epithelial layer and in the surrounding stroma. Cells are surrounded by a complex, 3-dimensional extracellular matrix (ECM) containing a mixture of glycoproteins, proteoglycans, cytokines, cells, and growth factors. The ECM provides structural supports for cells to determine the correct response to a given set of stimuli. Furthermore, there is strong evidence ECM also provides a functional context. For example, the ECM is able to influence mammary epithelial function through the control of the expression of genes that are a key regulator of cell growth, survival, and differentiation.[20-22] Mammary gland branching morphogenesis is dependent on the ECM, ECM-receptors such as integrins, and ECM-degrading enzymes, including matrix metalloproteinases (MMPs) and their inhibitors (tissue inhibitors of metalloproteinases [TIMPs]).[23] Other examples of similar molecular cross-talking between mesencyhme and epithelium in physiological processes include neovascularization, wound healing, and neurite overgrowth during embryogenesis.[14] The derangement of such mesenchymal-epithelial interaction can create a permissive field for the malignant cells. Tumor cells can modify the surrounding stroma through the production of cytokines and growth factors, and in turn this locally changed host microenvironment can influence the proliferative and invasive behavior of tumor cells.[14] (Figure 1)

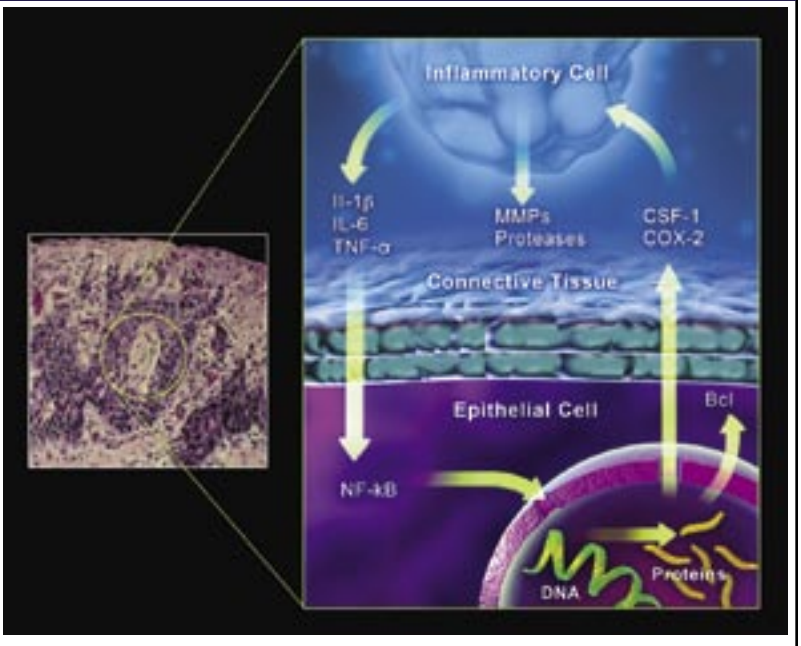
Several components of cancer-associated inflammation can promote tumor growth and progression. For example, innate immune cells termed tumor-associated macrophages can migrate into precancerous tissue, and can release factors that promote tumor growth and metastasis.[24,25] Accordingly, the infiltration of large numbers of macrophages is associated with poor prognosis in many human solid tumors, such as breast and prostate cancer.

Increased expression of genes associated with macrophage infiltration (such as CD68+) forms part of the mo-

lecular signatures associated with poor prognosis in certain malignancies, such as breast cancer.[24, 26]

In their recent review, O'Byrne and Dalgleish[3] analyzed in detail the role of chronic inflammation associated with the subsequent development of cancer, explaining how and by which processes the inflammatory environment is able to influence tumor development, angiogenesis, and inhibition of apoptosis. They concluded the inflammatory process itself provides the prerequisite environment for the development of malignancy through up-regulation of mediators of the inflammatory response (e.g., cyclo-oxygenase 2) leading to the production of inflammatory cytokines and prostaglandins, which themselves may suppress cell mediated immune responses, promote angiogenesis, impact on cell growth and survival signaling pathways, finally resulting in induction of cell proliferation and inhibition of apoptosis.[3] Furthermore, chronic inflammation may lead to the production of reactive oxygen species and metabolites such as malondialdehyde within the affected cells that may in turn induce deoxyribonucleic acid (DNA) damage and mutations and, as a result, be carcinogenic.[3] Again, Balkwill and Mantovani[4] have underlined the role of macrophages, dendritic cells, inflammatory cytokines and chemokines, which, belonging to the host stroma, are able to cause DNA damage, bypass p53 tumor suppression function, influence growth, survival, angiogenesis, and invasion.[4,27]

Figure 1: Inflammatory cycle of epithelial neoplasia



Inflammatory cells such as macrophages, mast cells, and lymphocytes produce several substances that can enhance tumor growth, including IL-1β, IL-6, and TNF-α, which can turn up NF-κB activity in target tissue cells. Inflammatory cells also produce MMPs and proteases that induce remodeling of extracellular matrix components, making it easier for tumor cells to invade adjacent tissues. Tumor cells produce substances such as CSF-1 AND COX-2 that continue to stimulate inflammatory cells giving a further boost to inflammatory processes, as well as proteins such as Bcl that inhibit apoptosis leading to immortalization of tumor cells.

Chronic inflammation as cause of tissue malignancy

If malignancy is to be considered the product of its local microenvironment,[14] it would be expected that the microenvironment would have to possess some tumorigenic properties prior to the onset of malignancy.[4,27]

Recent studies have been focused on the stromal inflammatory environment before the malignant lesions appear, and have underlined its active role during the transition from normal tissue to in situ and invasive carcinoma.[13,15,28,29] Several characteristics of the activated tumor-surrounding stroma are common to the sub-epithelial stromal changes of chronic inflammatory disorders associated with subsequent cancer development, hence supporting the notion that chronic inflammation may cause, or at least drive, malignancy.[27]

Stromal cells and their products, in association with insoluble ECM components, can act as oncogenic agents, causing the disruption of homeostatic regulation of adjacent cells, such as tissue architecture, cell death and proliferation, and leading to the development of solid neoplasia, such as breast, colon, and prostate carcinomas.[15,30,31]

Major factors of chronic inflammation and immune activation of the stroma which can contribute to pathogenesis of epithelial neoplasia (Figure 2) include cells (macrophages, mast cells, lymphocytes, and fibroblasts),[32-40] cytokines and chemokines such as tumor necrosis factor (TNF), interleukin 1 and 6 (IL-1 and IL-6), vascular endothelial growth factor (VEGF), regulated on activation, normal T-cell expressed and secreted (RANTES), matrix metalloproteinases (MMPs), nuclear factor-kappaB (NF-κB) and other components and events such as macrophage migration inhibitory factor (MIF), protease-induced remodeling of the ECM and unmasking of cryptic sites,[41-49] COX-2 enzymes,[50] and oxidative/nitrative DNA damage.[51] There is experimental evidence to suggest that carcinogen-induced epithelial malignant transformation can be prevented or at least slowed down through hampering the support of the components of the ''activated" inflammatory microenvironment. For example, mice genetically ''knocked out" for some tumorigenic stromal components, such as TNF and MMP-9, were shown to be resistant to

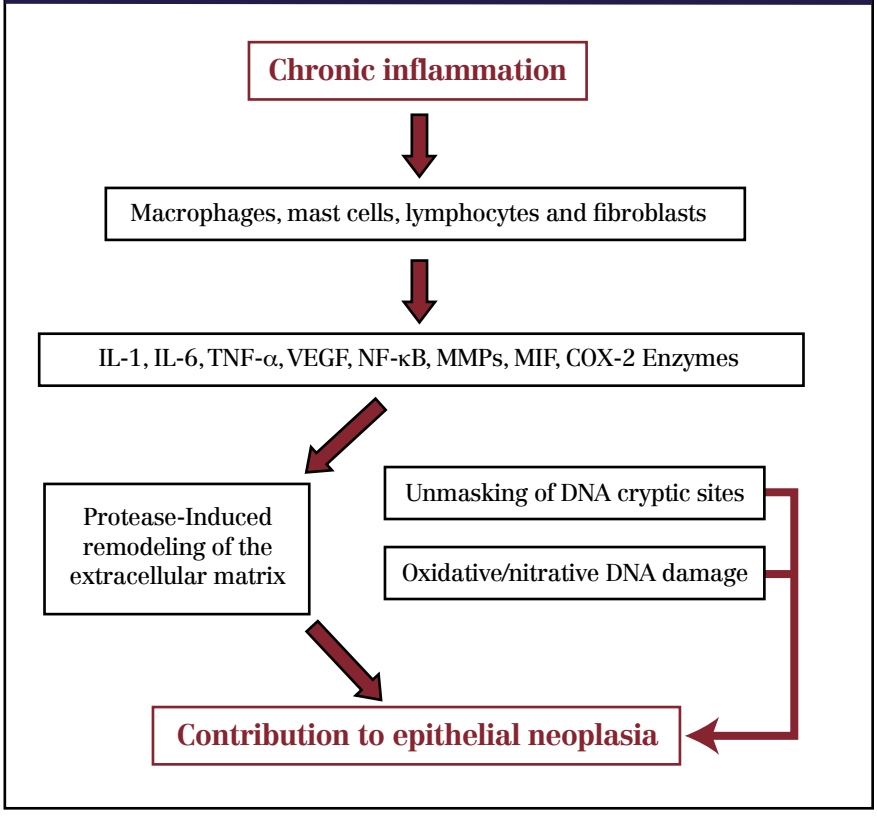
skin carcinogenesis induced by chemical carcinogens. On the other side, the *in vivo* and *in vitro* role of an "activated" stroma in stimulating tumor initiation (normal cells) and progression (genetically altered cells) has been clearly reported as well.

NF-κB as the most important component of tumor-promoting machine

Among the inflammatory components associated with cancer development, NF-κB has been extensively studied. NF-κB has been suggested to be one of the most important components of the tumor-promoting machine, as it provides a mechanistic link between inflammatory and neoplastic processes.[52] NF-κB is a major activator of anti-apoptotic gene expression in the context of TNF-α signaling, causing pre-neoplastic and malignant cells to resist apoptosis-based tumor-surveillance mechanisms.[52] NF-κB also regulates tumor angiogenesis and invasiveness.[52] NF-κB is known to interact with specific inhibitory factors, the IκBs, which retain NF-κB dimers in the cytoplasm. Many inflammatory stimuli can cause IκB kinase-dependent (IKK-dependent) phosphorylation and subsequent degradation of IκB proteins, which lead to the liberated NF-κB dimers to enter the nucleus, where they regulate transcription of diverse genes encoding cytokines, growth factors, cell adhesion molecules, and mainly anti-apoptotic proteins.[53] Current research has highlighted that the role of NF-κB is twofold: its activation in inflammatory cells leads to the production of secreted factors that enhance growth, survival and vascularization of cancer cells, as well as promotion of NF-κB activation in pre-malignant and malignant cells, which in turn results in elevated expression of cell-cycle genes, inhibitors of apoptosis and protease that promote the invasive phenotype.[53]

This has been demonstrated in experimental research and animal model of inflammation-related cancer. One example is the study by Pikarsky and colleagues,[55] who elegantly demonstrated that NF-κB is essential for promoting inflammation-associated hepatocellular carcinoma in Mdr2-knockout mouse strain (an animal model of inflammation-associated cancer as these mice spontaneously develop cholestatic hepatitis followed by hepatocellular carcinoma).[54] In this model the inflammatory process triggered chronic activation of NF-κB in hepatocytes, most likely through enhanced production of TNF-α by adjacent endothelial and inflammatory cells. Accordingly, the suppression of chronic NF-κB activation resulted in the apoptotic death of transformed hepatocytes and failure to progress to hepatocellular carcinoma.[54]

Figure 2: The theory of how chronic inflammation may contribute to epithelial neoplasia



Chronic inflammation of the oral mucosa associated with oral cancer: the case of oral lichen planus

Current concepts on oral lichen planus immuno-pathogenesis

Lichen planus is a chronic inflammatory disease that affects skin and mucous membranes of squamous cell origin.[55] The oral form of LP (OLP) seems more common, chronic and recalcitrant than the cutaneous type. It causes widespread erosions of the oral mucosa and significant oral pain and dysfunction of speech, swallowing and chewing, resulting in a significant impairment of the patient's quality of life.[56,57] OLP has been reported to affect 1-2% of the general adult population.[55,56] This is a prevalence higher or similar to other well-known chronic immune disorders such as rheumatoid arthritis (0.5-1% of general population), systemic lupus erythematosis (0.2% of general population), and other chronic inflammatory cutaneous diseases such as psoriasis (2% of general population). In addition to the possible deleterious effect upon patient quality of life, OLP has also been associated with a low but clinically relevant increased

risk of OSCC.[27,58-62] Figures 3-5 demonstrate the clinical presentation and histological features of 3 cases of lichen planus.

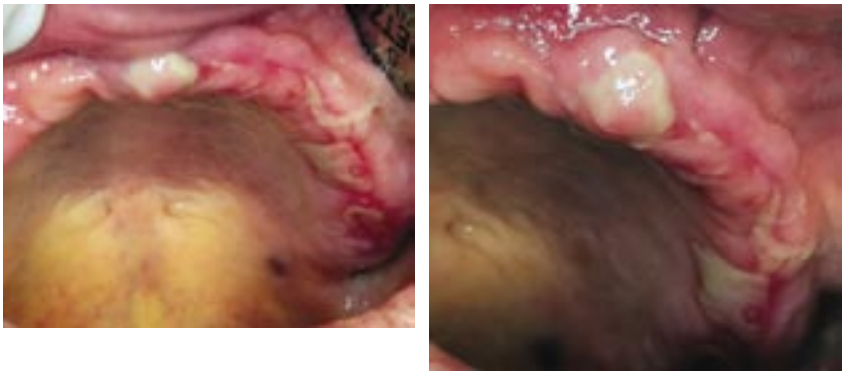
While the etiology of lichen planus is still unknown, significant progress has been made in understanding the likely pathogenesis and characterizing the typical inflammatory infiltrate which consists predominantly of T cells and macrophages.[55,56] While the majority of intra-epithelial lymphocytes in OLP are CD8+, most lymphocytes in the lamina propria are CD4+ T-cell clones with helper activity.[63-65] Furthermore CD4+ T-cell clones that lack cytotoxic activity can be isolated from oral and cutaneous LP lesions.[66,67]

These sub-epithelial T cells have been reported to express the mRNA for IFN-γ and TNF-α and thus to secrete these cytokines *in vitro*. In contrast, they do not secrete IL-4, IL-10, or TGF-β.[68,69]

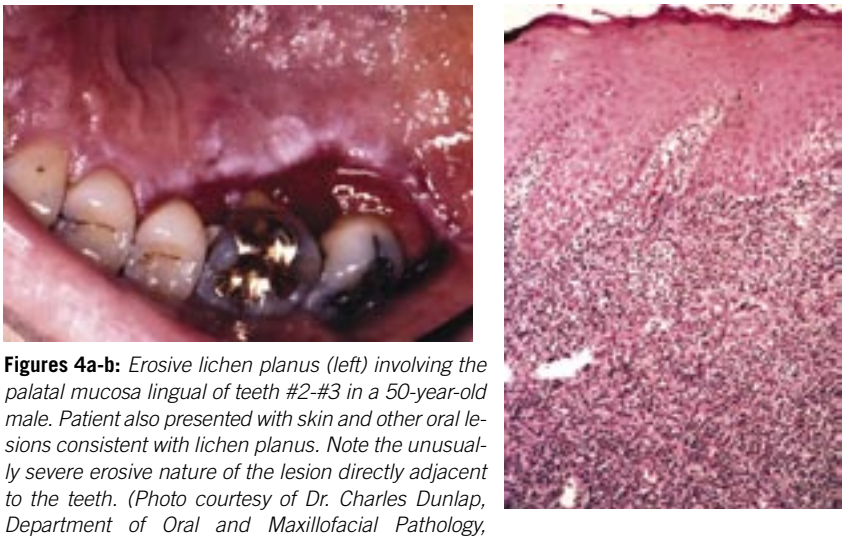
This is a profile of cytokine secretion produced by classically activated macrophages.[70] Activated intraepithelial CD8+ T cells isolated *in vitro* from LP lesions were found to be more cytotoxic against autologous lesional and normal skin keratinocytes than T-cell lines and clones from clinically normal uninvolved skin of LP patients. Other than these antigen-specific mechanisms, OLP pathogenesis is also characterized by non-specific machanisms which may contribute to keratinocytes apoptosis, such as the disruption of EBM, secretion and activation of MMPs, mast cell degranulation, and expression of RANTES chemokines. In addition, the expression of several other cytokines mediating the autoimmune process as well as contributing to disease chronicity has been reported, including TGF-β-1, IL-12, IL-4, IL-10, IL-6, GM-CSF, IL-1-β.

Langerhan's cells or keratinocytes in OLP may present antigen associated with MHC class II to CD4+ helper T cells that are stimulated to secrete

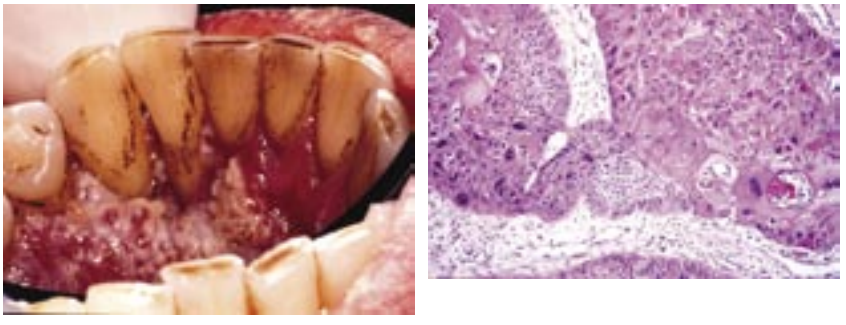
Figures 3-5: Clinical presentation and histological features of cases of lichen planus



Figures 3a-b: *52-year-old male with erosive lichen planus involving the maxillary edentulous alveolar ridge. Patient related a history of persistent lesions of varying degrees of severity occurring over a period of 6 years. Repeated biopsies over this period of time confirmed the diagnosis of lichen planus. (Photos courtesy of Dr. Charles Cobb)*



Figures 4a-b: *Erosive lichen planus (left) involving the palatal mucosa lingual of teeth #2-#3 in a 50-year-old male. Patient also presented with skin and other oral lesions consistent with lichen planus. Note the unusually severe erosive nature of the lesion directly adjacent to the teeth. (Photo courtesy of Dr. Charles Dunlap, Department of Oral and Maxillofacial Pathology, University of Missouri-Kansas City School of Dentistry) Biopsy (right) of lichen planus showing mild hyperkeratosis, slight epithelial acanthosis, and characteristic dense, band-like subepithelial infiltration of lymphocytes. Original magnification of x100. (Slide courtesy of Dr. Charles Cobb)*



Figures 5a-b: *Squamous cell carcinoma involving the mandibular incisor lingual gingiva extending onto the floor of the mouth. Patient was a 55-year-old female with a history of alcohol abuse and smoking 1-2 packs/day for about 35 years. Note the associated gingival inflammation. Biopsy of lesion (right) showing a poorly differentiated tumor featuring invasive pleomorphic epithelial cells, enlarged hyperchromic nuclei, abnormal keratin accumulation, and abnormal mitotic figures. (Photo and slide courtesy of Dr. Charles Cobb)*

the Th1 cytokines IL-2 and IFN-y. Subsequently, CD8+ cytotoxic T cells may trigger basal keratinocyte apoptosis. No autoantigens have been identified and a sensible working hypothesis is that the disease is a cell-mediated immunological response to some microbiological agent associated with the skin or mucosa. In the oral cavity, with its huge and diverse bacterial microbiota, the obvious inducing agent is some bacterium or an aberrant response to bacteria generally.[70] Other authors suggest that LP antigen may be a self-peptide, thus defining LP as a true autoimmune disease.[70] The role of autoimmunity in disease pathogenesis is supported by many autoimmune features of OLP, including disease chronicity, adult onset, female predilection, and association with other autoimmune diseases, occasional tissue-type associations, depressed immune suppressor activity in OLP patients and the presence of auto-cytotoxic T-cell clones in OLP lesions.[70] In addition, the autoimmune nature of OLP is also supported by its similarity with graft-versus-host-disease (GHVD) a common serious autoimmune complication following bone marrow transplantation. Mucocutaneous GVHD resembles OLP clinically and histologically, and even if the antigen specificity of LP and GVHD is probably different, it is likely that they share similar immunologic effector mechanisms, resulting in similar (i) T-cell infiltration, (ii) basal keratinocyte apoptosis, (iii) epithelial basement membrane disruption, and (iv) clinical disease.[70]

Malignant transformation of oral lichen planus

The World Health Organization (WHO) considered OLP to be a premalignant condition[71] as the majority of existing prospective and retrospective studies has demonstrated that OLP increases the risk of OSCC, and indeed there may be a risk of multiple and multifocal neoplastic events in the mouth.[61,72,73] However, this issue has been a matter of serious controversies.[74,75] Currently, there are few papers which have paralleled OLP to other chronic inflammatory disorders associated with cancer development, such as inflammatory bowel diseases, atrophic gastritis, chronic cholecystitis, and reflux esophagitis, among many others.[27]

Is chronic inflammation a major oncogenic drive for oral lichen planus?

Many inflammatory and immunological factors known to be related with cancer initiation, progression, and invasion are expressed within OLP-related chronic inflammatory infiltrate, and thus there is at least a potential for OSCC of OLP to be caused, or driven, by this inflammatory process.[27] These include inflammatory cells and their products, cytokines, chemokines and other ECM components. It can be suggested that the OLP-related inflammatory microenvironment can initiate tumorigenesis in normal epithelium as the cells and cytokines characterizing OLP infiltration have been clearly associated with DNA damage, cell growth and immortalization, and angiogenesis. One recent study has suggested that epithelial cells respond to inflammatory T-lymphocyte aggression with increasing proliferative activity in order to avoid apoptosis, subsequent tissue breakdown and severe clinical lesions.[76] However, the molecular alterations related to such cell cycle control may produce an epithelial substrate that favors malignant transformation.[76,77] Other authors have focused their analysis on oxidative and nitrative DNA damage in relation to inflammation-related carcinogenesis.[78,79] In 1 study specimens from animal models of inflammatory bowel disease and liver fluke infection (associated with colon cancer and cholangiocarcinoma respectively), as well as from patients with *Helicobacter pylori* infection, Hepatitis C virus infection, and OLP were studied and nitrative and oxidative DNA lesion products, 8-nitroguanine and 8-oxo-7, 8-dihydro-29-deoxyguanosine (8-oxodG), and inducible nitric oxide synthase (iNOS) were found in epithelial cells and inflammatory cells and at the site of carcinogenesis, thus suggesting that oxidative and nitrative DNA damage (mainly 8-nitroguanine) could represent promising biomarkers for evaluating the risk of inflammation-related carcinogenesis.[78]

Conclusions and clinical considerations

Recent and ongoing molecular studies are rapidly changing our view of neoplastic processes. One of the most important novel findings has been the understanding of the real role of the peritumoral inflammatory microenvironment which is now known to actively participate in the induction, selection and expansion of the neoplastic cells.[27] This has significantly contributed to the institution of novel, so-called "stromal therapy" in cancer prevention and therapy. Furthermore, it has led to better understand the relationship between several chronic inflammatory disorders and cancer development. As a consequence, there is now enough evidence that the increased risk for malignant transformation in these disorders is related to inflammation-associated damage to DNA (such as oxidative damage) and disruption of tissue architecture and function via the "activation" of stromal cells and components able to influence cell survival, growth, proliferation, differentiation and movement.[27] The reported association between OLP and an increased risk of developing OSCC seems to fit this model and presents several aspects in common with the other inflammation-related cancers. Other than contributing to our knowledge about disease behavior and pathogenesis, these findings have important clinical applications. In the near future, in fact, anti-inflammatory (e.g., selective cyclooxygenase-2 inhibitors) and/or anti-oxidant agents may be tested in the management of OLP with the aim of reducing the risk of malignant transformation. Furthermore, inflammatory biomarkers may be used to monitor OLP and diagnose malignant transformation early, as well as evaluate the effectiveness of potential chemo-preventive treatment.

The research group of N. Rhodus has recently performed a first step in this direction.[80] They reported that change of NF-κB dependent cytokines (TNF-α, IL-1, IL-6 IL-8) in saliva may in part reflect the malignant transformation of OLP and suggested that analysis of these cytokines may provide a useful, non-invasive surrogate endpoint for monitoring malignant transformation.[80] However, further studies are required to support these findings and to correlate the level of NF-κB dependent cytokines to the stage of malignant transformation of OLP.

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