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Review Article

The roles of odontoblasts in dental pulp innate immunity

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Summary Odontoblasts located in the outermost layer of dental pulp form a natural barrier between mineralized tissues, dentin, and soft tissues, dental pulp, of the vital tooth, and they first recognize caries-related pathogens and sense external irritations. Therefore, odontoblasts possess a specialized innate immune system to fight oral pathogens invading into dentin. Generally, the rapid initial sensing of microbial pathogens, especially pathogen-associated molecular patterns (PAMPs) shared by microorganisms, are mediated by pattern recognition receptors (PRRs), such as Toll-like receptor and the nucleotide-binding oligomerization domain (NOD). The innate immune responses in odontoblasts initiated by sensing oral pathogens provide host protective events, such as inflammatory reactions, to produce a variety of pro-inflammatory mediators, including chemokines and cytokines. These attract various inflammatory cells and cause antibacterial reactions, such as the production of defensins, to kill microorganisms in the proximal region of the odontoblast layer. This review focuses on innate immunity, especially cellular and molecular mechanisms regarding the sensing of PAMPs from oral pathogens by PRRs, in odontoblasts and provides information for future studies for the development of novel therapeutic strategies, including diagnosis and treatment, to prevent exceeding dental pulp inflammation and preserve the dental pulp tissues.

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Contents

1. Introduction

Odontoblasts have a long cell process extended to the dentinal tubule and their cell bodies are located on the surface of the dental pulp. Odontoblasts also form a layer along the interface between the dental pulp tissue and dentin, and they function as a natural barrier between mineralized tissues, dentin, and soft tissues, dental pulp, of the vital tooth [1]. Therefore, odontoblasts are the primary biologically active cells that maintain the dentin and protect the living pulp tissue by the deposition of reactionary dentin in response to mild stimulation with bacterial products at an early stage of dental caries and are involved in innate and adaptive immunity of the dental pulp to combat invading bacteria. The dental pulp under this odontoblast layer is a vascularized tissue with a dense capillary plexus. When bacteria and their products invade deeply into dentinal tubules, odontoblasts are the first pulpal cells encountered by these dentin-invading microorganisms and sense pathogen-associated molecular patterns (PAMPs) shared by microorganisms through specialized pattern recognition receptors (PRRs) at the dentin-pulp interface. This triggers host-protective events, such as inflammatory reactions, to produce a variety of pro-inflammatory mediators, including chemokines and cytokines. These attract various inflammatory cells and antibacterial reactions, such as the production of defensins, to kill microorganisms in proximity to the odontoblasts by initiating innate immune responses. When low-grade inflammation occurs, odontoblasts act to promote regenerative mechanisms through angiogenesis and dentinogenesis pathways and to increase pulp defense capability, finally leading to reactionary dentin formation. However, when intense and/or prolonged inflammation are occurs and dentin regenerative processes are blocked, copious amounts of pro-inflammatory mediators are produced from odontoblasts and infiltrating inflammatory cells activate various molecular and cellular signaling pathways that lead to the breakdown of dental pulp tissue [2]. This review focuses on the roles of odontoblasts in the innate immunity of dental pulp tissues, especially the expression profiles and functions of PRRs expressed in odontoblasts and the innate immune responses of odontoblasts triggered by the interaction between these PRRs and PAMPs shared by microorganisms.

2. Pattern recognition receptors (PRRs), their ligands and pathogen-associated molecular patterns (PAMPs)

The innate immune system is the major contributor to acute inflammation and effective defense induced by microbial infection, and it is also important in activating acquired immune responses [3,4]. Generally, the rapid initial sensing of invading microbial pathogens is mediated by specialized PRRs for PAMPs, which are structures conserved among microbial species. Recent studies have demonstrated that PRRs also recognize damage-associated molecular patterns (DAMPs), which include endogenous molecules released from damaged cells [4]. PRR families can be divided into 4 different classes including Toll-like receptors (TLRs), nucleotide-oligomerization binding domain (NOD)-like receptors (NLRs), C-type lectin receptors (CLRs), and retinoic acid-inducible gene (RIG)-I-like receptors (RLRs) (Table 1). TLRs and CLRs localize to the plasma membrane or endolysosome, whereas NLRs and RLRs are cytoplasmic proteins and serve as a second line of defense against pathogens that have evaded cell-surface-associated or endolysosomal PRRs. These receptors are expressed at different levels in various tissues, and they activate different signaling pathways and host immune responses after engagement with their ligands.

The best-characterized human PRR family is the TLRs. To date, 10 TLRs have been identified in humans and 13 in mice. TLRs were first identified as PRRs for various molecules derived from pathogens, such as bacteria, fungi, viruses, and parasites, and they form heterodimers, including TLR1/TLR2 and TLR6/TLR2, or homodimers, such as TLR3-TLR3 [5]. All TLRs are single-spanning type I transmembrane proteins with an ectodomain composing of leucine-rich repeat motifs that mediate the recognition of PAMPs, a transmembrane domain, and an intracellular Toll—interleukin 1 (IL-1) receptor (TIR) domain, which contains the sites

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