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Etiology of leukocyte adhesion deficiency-associated periodontitis revisited: Not a raging infection but a raging inflammatory response

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Abstract

In leukocyte adhesion deficiency type I (LAD-I), neutrophils fail to adhere to blood vessels' walls and thus cannot transmigrate to peripheral tissues. LAD-I patients invariably experience an aggressive form of generalized periodontitis, which has been historically attributed to defective neutrophil surveillance of the periodontal infection. This time-honored notion has now been challenged by a recent study, which showed that the underlying etiology involves a dysregulated host response that leads to overexpression of the proinflammatory and bone-resorptive cytokine IL-17.

Leukocyte adhesion deficiency type I(LAD-I) is an autosomal recessive immunodeficiency caused by mutations in the CD18-encoding *ITGB2* gene. Single gene disruptions are rare occurrences yet often lead to severe clinical phenotypes providing unique opportunities for understanding the role of specific molecules in human biology. In the case of LAD, CD18 mutations clearly compromise neutrophil adhesion and extravasation to sites of infection or inflammation (1). Affected individuals display blood neutrophilia, suffer from recurrent infections at mucosal or skin surfaces, and experience severe generalized aggressive periodontitis featuring pathologic bone resorption and premature loss of primary and permanent teeth. This has adverse psychological and functional consequencesin affected individuals (1–4). The severity of LAD-I–associated periodontal disease serves as one of the clearest pieces of evidence that neutrophils within oral tissues are required for the maintenance of periodontal health. Given the documented antimicrobial activities of neutrophils and the fact that the periodontal tissue of LAD-I patients is specifically devoid of neutrophils (which are confined in blood vessels), LAD-I–associated periodontitis has been historically attributed to defective neutrophil surveillance of the periodontal infection. This notion was so commonsensical that it was never questioned or challenged until recently.

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Conflict of interest

The authors declare no conflicts of interest.

In a collaborative project which examined the disease in patients and relevant mouse models, our groups have shown that LAD-I periodontitis does not represent a raging infection but rather is caused by dysregulated overexpression of the bone-resorptive cytokine IL-17(5), implicating for the first time in humans the role of neutrophils in the regulation of IL-17 responses. These findings in LAD-I are consistent with a disruption of a major neutrophil homeostatic mechanism ('neutrostat'). This mechanism senses neutrophil recruitment and clearance in tissues and regulates neutrophil production through a negative-feedback loop involving a cascade of cytokines, specifically the IL-23–IL-17–G-CSF axis(6). When neutrophils cannot transmigrate to peripheral tissues, as in LAD-I, the neutrostat regulatory circuit is disrupted leading to unrestrained expression of IL-23 and downstream cytokines including IL-17 and G-CSF. Whereas the overproduction of G-CSF explains the increased granulopoiesis and blood neutrophilia in LAD-I patients, the overproduction of IL-17 was not previously linked to an IL-17–driven disease in animal models or in humans. Moreover, as the neutrostat mechanism was dissected in mice, it remained uncertain whether IL-17 is excessively elevated also in humans with LAD-I (or other conditions with defective neutrophil recruitment) and contributes to any of its clinical manifestations or associated pathologies. Our findings showed abundant expression of T cell-derived IL-17 mRNA and protein in the periodontal tissue of LAD-I patients, whereas antibody-mediated neutralization of this cytokine in a mouse model of the disease reversed inflammatory bone loss (5), thereby demonstrating a pathogenic role of IL-17 in LAD-I periodontitis.

Interestingly, our mechanistic studies in murine models that mimic the LAD-I phenotype not only show that IL-17-driven inflammatory bone loss underlies LAD-I periodontitis, but also that IL-17–dependent inflammation promotes bacterial overgrowth in this condition. In this regard, both LAD-I patients and mice exhibiting the LAD-I phenotype have higher periodontal bacterial load (tooth-associated biofilm) than their respective healthy controls. Intriguingly, however, the neutralization of IL-17 diminished the total periodontal bacterial counts in treated mice to normal levels (5). This finding suggests that the high bacterial burden was driven by IL-17–dependent inflammation rather than by defective immune surveillance due to the lack of neutrophils. This finding can moreover be explained by the fact that destructive inflammation generates abundant tissue-breakdown products (*e.g.*, collagen-derived peptides and heme-containing compounds) that serve the nutritional needs of periodontal bacteria (7, 8); it thus follows that the inhibition of inflammation with anti-IL-17 can limit the food supply and hence bacterial growth. Histological and quantitative microbiological analysis of tissue samples from LAD-I patients provided further support that LAD-I periodontitis does not involve an unusual tissue-invasive or raging infection within the lesion driving tissue destruction (5). This novel concept that LAD-I periodontitis does not represent an uncontrolled infection is consistent with the fact that this form of periodontitis is recalcitrant to antibiotic treatment and/or mechanical removal of the tooth-associated biofilm (2, 9). It should be noted, however, that the above do not exclude the involvement of the tooth-associated microbiota in the pathogenic process. The periodontal microbiota acts as the initial stimulus to unleash the disinhibited IL-23–IL-17 axis. In this regard, the bacteria do not have to invade the periodontal tissue to stimulate inflammatory

cells, as their released bacterial products (*e.g.*, lipopolysaccharide) can readily penetrate through the gingival junctional epithelium and activate inflammatory cells.

The notion that defective immune surveillance by neutrophils is not an overriding factor in susceptibility to periodontitis is consistent with clinical findings in individuals with chronic granulomatous disease (CGD). These patients exhibit impaired neutrophil oxygen-dependent bactericidal activity and suffer from frequent infections, including pneumonia and abscesses of the skin. However, in contrast to LAD-I patients, CGD patients are not more susceptible to periodontitis than the general population(10, 11). On the other hand, the transmigration competency *per se* of neutrophils so as to complete a normal life cycle is crucial for periodontal tissue homeostasis. The recent demonstration that neutrophils migrate normally to the periodontal tissue even in the absence of bacterial colonization as in germ-free mice(12) is consistent with the notion that neutrophil recruitment mediates homeostatic functions that are not necessarily related to infection control. For instance, a subset of human mature neutrophils was recently identified that can inhibit T cell activation by delivering H_2O_2 into the immunological synapse in a Mac-1 integrin–dependent manner (13). Taken together with our previous demonstration that unrestrained neutrophil recruitment to the periodontium causes destructive inflammation(14), it would be safe to state that both impaired and excessive neutrophil recruitment can lead to periodontitis, in turn highlighting the notion that neutrophil homeostasis is key to periodontal health. In contrast to the regulatory defects associated with the absence of neutrophils in the periodontium, when neutrophils contribute to periodontitis by their presence in excessive levels, the underlying mechanism likely involves bystander tissue damage by degranulation of extracellular proteases, formation of reactive oxygen species, and release of proinflammatory cytokines (7). However, when excessive neutrophil infiltration is due to deficiency of developmental endothelial locus-1 (Del-1), an endothelial cell-secreted regulatory protein, the resulting inflammation is also characterized by excessive IL-17 production (14). This is because Del-1 and IL-17 are reciprocally regulated, and low levels of either molecule lead to overproduction of the other (14).

An important implication of our findings is that the neutralization of IL-17 can be an effective therapeutic treatment for LAD-I periodontitis which is recalcitrant to conventional treatments. A similar IL-17–driven mechanism for periodontal tissue destruction could be relevant to additional conditions associated with poor or no accumulation of neutrophils in extravascular sites, owing to defective chemotaxis (*e.g.*, Chediak-Higashi syndrome, and Papillon-LeFevre syndrome) or neutropenic states (*e.g.*, congenital agranulocytosis, cyclic neutropenia, and autoimmune neutropenia). Similar to LAD patients, individuals with defective chemotaxis develop rapidly advancing inflammatory periodontal bone loss at very young age. The same pathology is observed in neutropenic patients unless the neutrophil count is appropriately corrected, whereas cyclic neutropenia has been associated with significant periodontal bone loss during the cyclical episodes where neutrophil counts are diminished(2, 4, 9, 10, 15). Although diminished neutrophil recruitment in these conditions would also be expected to lead to dysregulated overproduction of IL-23 and IL-17, this hypothesis has yet to be empirically confirmed.

In recent years, IL-17 has also been implicated in the pathogenesis of common, chronic forms of periodontitis(16–18). Treatments with biologics targeting IL-17 or the IL-17 receptor have already been shown to be safe after systemic administration in human volunteers and are promising for the treatment of rheumatoid arthritis and psoriasis (19, 20). Such treatments should be even safer for periodontitis since the administration of the drugs could be performed locally in the periodontal tissue. In this regard, anti-IL-17 treatment is a valid candidate therapeutic target for the treatment of LAD-I periodontitis and may provide the first setting for evaluating the use of targeted IL-17 biologics in the treatment of periodontal diseases.

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