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Review Article

Role of *Streptococcus mutans* two-component systems in antimicrobial peptide resistance in the oral cavity[☆]

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Summary Approximately 100 trillion microorganisms exist in the oral cavity. For the commensal bacteria of the oral cavity, it is important to adapt to environmental stimuli, including human- or bacteria-derived antimicrobial agents. Recently, bacterial-specific signal transduction regulatory systems, called two-component systems (TCSs), which appear to be focused on sensing and adapting to the environment, were discovered. *Streptococcus mutans* is an oral commensal bacteria and is also known as a cariogenic bacteria. Although the virulence factors of *S. mutans* have been well demonstrated, the mechanism underlying the adaptation of the species to the oral cavity is poorly understood. *S. mutans* UA159 has 15 sets of TCSs. Among them, several have been demonstrated to be involved in acid tolerance, competence and biofilm formation. Recently, together with our findings, it was demonstrated that 5 TCSs were involved in resistance to antimicrobial agents. Furthermore, another TCS was associated with the production of bacteriocin. Six of 15 TCSs are associated with antimicrobial agents, implying that *S. mutans* can survive in the oral cavity by resisting various antimicrobial peptides.

In this review, we highlight the role of antimicrobial peptides in the oral cavity.
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1. Introduction

Approximately 100 trillion microorganisms exist in the human body; however, little information about the role and character of these commensal bacteria has been reported.

Recently, it was proposed that the human body establishes a symbiotic relationship that contributes to the maintenance of immune function by providing a niche for commensal bacteria called as microbiome [1–3]. Currently, the study of microbiomes in the human body is progressing via comprehensive gene analyses, using samples collected from saliva, skin, and feces [4–6]. Because the constitution patterns of the intestinal flora are of an infinite variety among humans, microbiomes may affect human physical and mental health because of their diversity [3,7,8]. It can be said that the study of microbiomes has changed the traditional concepts of microbial research.

In the process of indigenous flora formation, it is necessary to colonize the host by adapting to external stresses, including the immune system. Furthermore, bacteria must also compete with other commensal bacteria.

In the oral cavity, several hundreds of bacterial species exist, forming a complex bacterial floral community [9]. Oral flora, as well as intestinal flora, are also expected to exert various effects on the host. Although many studies of oral bacteria have focused on the pathogenesis of cariogenic bacteria and periodontal bacteria, future research on the association between oral flora and the host has attracted attention.

We first focused on *Streptococcus mutans*, a cariogenic bacteria, and sought to elucidate the colonization mechanism of this organism in the oral cavity. *S. mutans* plays a key role in the formation of dental plaque, as well as in tooth decay, via the production of acids [10–12]. Although the mechanism underlying caries development due to *S. mutans* is known, it is not clear why this bacterium is able to reside in the oral cavity. There are numerous antimicrobial agents in the oral cavity, and resistance to these antimicrobial agents is largely responsible for the colonization of *S. mutans*. To form the biofilm (dental plaque) physical barrier to resist the antimicrobial agents. Furthermore, bacteria including *S. mutans* possess two-component systems (TCSs)

which sense the environmental stimuli including antimicrobial agents and regulate the expressions of several factors to be responsible for the adaptation to the stimuli.

Two-component systems are prokaryote-specific signal transduction systems that comprise a sensory histidine kinase (HK) and a cognate response regulator (RR) [13]. The sensory HK undergoes autophosphorylation of a histidine residue in response to an environmental signal and relays the phosphate group to an aspartic acid residue on the cognate RR [14,15]. The phosphorylated RR then binds to target DNA elements with strong affinity, activating or repressing transcription of target genes (Fig. 1). We focused on the relationship between TCSs and resistance to antimicrobial peptides. Through these results, we have gained new knowledge of the above phenomena.

In this review, we present an overview of antimicrobial peptides and TCSs, including the results of our study regarding the acquisition of resistance mechanisms in *S. mutans* against human- and bacteria-derived antimicrobial peptides.

2. Human-derived antimicrobial peptides

In the oral cavity, there are many antimicrobial factors, such as antimicrobial peptides, lysozymes, hydrogen peroxide and lactoferrin [16,17]. Among these antibacterial factors, antimicrobial peptides are believed to have bactericidal activity against various oral bacteria, including cariogenic and periodontopathogenic bacteria [17]. Human-derived antimicrobial peptides originate from various sources, such as the saliva, gingival epithelium, mucosa, neutrophils and gingival crevicular fluid [18,19]. These peptides are considered the first defense against bacterial infections as a form of innate immunity. Fig. 2 shows the varieties of human-derived antimicrobial peptides.

2.1. Defensins

Defensins have three disulfide bonds among 6 cysteines in peptides, which distinguishes them from other antimicrobial

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