Why and how do teeth come off? –New insights into the tooth loss during periodontitis–

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Inadequate toothbrushing leads to the accumulation of dental plaque, which contains enormous number of bacteria inside. These bacteria stimulate immune cells to elicit inflammation in the periodontium, periodontitis. Periodontitis is the most common infectious disease and a major cause of tooth loss [1]. Because patients with multiple tooth loss suffer from mastication disorder and are subsequently exposed to a higher risk of aspiration pneumonia and dementia [2], dentists make every effort to preserve teeth. To date, there has been a substantial development in the treatment procedures of periodontitis [3-5].

In the periodontium under inflammation, there is an infiltration of many types of immune cells and these cells produce a variety of inflammatory cytokines [6]. Some of these cytokines are known to induce the expression of receptor activator of NF-κB ligand (RANKL), the essential cytokine for osteoclastogenesis [7,8]. Thus, it is widely accepted that bacteria induce inflammatory bone loss and subsequent tooth loss. However, the reason why and the mechanism of how teeth come off in the context of periodontitis have not been sufficiently addressed.

Recently, Tsukasaki, *et al.* demonstrated that a special IL-17–producing T cell subset plays a crucial role in eradication of bacteria and alveolar bone resorption in a mouse model of periodontitis [9]. In the process of periodontitis, the number of T_H17 cells derived from Foxp3+Treg cells (exFoxp3 T_H17 cells) and the number IL-17–producing T cells showed a robust increase. In mice deficient in IL-17, there was an increase in bacterial load and alveolar bone resorption decreased. In mice deficient in αβ T cells, alveolar bone resorption also decreased. On the other hand, injection of exFoxp3 T_H17 cells was shown to exacerbate alveolar bone loss, indicating the contribution of them to bone loss in periodontitis. Conversion of Treg cells to exFoxp3 T_H17 cells is known to be mediated by IL-6. The expression of this cytokine was also significantly upregulated after the induction of periodontitis. Its blockade or deficiency led to the decrease of the bone loss.

Bone resorption is mediated by osteoclast, the differentiation of which is induced by RANKL. RANKL is expressed by various types of cells including lymphocytes (T cells and B cells) and mesenchymal cells such as bone marrow stromal cells, osteoblasts and osteocytes [8]. Because exFoxp3 T_H17 cells are known to highly express RANKL to drive osteoclastogenesis and IL-17 induce RANKL expression on mesenchymal cells [10,11], the source of RANKL during bone loss in periodontitis was investigated. As a result, osteoblasts and periodontal ligament cells have turned out to be key sources of RANKL in periodontitis. RANKL adopts two forms (membrane–bound and soluble) and their physiological roles have been discussed for long [8]. Using a novel mouse strain which is deficient only in soluble form of RANKL but not in membrane–bound form [12], it was shown that membrane–bound form has a crucial role in inducing bone resorption in periodontitis. These results taken together clarified the mechanism of how periodontal inflammation occurs.

What is the reason for the tooth loss by periodontitis? Is it only a secondary effect of inflammation? Gingiva is the only region of the body where the continuity of epithelium is interrupted in the physiological condition, thus forming an entry site of bacteria into the periodontium, and tooth loss leads to the closure of the epithelial gap. Therefore, it is speculated that infection–induced tooth loss would save the body from the progression of infection. Extraction of periodontitis–affected teeth alleviated systemic infection, supporting this hypothesis.

This article revealed that, in periodontitis, T_H17 cells converted from Foxp3+ cells protect the body by both eradication of pathogens and blocking the entry site. These cells have been previously shown to be a crucial arthritogenic T cell subset [11]. The effector cytokine of T_H17 cells, IL-17, is reported to have both catabolic and anabolic effects on bone [13-15]. It seems interesting to note that these cells and cytokines can exert both destructive and protective effects depending on the situations they function. It is also noteworthy that this article has defined tooth loss as a termination of infection; otherwise it would remain to be regarded as mere a secondary effect of inflammation. Provided with a clearer view of tooth loss by periodontitis, we will be able to have a novel therapeutic strategy for periodontitis in the future, targeting exFoxp3 T_H17 cells and related cytokines to control both microbial infection and bone resorption.

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