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Interleukin-18 and oral mucosal immunity

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Abstract. Oral mucosal cells such as epithelial cells and fibroblasts are the first cells encountered by bacteria in our body. In addition to acting as a physical barrier, oral mucosal cells appear to express adhesion molecules and secrete many proinflammatory mediators, implying that the cells actively participate in mucosal immunity. Oral epithelial cells express a precursor form of interleukin (IL)-18, an important regulator of innate and acquired immune responses. An active form of IL-18 was secreted from the cells on co-stimulation with neutrophil proteinase 3 (PR3) and lipopolysaccharide after interferon-γ-priming. Subsequently, it was evident that neutrophil serine proteases including PR3 activate oral mucosal cells through protease-activated receptor-2 (PAR-2) pathway and play a critical role in IL-18 induction in vivo. These results indicate that induction of IL-18 and PAR-2 activation by neutrophil serine proteases may be critical in regulation of oral mucosal immunity.

Keywords: Oral mucosal immunity; Interleukin-18; Protease-activated receptor; Neutrophil; Serine protease

1. Introduction

Oral mucosal cells such as epithelial cells and fibroblasts are the first cells encountered by bacteria in our body. In addition to acting as a physical barrier, oral mucosal cells appear to express adhesion molecules [1] and secrete many proinflammatory mediators, i.e. interleukin (IL)-1β, IL-6, IL-8, tumor necrosis factor (TNF)-α and monocyte chemoattractant protein-1 (MCP-1) [2], implying that the cells actively participate in mucosal immunity.

IL-18 was originally identified as an interferon (IFN)-γ inducing factor [3] and is a multifunctional regulator of innate and acquired immune responses through its activation of both T helper cell type 1 (Th1) and type 2 (Th2) responses [4–6]. IL-18 has also been

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suggested to be a potent proinflammatory cytokine that regulates autoimmune and inflammatory diseases [4–6]. IL-18 is intracellularly produced as a 24-kDa inactive precursor form and secreted as an 18-kDa active cytokine after cleavage by IL-1β converting enzyme (caspase-1) in the same manner as IL-1β [4–6]. Furthermore, IL-18 is identified in both immune cells (activated macrophages, dendritic cells and Kupffer cells) and non-immune cells (keratinocytes, osteoblasts, adrenal cortex cells, epithelial cells, microglial cells and synovial fibroblasts) [4–6]. This wide range of distribution implies that IL-18 plays physiological roles and acts as a component of immune regulation.

Neutrophil-derived serine proteases, neutrophil elastase (NE; C3.4.21.37), cathepsin G (Cat G; EC3.4.21.20) and proteinase 3 (PR3; EC3.4.21.76) are stored in the azurophilic granules of neutrophils, and assist killing and digestion of microorganisms in neutrophils [7,8]. Primary action of proteases is considered to degrade extracellular proteins, but they exert biological actions in immune responses and inflammation by activation of a new subfamily of G protein-coupled receptors, protease-activated receptors (PARs), which are ubiquitously expressed in various tissues and cells. PAR family members undergo proteolytic cleavage of the N-terminus, thereby exposing tethered ligands and permitting autoactivation of the receptor function so that each receptor can initiate multiple signaling cascades [9–11]. Four members of the PAR family have thus far been cloned. PAR-1, -3 and -4 are mainly activated by thrombin, whereas PAR-2 is activated by a number of proteases such as trypsin, mast cell tryptase and coagulation factors VIIa and Xa, but not by thrombin [9–11]. Synthetic peptides of the tethered ligands of PARs can also activate PARs in an enzyme-independent manner. PAR-2 was identified by Nystedt et al. [12] and is expressed in a wide variety of tissues, including the gastrointestinal and respiratory tracts, pancreas, kidney, muscles, ovary and skin, but not in platelets [13]. Also, recent studies suggest that PAR-2 regulates several physiological processes, including growth, development, gastrointestinal functions, tissue repair and inflammation [9–11,14]. Mice that lack the PAR-2 gene exhibit diminished ear swelling and infiltration of inflammatory cells in a model of allergic dermatitis [15] and are immune to a form of adjuvant-induced arthritis [16].

This article will summarize recent studies of my group on IL-18 and oral mucosal immunity, especially on involvement of neutrophil serine proteases and PAR-2 [17–20].

2. Materials and methods

2.1. Cell and cell cultures

Human oral epithelial cells were prepared from explants of normal human gingival tissues with informed consent as described [17]. Human oral epithelial cell lines established from squamous cell carcinoma, HSC-2 and HO-1-u-1, and KB were obtained from the Cancer Cell Repository, Institute of Development, Aging and Cancer, Tohoku University (Sendai, Japan) and from the Health Science Research Resources Bank (Tokyo, Japan), respectively. HSC-2 and HO-1-u-1 were grown in RPMI 1640 with 10% heat-inactivated fetal calf serum (FCS). KB was grown in alpha-minimum essential medium (α-MEM) with 10% FCS. Human gingival fibroblasts (HGF) were prepared from the explants of normal gingival tissues of 6- to 10-year-old patients under informed consent, which also was given by the parents considering the age of donors. The explants were cut into pieces