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SPECIAL ARTICLE

The Interleukin Network in the Immunopathogenesis of Oral Diseases

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SUMMARY Interleukins produced by both lymphoid and non-lymphoid cells play a crucial role in the immune response. This paper discusses the possible interleukin network in the immunopathogenesis of some oral diseases. In chronic inflammatory periodontal diseases and periapical inflammation, interleukins such as IL-1 and IL-6 may be responsible in tissue destruction. High levels of IL-12 but not IL-4 and IL-10 may reduce the course of candidal infection. The progression of HIV infection has been associated with the regulation of distinct cytokines; thus, the pathogenesis of Kaposi's sarcoma may be regulated by IL-6. In autoimmune-associated oral diseases such as lichen planus, the role of Langerhans cells in presenting autoantigens may parallel with increased levels of IL-6. It seems, therefore, that the course of these diseases is regulated by these polypeptides which may in turn modulate the disease severity. However, whether altered levels of interleukins in certain oral disorders can be used as a diagnostic marker requires further investigation.

A remarkable breakthrough in the understanding of both cellular and molecular mechanisms of cell to cell communication has been documented in the past two decades. It is now clear that signals provided by accessory molecules such as adhesion molecules and cytokines are necessary for cell activation.[1,2] Of these cytokines, interleukins produced by both lymphoid and non-lymphoid cells play a crucial role in the immune response.

By the end of 1993, at least 13 interleukins had been discovered. The biochemical and biological properties of the interleukins are beyond the scope of this paper and readers may refer to extensive reviews elsewhere.[2-8] The functions of interleukins depend upon their specific receptors on the cell surface; however, a precise mechanism of signal transduction resulted from interleukin-receptor binding remains to be elucidated. The molecular and functional characteristics of these receptors have been reviewed recently.[9]

The exact pathogenesis of certain oral diseases such as chronic inflammatory periodontal disease and lichen planus remains unclear. Yet, accumulating evidence suggests that the progression of these diseases are under the control of immune response; therefore, interleukins produced by activated immunocompetent cells would obviously play a significant role in both diseases, although its exact mechanism is largely unknown.[10,11] The aim of this paper is to provide some insights into the possible role of the interleukins in some oral soft tissue disorders.

Chronic inflammatory periodontal diseases (CIPD)

The precise immunopathogenesis of CIPD is still enigma. It appears that all periodontopathic bacteria-activated immunocompetent cells are involved in the course of this disease.[11,12] Thus, the number of T cells in the initial or stable lesion are higher than that of B cells, whereas the progressive or

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advanced lesion is dominated by B cells; therefore, the former and latter lesions can also be termed the T and B cell lesions, respectively.[11] The interconversion of these lesional stages remains however questionable. The type and nature of periodontopathic bacteria, type of antigen presenting cells (APC) and the cytokine network may determine the nature and course of CIPD.[11-13]

Altered levels of IL-1, IL-2, IL-4, IL-5, IL-6 and IL-8 have all been implicated in the course of CIPD.[12-14] High levels of IL-1 released by periodontopathic bacteria-stimulated human mononuclear cells[15] are detected in gingival crevicular fluid (GCF) and gingival tissues from periodontal patients[16,17] suggesting that this cytokine plays a significant role in CIPD, perhaps, by mediating both soft and bone tissue destruction.[13,14] Likewise, elevated serum but reduced gingival IL-2 levels in these patients have also been observed.[18,19] The extrapolation of these findings in the immunopathogenesis of CIPD is however unknown. One may assume that lack of gingival diseased site-derived IL-2 production suggests that suppressed local T (Th1?) cell activation occurs, particularly in the progressive lesion. This speculation remains, however, to be further investigated.

In periodontal patients, elevated levels of IL-5 and IL-6 released by diseased gingival have also been detected.[15,19-21] Both cytokines are extremely important in both T cell activation and terminal differentiation of activated B cells.[22,23] Therefore, it seems possible that these interleukins play a pivotal role in the progressive lesion, by activating Th2 cells which in turn suppress Th1 cells and help B cell activation (Sosroseno W and Herminajeng E, *submitted*). Alternatively, since IL-6 has been shown to induce HLA-DR expression on the gingival Langerhans cells,[24] increased levels of IL-6 in the inflamed gingival tissues may enhance the antigen presentation function of these Langerhans cells which in turn modulate the local immune response. This cytokine may also have bone resorbing activity, since antibody to IL-6 reduced bone resorption in ovariectomized mice.[25] The ability of this cytokine in periodontal bone destruction in CIPD can not, therefore, be ruled out and needs to be further investigated.[11]

Perhaps one of the most intriguing questions is the role of IL-8 in CIPD. In the presence of IL-1, gingival fibroblasts are able to produce IL-8, suggesting that this cytokine acts as a chemotactic factor for neutrophils during the course of CIPD.[26] It is also possible that IL-8 may recruit T cells at the gingival inflamed site, since this cytokine is also chemotactic for T cells.[27] This question needs to be further investigated.

Periapical inflammation

Periapical inflammation is also known as an inflammatory dental pulp reaction induced by oral bacteria such as *Porphyromonas endodentalis*. The progression of this inflammation may be under the control of the immune network.[28] Following bacterial invasion and tissue responses, it has been speculated that the activated cells-derived IL-1 induces periapical bone destruction.[29] In an animal model, extracts of periapical tissues derived from exposed dental pulp contained polypeptides, including IL-1 and TNF-alpha.[30] In this study the induction of fetal rat long bone resorption mediated by these extracts could be suppressed in the presence of anti-IL-1 alpha antibodies, suggesting that IL-1 production in the inflamed dental pulp may be responsible for periapical bone damage. It is however unclear whether other interleukins would be involved in the course of this lesion; it may be that IL-6 produced by various cells in this site participates in the tissue destruction by activating osteoclasts as speculated in the immunopathogenesis of CIPD.[11]

Candidiasis

Candidiasis caused by *Candida albicans* is perhaps one of the best example of oral fungal diseases. It appears that antigen-specific T cell response is dominant during the course of *C.albicans*-induced immunological reaction; thus, depletion of CD4 cells *in vivo* inhibits *C.albicans*-induced DTH reaction and enhances the disease severity.[31,32] More recent studies revealed that, dependent upon distinct *C.albicans*-isolated antigens used, both IL-2 and IFN-gamma-producing Th1 cells are activated in genetically resistant mice such as BALB/cCr mice, whereas IL-4 and IL-6-producing Th2 cells are associated with genetically susceptible mice such as DBA/2 mice,[33,34] suggesting that the progression of candidal infection may be associated with the function of these distinct cytokines (Fig. 1). The fact that Th1 cell-derived IFN-gamma enhances the antifungal activity of macrophages, perhaps by increasing nitric oxide production especially in a murine model[35,36] supports a pivotal role of cytokines in candidiasis. However, whether elevated levels of IL-4 reflect a late protection or increased susceptibility remains to be elucidated. It appears in this respect that the latter speculation may be the case, since the course of the disease could be inhibited and both DTH responsiveness and long lasting protection were observed in IL-4-neutralized murine candidiasis.[37] Blocking IL-4 activity by injection of recombinant IL-4 receptor resulted in depressed candidal infection in genetically susceptible mice.[38] Likewise, the induction of IL-4 mRNA expression following a single injection of

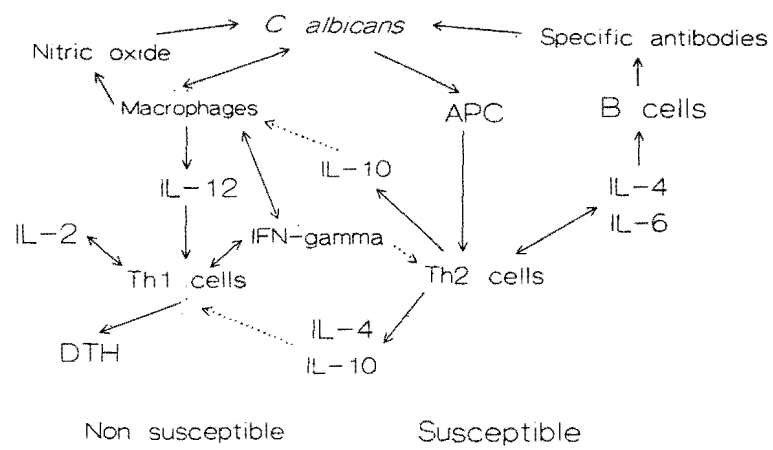

Fig. 1 A simplified model of the immunopathogenesis of candidiasis based upon studies using a murine model. In this model, the type of *C.albicans*-activated antigen presenting cells would determine the activation of helper T cell subsets which in turn release distinct cytokines and exert the course of candidiasis. Solid arrows represent either activation, production or effects. Dotted arrows represent an inhibitory effect. DTH = Delayed-type hypersensitivity; APC = Antigen presenting cells. See text for detail.

monoclonal anti-IFN-gamma antibodies parallels the loss of DTH response and specific protection in murine candidiasis.[39]

The exact mechanism by which Th1 to Th2 cell shift is associated with the progression of candidiasis remains to be elucidated. Romani and colleagues have shown that IL-12 mRNA expression in macrophages of genetically resistant but not susceptible mice is detected.[40] In this study, IL-12 was required to develop *C.albicans* specific-Th1 cells, suggesting that *Candida*-activated macrophages produce IL-12 to develop antigen-specific Th1 cells. It is also possible that certain *Candida*-derived superantigens such as heat shock protein 90kD (HSP 90) may suppress the development of Th2 cells and induce Th1 cells which in turn enhance resistance to candidal infection.[41,42] In sharp contrast, addition of IL-4 and IL-10 downregulates the production of nitric oxide and murine macrophage antifungal activity to *C.albicans in vitro*.[36] *In vivo*, injection of antibody to IL-10 enhanced nitric oxide and IFN-gamma productions and protected genetically susceptible mice to candidiasis,[43] suggesting that IL-10 plays a major role in suppressed Th1 cell development and thus, enhances susceptibility to candidal infection.

The extrapolation of these findings to humans is speculative, however, since unlike the murine model, IL-10 is produced both by human Th1 and Th2 cells.[44] Notwithstanding, the cytokine profiles in *C.albicans*-induced immune response which may determine the susceptibility of the infected individuals certainly provide a new insight into the immunopathogenesis of candidiasis and therapeutic bimodality of cytokines in this pathological entity.

AIDS-associated oral diseases

The precise immunopathogenesis of AIDS (acquired immunodeficiency syndrome) caused by HIV-1, a retrovirus, is still an enigma. Candidiasis, hairy leukoplakia and Kaposi's sarcoma are among the most common oral disoders seen in the HIV-infected patients.[45]

IL-1, IL-2, IL-6, TNF-α and IFN-gamma have all been implicated in the immunopathogenesis of AIDS.[46,47] For example, despite a T cell defect, hyperactivated B cells have been suggested to be due to overproduction of IL-6 in HIV-infected patients.[22,23] Increased levels of IL-4 are also detected and accompanied by a lack of IL-2 production in the progression of AIDS; however, the levels of IL-2 but not IL-4 are dominant in asymptomatic seropositive patients.[48] Based upon these findings, it is believed that during the course of HIV infection, Th1 cell-derived IL-2 provides protection, whereas Th2 cell-derived IL-4 and IL-6 would induce progressive or symptomatic disease.[49] It may therefore be that lack of IL-2 and IFN-gamma production reduces CD8 cell activities to lyse the HIV-infected cells in the symptomatic stage.[49] In this hypothesis, the switch may be due to the production of Th2 cell-derived IL-10 which in turn suppresses Th1 cell activation.

Yet, this hypothesis remains arguable. Unlike the murine system, both human Th1 and Th2 cell clones produce IL-10 which in turn inhibits their proliferation and cytokine production.[44] Should the Th1 and Th2 cell shift occur, it may require explanations other than simple mediation by IL-10 *per se*. One possibility is that HIV-infected APC induces Th1 cell anergy, thereby preferentially expanding Th2 cells.[50] In this respect, lack of APC-derived IL-1 and/or IL-12 may play a major

role in inducing IL-2 and IFN-gamma-producing Th1 cell anergy and vice versa.[51,52] Whether this shift which determines the course of AIDS is orchestrated by these pathways remains speculative.

The most recent studies have shown clearly that the progression of HIV infection is not merely associated with Th1 to Th2 cell shift.[53,54] In these studies, peripheral blood and lymph node cell-derived IFN-gamma and IL-10, but not IL-2 and IL-4 could be detected in both HIV-seronegative and -seropositive subjects. Following HIV stimulation *in vitro*, CD4 cells from these subjects produced IFN-gamma, IL-4 and IL-10, cytokines belonging to Th0 cells. These results suggested that HIV infection did not induce a Th1 to Th2 cell shift, rather it would stimulate the development of Th0 cells.

Although the hypothesis based upon the HIV-induced cytokine profiles remains to be clarified further, progressive AIDS-associated oral diseases may be predicted from this point of view. With respect to Kaposi's sarcoma, spindle-like cells isolated from this disease produce cytokines such as IL-6 and IL-1, but not IL-2 and IFN-gamma, suggesting that the progressive stage of this disease is associated with the cytokine profile.[55] This idea needs, however, to be investigated further.

Autoimmune-associated oral diseases

Autoimmune response can perhaps be considered as a failure of the immune system to discriminate between self-and non self-antigens. In the oral cavity, various soft tissue lesions have been associated with autoimmune diseases such as lichen planus,[10] Sjörgren's syndrome,[56] pemphigoid,[57] Behçet syndrome,[58] and systemic lupus erythematosus.[59] With the exception of pemphigoid, the exact autoantigens, if these are the cause of autoimmune diseases, are largely unknown and their clinical appearances in the oral cavity are likely to be a manifestation of systemic rather than local immune disorders.

The detailed mechanisms of autoimmunity such as failure of deleted self-reactive T and B cells[60,61] and of gene-induced apoptosis,[62] as well as downregulated CD8 cell functions[63] and super-antigens-induced immune response[64] are beyond of the scope of this paper. Of interest, cytokines released by the autoantigens-activated immunocompetent cells are a crucial factor in expanding autoreactive T and B cells as well as generating tissue destruction which exposes the hidden autoantigens.[65,66] Thus, in insulin-dependent diabetes mellitus, IL-1 produced by activated macrophages could induce islet Beta cell damage which results in releasing its autoantigens.[67] Likewise, increased levels of IL-4 may maintain B cell hyperactivation seen in SLE patients.[68] Joint destruction seen in rheumatoid arthritis may be ameliorated by TGF-β which may inhibit IL-1 production.[69]

Lack of conclusive evidences concerning altered interleukin levels in autoimmune-related oral diseases leads to a difficulty in determining the role of these biologically active polypeptides. In lichen planus, it has been hypothesized that damaged keratinocytes would release IL-1 and IL-6 to stimulate Langerhans cell functions.[10] The IL-6 levels were significantly elevated in active disease and decreased following remission, suggesting that it plays a significant role in lichen planus, perhaps by enhancement of MHC class II expression on Langerhans cells.[24,27] In Sjorgren's syndrome, salivary gland biopsies obtained from the patients and cultured *in vitro* produced IL-2 and another B cell growth factor, perhaps IL-10.[71,72] It was thought that these cytokines would maintain autoreactive T and B cell growth in this syndrome.[56] However, since IgG1 antibodies of Sjörgren's syndrome patients are selectively produced in high levels,[73] an excessive production of IL-4 may also occur.

Oral neoplasia

The development of cancer cells requires a complex network including growth factors. The roles of transforming growth factor-alpha and -beta as well as of epidermal growth factor in cancer cells are beyond the scope of this paper. Certain interleukins appear to be important factors in cancer growth. Lung cancer cells spontaneously produce significant levels of IL-8[74,75]; however, the role of this cytokine in tumor growth remains unclear. In IL-9 transgenic mice, 7% of these mice developed thymic lymphomas.[76] In this study, expression of IL-9 was required for optimal tumor growth, suggesting that overproduction of IL-9 may induce the development of thymic tumor cells. These results are also confirmed by the fact that human anaplastic large cell lymphomas require IL-9 in an autocrine fashion.[77] Possibly cancer cell-derived IL-10 is one of the examples of ways by which these cells evade the host immune defences. Human B cell lymphomas, lung cancer and melanoma are capable of producing IL-10 which suppresses tumoricidal functions of monocytes and macrophages.[78-81] Nabioullin and colleagues have also shown that a cocktail of IL-10 and IL-14 is much more potent as an inhibitory factor to these cells than either IL-10 or IL-4 alone.[81] Melanoma-derived IL-10 inhibits the production of TNF-alpha, IFN-gamma, and IL-2 and suppresses mixed lymphocyte reactions.[82]

The concept of the immunosurveillance carried out by NK cells, T cells and macrophages is important in tumor rejection.[83-85] In fact,

activated cells-derived cytokines which have anti-tumor activities are also crucial effectors in rejecting tumor growth. Dependent upon the tumor origin, expressed IL-2 and IFN-gamma mRNA were observed in basal cell carcinoma biopsies, whereas IL-4, IL-5 and IL-10 mRNA were highly expressed in seborrheic keratosis, a benign growth of the epidermis.[86] It seems therefore that along with other cytokines such as TNF-alpha, IL-2 and IFN-gamma play an important role in tumor rejection, despite the fact that tumor-activated IL-4 and IL-6-producing T (Th2) cells can inhibit tumor growth.[87] Perhaps IL-2 and IFN-gamma are needed to recruit and activate cytotoxic CD8 T cells and NK cells as well as macrophages. IL-6 may augment the host anti-tumor defences by, for example, increased antibody production and elevated T and B cell activation; on one hand, IL-4 could induce the LAK (lymphokine-activated killer) cells activity.[88,89] It should be noticed that the anti-tumor function of IL-6 is only limited on the early but not advanced stage of the tumor growth,[90] implying that IL-6-induced the host's defences only act on the initial tumor growth, whilst IL-2 and IFN-gamma-activated defences function in the advanced disease stage. It has been revealed that IL-7 is able to act as an anti-tumor agent, by inducing monocyte and macrophage-derived IL-1 alpha, IL-1 beta and TNF-alpha production.[91]

Surprisingly, evidence for a role of interleukins in the development of oral neoplasia is lacking. The work of Gangal and Tatake[92] has shown that impaired IL-2 production is observed in patients with oral leukoplakia; however, normal production of this cytokine is seen in untreated oral cancers. It is of interest that reduced cytotoxic functions of NK cells and LAK cells could be restored in addition of IFN-gamma and IL-2,[92] implying that in oral cancers, altered IFN-gamma rather than IL-2 production occurs. Yet, it is unclear whether IL-4, IL-6 and IL-7 would contribute to inhibition of the development of oral neoplasia.

Conclusion

The signals provided by the interleukins in the immune response prove to be prerequisites. Thus, transient levels of interleukins would determine the efficacy of the immune response against various antigens. In microbial antigen-induced oral diseases, the levels of IL-1, IL-2, IL-4, IL-5 and IL-6 would affect the course of the diseases and individual susceptibility. Likewise, these biologically active polypeptides may cause deterioration in the progression of autoimmune diseases, determining some of the clinical features in the oral cavity. In AIDS-associated oral diseases, the interleukin profiles seen in HIV-infected humans may be parallel with the course of these diseases. Furthermore, although altered IL-2 levels could be observed in oral cancers, it is not clear whether it reflects suppressed host immune defences and whether other cytokines are involved in the cancer growth and regression.

Despite the fact that production of some interleukins is impaired in some oral diseases, it is still uncertain whether they can be utilized as diagnostic markers. In this respect, the levels of other cytokines, such as TNF-alpha and TGF-beta which regulate the production of interleukins during the course of oral diseases need to be considered.

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