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Editorial

Immune-mediated mucosal diseases: tales about battles lost and won

The following articles constitute the second part of the proceedings of the international conference 'New Frontiers in Oral Immunological Diseases', which was held in Lillehammer, Norway, 23–27 February 2001. The first series of articles (1–12) was published in the previous issue of *Acta Odontologica Scandinavica*, and the last series will appear in the next issue of the journal. The aim of the congress was to introduce new perspectives in oral immunological diseases through integration with non-oral fields. The present reviews address immune-mediated mucosal diseases.

Mucosal immunity

Individual hosts are well armed to win battles over infecting microorganisms: both anatomical structures and chemical secretions shield and defend the body's mucosal surfaces from attack by bacteria, viruses, and other parasites. The first anti-parasite strategies in effect in mucosal defense are *interference with parasite adherence* and *immune exclusion*: parasites are hampered in their efforts to adhere to mucosal surfaces and find foothold in their ecological niches. Under certain conditions specific responses are generated and aid in the processes of both immune exclusion (secretory antibodies) and *immune elimination* (antibodies in tissue and blood, cytotoxic T cells). This happens when the immune system receives 'danger' signals—for example, when bacteria invade mucosal (or other) tissues. Acquired responses operate in close concert with innate defense mechanisms, the latter having the most potent effector functions. Main tasks for the acquired immune system are specific and selective recognition of threatening foreign antigens and aid in antigen removal.

For the host, defeat in the mucosal 'battle' can result in direct loss of organ function or even death, but side effects of acquired immune responses can also lead to new disease. So-called *hypersensitivity* reactions are responsible for the clinical symptoms associated with such immune-mediated diseases. The acquired immune reactions are meant to detect and eliminate foreign antigens of pathogenic parasites, but the ensuing inflammation can in several ways result in unwanted damage to host tissues. Hypersensitivity reactions can be categorized into four theoretical types according to Coombs & Gell (Fig. 2, in Ref. 17, p. 244). In brief, the reactions can be due to prolonged antigen persistence (for example, chronic infection and autoimmunity), exposure to foreign antigens under abnormal conditions (exposure to the indigenous microflora such as in inflammatory bowel disease (IBD) and 'allergies'), or inadequate responses inherent to the genetic make-up of the host.

In the first article in this series the latter issue is elaborated further by Frode Vartdal (13). Gene variants (alleles) involved in the immune response are selected during evolution, ensuring that at least some individuals in a species can cope with harmful microbial infections. Such allelic polymorphisms, advantageous in fighting harmful infecting microorganisms, may, however, predispose for unwanted immune responses. Thus, immune-disease susceptibility genes are probably normal variants of genes selected during evolution. Vartdal also briefly discusses how the genes may predispose for disease and further presents some strategies and techniques for their identification, which is important for improvement of the understanding of the pathogenesis and hence the development of preventive and therapeutic measures.

Immune-mediated mucosal diseases

The next review articles exemplify characteristics and mechanisms of immune-mediated mucosal diseases caused by prolonged antigen persistence (chronic infection (14, 15), autoimmunity (16)) and exposure to foreign antigens under abnormal conditions (exposure to the indigenous microflora in IBD (17, 18), delayed-type hypersensitivity (19)).

Failure of the mucosal immune system to eliminate pathogenic bacteria, with chronic infection as a consequence, can result in tissue damage. *Helicobacter pylori*

infects more than half of the human population and is responsible for severe gastroduodenal diseases. Peter Ernst and Jacques Pappo (14) describe how this often life-long infection induces gastric IgA responses but fails to yield protective immunity. Natural anti-*H. pylori* immune responses are primarily Th1-cell-dominated, which enhances cell-mediated immunity. The chronic inflammation contributes to tissue damage and disease, such as atrophic gastritis, peptic ulcer, and gastric cancer. Animal models indicate, however, that effective mucosal vaccines can be developed by using adjuvants. The effectiveness of these vaccines seems to be due to their ability to alter the gastric immune response from a homogeneous Th1 response towards a mixed Th1 and Th2 response. Interestingly, immunity to *H. pylori* can occur in the absence of B cells, suggesting that novel IgA-independent mechanisms exist which confer protection. Curbing immune responses by vaccination may also be a fruitful approach for oral infectious disease like periodontitis.

Periodontitis is another mucosal disease in which pathogenic bacteria are not totally eliminated by the mucosal immune system. As in *H. pylori* infection, periodontitis also induces specific immune responses (antibodies and activation of T cells) that are unable to eliminate infecting microorganisms and may precipitate breakdown of attachment for the teeth (6). Pamela Baker, Jessica Garneau, Lisa Howe, and Derry Roopenian (15) focus on the role of T cells in the pathogenesis of the disease. A mouse model was developed in which alveolar bone loss can be induced by oral infection with *Porphyromonas gingivalis*. Pam Baker's group used immune knockout mice to explore which parts of the immune system may be protective and which may confer bone resorption. Infected severe combined immunodeficient (SCID) mice, without T or B lymphocytes, were found to have far less bone resorption than infected immunocompetent mice. Further experiments showed that $CD8^+$ T-cell-deficient mice, orally infected with *P. gingivalis*, had unchanged bone loss as compared with immunocompetent mice. In contrast, mice lacking $CD4^+$ T cells lost less bone, indicating that $CD4^+$ T cells are likely to play an important role in bone resorption. The T cells are likely to act through the secretion of cytokines. Baker's group indeed showed that mice lacking the Th2 cytokine IL-6 did not lose alveolar bone in response to *P. gingivalis* infection, in contrast to infected immunocompetent mice. Similarly, mice lacking the Th1 cytokine interferon (IFN) also had less bone loss than normal mice. Perhaps a confusing constellation (Th2 cytokine cooperating with Th1 cytokine)—but an interesting potential pathway for a cooperation is proposed (Fig. 1, in Ref. 15, page 222).

Autoantigens are inherently persistent antigens in the body. Central and peripheral tolerance normally ensures that lymphocytes with autoreactive receptors are deleted or remain suppressed. Yet, under certain conditions, still largely unknown, autoimmune reactions may occur. Stephen Challacombe and co-authors review the latest knowledge on bullous diseases affecting oral mucosa and skin (16). Mucous membrane pemphigoid (MMP) is a group of disorders characterized by subepithelial separation and deposition of immunoglobulins and complement along the basement membrane zone. Pemphigus is characterized by clefting and acantholysis within the epithelium and is due to binding of IgG autoantibodies to desmogleins. Little is known about the environmental factors that may trigger the diseases, and, obviously, there is a strong genetic component. HLA-DQB1*0301 was found to be associated with clinical forms of MMP. In pemphigus vulgaris, anti-desmoglein (Dsg) 1 antibodies and/or anti-Dsg3 antibodies can be found and HLA class-II allele associations are described. Recent increased knowledge of the structure and function of epithelium and of the basement membrane zone allows better analysis of samples obtained from patients. Analysis of autoantibody responses in MMP has shown that distinct subgroups exist with either specific antigens or specific antibodies. Challacombe and colleagues indicate that earlier therapeutic intervention are likely to reduce complications and may improve remission. However, further studies are needed to elucidate pathogenesis because such detailed knowledge will be needed to develop specific modulating immunotherapy.

The next papers (17, 18) deal with IBD, which comprises two chronic clinical entities—Crohn disease (CD) and ulcerative colitis (UC). Oral tolerance is the immunological down-regulating mechanism against dietary antigens and indigenous microbiota. In IBD, oral tolerance to commensal gut bacteria is likely to be disturbed, which causes immunological hypersensitivity. Per Brandtzaeg (17) outlines how local homeostasis is disturbed in IBD, leading to hyperactivation of Th1 cells, with secretion of interferon-γ and tumour necrosis factor and production of IgG antibodies against commensal bacteria. In an interesting comparison, Brandtzaeg points to similarities between IBD and periodontitis. First, in both diseases excessive exposure to antigens from the indigenous microbiota is obviously involved. Second, both IBD and periodontitis appear to be triggered by alterations in leukocyte extravasation and in antigen-presenting mechanisms (aberrant expression of major histocompatibility complex class-II molecules and changed local profile of costimulatory molecules). Disturbances in cytokine networks, with abnormal cross-talk between cell types, seem to be a cause of both diseases and of chronic inflammatory mucosal diseases in general. Although the understanding of mucosal immunopathogenesis is increasing, the only curative treatment for periodontitis and ulcerative colitis, however, is still removal of dental plaque and the total large bowel, respectively.

Warren Strober, Ivan Fuss, and Atsushi Kitani (18) expand on the regulation of mucosal inflammation, with focus on CD and Crohn-like disease in mice. Their studies have shown that inflammation in CD is due to Th1 T-cell abnormality involving overproduction of interleukin (IL)-12, IFN-γ, and TNF-α. Treatment of mice with anti-IL-12 decreases inflammation, due to the apoptotic effect of anti-IL-12 on activated Th1 T cells. A second approach, used

by Strober's group, was to deliver TGF-β to mice with experimental intestinal inflammation. Mice were successfully treated with intranasally administered DNA encoding active TGF-β. This indicates that it in the future it might be possible to treat patients with an excessive effector cell response by curbing this response, whereas patients with inadequate regulatory responses could be treated by providing them with some exogenous source of regulation. Conceivably, these same principles could be applied to oral mucosal diseases such as periodontitis, lichenoid reactions, and recurrent aphthous ulcerations.

Eva Ahlfors and Torstein Lyberg pose the question whether contact sensitivity (CS) reactions can occur in oral mucosa (19). In skin, CS immune reactions and their cellular mechanisms have been well characterized, but much less is known about the occurrence of CS in oral mucosa. In the latter site, one of the main problems is to distinguish between immunological and irritant reactions, particularly because mucosa is more easily than skin affected by irritative compounds. Ahlfors and colleagues have obtained convincing evidence that specific immunological reactions to foreign materials ('allergies') indeed can take place in oral mucosa. For example, hapten feeding of mice will induce oral tolerance. When the mice after such feeding were hapten-induced in skin, elicitation in skin was suppressed but not that in oral mucosa. Vice versa, hapten feeding suppressed oral mucosa-induced but not skin-induced CS responses in the oral mucosa. These and other observations indicate that reactions to dental materials can have an immunological cause. An important byline is that Ahlfors and Lyberg's results also suggest that the value of skin patch testing in cases of suspected oral mucosal CS reactions should be questioned because regulatory mechanisms in skin and oral mucosa appear to differ.

In sum, as remarked by Brandtzaeg (17), whereas there are differences in the immunological reactions in different mucosal compartments, similarities also are evident. This is clearly shown in the collected articles in this series. Perturbation of a tightly regulated cytokine network, with abnormal crosstalk between mucosal cell types, may be the first step in a progressive drive of inflammatory mucosal diseases in general. Individual patterns of disease progression may be explained both by microbial and immunological variables and by more or less well-defined host factors, irrespective of mucosal site.

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