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Review

Autoimmunity—Basics and link with periodontal disease

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ABSTRACT

Autoimmune reactions reflect an imbalance between effector and regulatory immune responses, typically develop through stages of initiation and propagation, and often show phases of resolution (indicated by clinical remissions) and exacerbations (indicated by symptomatic flares). The fundamental underlying mechanism of autoimmunity is defective elimination and/or control of self-reactive lymphocytes. Periodontal diseases are characterized by inflammatory conditions that directly affect teeth-supporting structures, which are the major cause of tooth loss. Several studies have demonstrated the involvement of autoimmune responses in periodontal disease. Evidence of involvement of immunopathology has been reported in periodontal disease. Bacteria in the dental plaque induce antibody formation. Autoreactive T-cells, natural killer cells, ANCA, heat shock proteins, autoantibodies, and genetic factors are reported to have an important role in the autoimmune component of periodontal disease. The present review describes the involvement of autoimmune responses in periodontal diseases and also the mechanisms underlying these responses.

Contents

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1. Introduction

Autoimmune diseases are the result of specific immune responses directed against structures of the self (Burnet and Fenner, 1949). The immune system is an intricate constellation of cellular and molecular elements that have evolved to guard the body against attack. Under normal conditions, the immune system exhibits tolerance (an inability to react) to molecules recognized as "self," and thus does not respond to elements (whether carbohydrate, nucleic acid, or protein) that are expressed in endogenous tissues. When self-tolerance is lost, the immune system is deployed against one or more of the body's own molecules. The civil war directed against autologous tissue resulting from the loss of self-tolerance is the hallmark of the autoimmune diseases (AIDx).

Periodontal diseases are characterized by localized infections and inflammatory conditions where anaerobic Gram-negative bacteria are mainly involved and directly affect teeth-supporting structure. In 1965, Brandtzaeg and Kraus were the first to postulate the autoimmune basis in the pathogenesis of periodontal disease. It has been more than 30 years since the concept of autoimmunity has been considered for periodontal disease. An increasing number of reports in the past decade have lent support to the concept of an autoimmune component of periodontal disease [1]. This review is an attempt to throw light on the autoimmune basic concepts and highlighting the autoimmune component in the etiopathogenesis of periodontal disease.

2. Concept of autoimmunity

Theories of immune system recognition and AIDx development have evolved extensively over the past 50 years. During the mid twentieth century, the "self–non-self" (SNS) model was the prevailing explanation for immune reactivity [2,3]. The key perils envisioned in this paradigm as means for invoking an immune response were external invaders (i.e., pathogenic microbes and parasites) and internal threats (e.g., neoplasia). Inadvertent attacks directed against "self" molecules were thought to result from immune system confusion in distinguishing between true foreign molecules and structurally similar "self" constituents. Three decades later, the "infection–non-self" (INS) model was devised [4] as a modified version of the traditional SNS scheme. In this scenario, the focus of the SNS discriminatory capacity resides in the requirement by antigen-presenting cells (APCs) that antigens be presented in combination with a co-stimulatory molecule before an immune response will be mounted; thus, resting APCs will be activated when one of their germ line-encoded pattern recognition receptors (PRRs) recognizes a microbial pathogen-associated molecular pattern (PAMP). The most recent hypothesis is the "danger" model [5], in which the spur that activates quiescent APCs is the generation of one or more alarm signals by injured cells. The injury can result from many causes (neoplasia, pathogens, toxicants, trauma, etc.) since all can release elements that comprise a damage-associated molecular pattern (DAMP). However, programmed cell death would not activate APCs since apoptotic cells are scavenged before their "self" constituents are released to interact with nearby cells. Further adaptations to our understanding of immunity will arise in the future because the INS and danger models begin with divergent assumptions about what elicits an immune response and thus provide different predictions about the immune system's responsiveness to foreign-but-harmless (i.e., fetuses) and self-but-harmful (i.e., certain mutations) materials. At present, the danger model appears to provide the more useful perspective of potential AIDx pathogenesis since its tenets encompass possible AIDx mechanisms that fall outside the SNS/INS model, such as the induction of cell death by excessive stress or toxicants as well as disruption in the extent and clearance of physiologic cell death [6].

2.1. Basic immunological mechanisms of autoimmunity

The distinction between "self" and "non-self" by the mature immune system depends on an intricate meshwork of sequential and well-regulated interactions between the afferent arm (APCs) and the efferent branch (effector cells and their products) to ensure that self-elements are tolerated. In general, such self-tolerance is mediated chiefly by constituents of the acquired immune system (i.e., highly specific but must first be built), in particular the complement of B- and T-lymphocytes with their membrane-bound, antigen-specific recognition molecules.

Current dogma is that both spontaneous and induced AIDx are launched and perpetuated primarily by T-lymphocytes [7–9]. Cells of the CD4+ T-helper (Th) class are especially potent in this regard, releasing a broad spectrum of cytokines that promote the actions of other immune effector cells. Multiple classes of Th-lymphocytes have been defined. The most notable contributions to promoting AIDx appear to come from the Th1 class, which boosts immune cell activity; the Th2 class, which stimulates the humoral (antibody) response; and the Th17 class, which secretes factors to recruit and stimulate neutrophils. These master Th-cell phenotypes are activated by immediate proximity to APCs (commonly dendritic cells but on occasion also mitogen-stimulated B-cells) that express major histocompatability complex (MHC) type II as well as a co-stimulatory molecule (e.g., B7 [CD80/86]). Lymphocyte activation occurs only if the T-cell forms an immune synapse with an APC using three signals at once: (1) the primary T-cell receptor (TCR) binding to MHC II, (2) the T-cell co-stimulatory receptor (e.g., CD28) linking with the APC's co-stimulatory molecule, and (3) APC secreted cytokines interacting with T-cell receptors in a paracrine fashion. Stimulation by a single receptor-ligand modality is not sufficient to prime the lymphocyte. A comparable receptor-mediated event in which surface-anchored immunoglobulin (Ig) serves as the B-cell receptor is required for B-cell activation. In AIDx, autoreactive T- and B-lymphocytes engage in mutually assisted positive feedback to perpetuate the disease over time [10].

2.2. Cellular mechanisms of autoimmunity

Normal individuals preserve self-tolerance in T-lymphocytes through many mechanisms, all of which must be actively maintained throughout life. Accordingly, the loss of self-tolerance may occur through multiple mechanisms. The three main cell-oriented means for preventing autoimmunity are deletion (removal), anergy (relaxation), and suppression (restraint). The first option, deletion, involves irreversible pruning of self-reactive T-cells. This process of "central tolerance" (i.e., occurring in a core immune organ) occurs mainly in the thymus, the primary lymphoid organ for lymphocyte production. In the thymic cortex, naive lymphocytes (Th0 class) that learn during development to ignore self-elements as potential targets are positively selected for continued survival, while T-cell precursors that exhibit any affinity for