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Role of bacteria in leukocyte adhesion deficiency-associated periodontitis

George Hajishengallis [a, *], Niki M. Moutsopoulos [b, **]

[a] Department of Microbiology, University of Pennsylvania Penn Dental Medicine, Philadelphia, PA 19104, USA
[b] Oral Immunity and Inflammation Unit, National Institute of Dental and Craniofacial Research, NIH, Bethesda, MD 20892, USA

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ABSTRACT

Leukocyte adhesion deficiency Type I (LAD-I)–associated periodontitis is an aggressive form of inflammatory bone loss that has been historically attributed to lack of neutrophil surveillance of the periodontal infection. However, this form of periodontitis has proven unresponsive to antibiotics and/or mechanical removal of the tooth-associated biofilm. Recent studies in LAD-I patients and relevant animal models have shown that the fundamental cause of LAD-I periodontitis involves dysregulation of a granulopoietic cytokine cascade. This cascade includes interleukin IL-23 (IL-23) and IL-17 that drive inflammatory bone loss in LAD-I patients and animal models and, moreover, foster a nutritionally favorable environment for bacterial growth and development of a compositionally unique microbiome. Although the lack of neutrophil surveillance in the periodontal pockets might be expected to lead to uncontrolled bacterial invasion of the underlying connective tissue, microbiological analyses of gingival biopsies from LAD-I patients did not reveal tissue-invasive infection. However, bacterial lipopolysaccharide was shown to translocate into the lesions of LAD-I periodontitis. It is concluded that the bacteria serve as initial triggers for local immunopathology through translocation of bacterial products into the underlying tissues where they unleash the dysregulated IL-23–IL-17 axis. Subsequently, the IL-23/IL-17 inflammatory response sustains and shapes a unique local microbiome which, in turn, can further exacerbate inflammation and bone loss in the susceptible host.

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1. Introduction

Periodontitis is an inflammatory disease that typically affects adults [1]. The disease causes destruction of the periodontium (*i.e.*, tooth-supporting tissues such as gingiva and alveolar bone) and constitutes a potential risk factor for certain systemic diseases [2–4]. However, individuals with disorders affecting neutrophil recruitment to the periodontium, such as the rare condition leukocyte adhesion deficiency (LAD), rapidly develop severe periodontitis early in life affecting both the primary and permanent dentition [5–11] (Fig. 1). In addition to severe periodontal bone loss (Fig. 1A) [11], LAD-I patients display neutrophilia (increased blood neutrophil counts) and are susceptible to persistent infections (*e.g.*, pneumonia) [6–9,12,13]. Rare monogenic diseases represent an important medical and social issue in its own right, cumulatively affecting 25 million patients in North America alone [14]. Importantly, however, the study of rare diseases, such as LAD-I, is not only relevant to the treatment of patients with these specific disorders; these diseases constitute real-life models to understand human biology and (patho)physiological mechanisms, thereby providing critical insights into common diseases [15–18].

LAD represents a group of distinct inherited disorders, which inhibit the normal extravasation of neutrophils and their recruitment to sites of infection or inflammation [6,8,10,11,19,20]. LAD patients have defects in the expression or function of the leukocyte-restricted β_2 integrins (heterodimeric molecules, each with a distinct CD11 subunit and a common CD18 subunit), or other adhesion molecules. Consequently, their circulating neutrophils cannot adhere to vascular endothelial cells, a function that is required for extravasation [21–23]. LAD type I (LAD-I) is caused by deficiency in β_2 integrins, LAD-II is due to defective glycosylation of selectin ligands, and LAD-III involves dysfunction of signaling intermediates affecting integrin activation [13].

The most common type of LAD is LAD-I, an autosomal recessive

* Corresponding author.
** Corresponding author.
E-mail addresses: geoh@upenn.edu (G. Hajishengallis), nmoutsopoulos@dir.nidr.nih.gov (N.M. Moutsopoulos).

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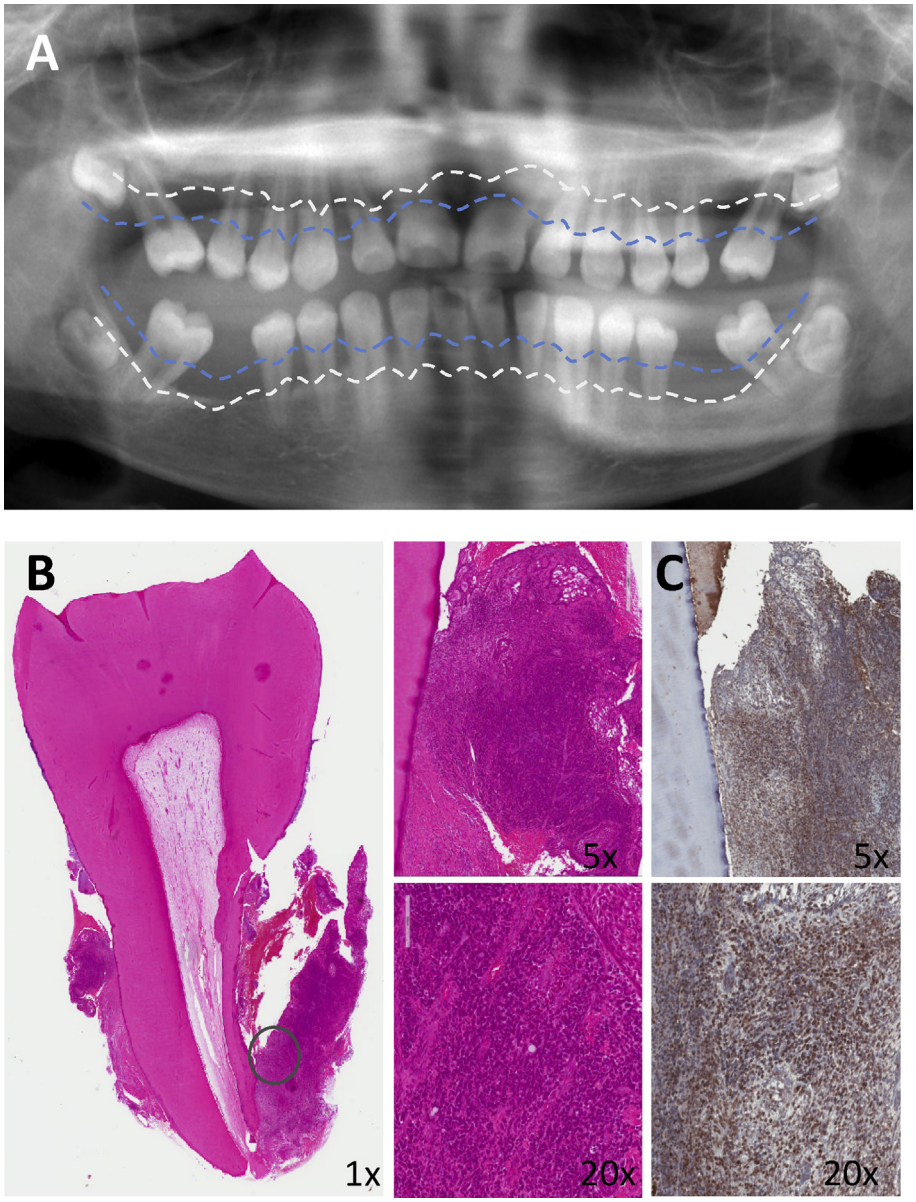

Fig. 1. Clinical and histological profile of LAD-I periodontitis. (A) Panoramic radiograph of 11-year-old LAD-I patient with severe bone loss. Blue dotted line represents physiologic bone levels and white dotted line demonstrates current bone levels. (B) H&E staining of extracted tooth and surrounding soft tissues. Encircled soft tissue reveals dense inflammatory infiltrate in the lesion (shown in lower and higher magnification, 5x-20x). (C) Immunohistochemistry for IL-17 in LAD-I tissues. Brown staining indicates IL-17-positive cells (original magnification 5x-20x). Patients were enrolled in an IRB approved protocol and had signed informed consent. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

immunodeficiency caused by mutations in the CD18-encoding *ITGB2* gene; therefore, LAD-I patients have defective expression in all β_2 integrins [8,11,12,20]. The LFA-1 integrin (CD11a/CD18) plays a crucial role in firm adhesion by interacting with endothelial cell counter-receptors (e.g., intercellular adhesion molecule-1) and is thus required for extravasation of the neutrophils to peripheral tissues [21–23]. In contrast to neutrophils, other types of leukocytes use different or additional adhesion molecules (*e.g.*, VLA-4; very late antigen-4) for firm adhesion and extravasation [24–29]. Consistent with this, the heavy inflammatory infiltrate (Fig. 1B) in the periodontium of LAD-I patients is specifically devoid of neutrophils (which are confined in vessels), whereas lymphocytes and other cells of hematopoietic origin are found in abundance in the periodontium [11].

LAD-I–associated periodontitis (hereafter "LAD-I periodontitis") has been historically attributed to lack of neutrophil surveillance of the periodontal infection; yet, this form of periodontitis has proven unresponsive to antibiotics and/or mechanical removal of the tooth-associated biofilm [5–7,11,19,30–32]. A recent study in LAD-I patients and relevant animal models has shown that the fundamental cause of LAD-I periodontitis involves dysregulated overproduction of interleukin (IL)-23 and hence IL-17 (Fig. 1C) [11], a pro-inflammatory and pro-osteoclastogenic cytokine implicated in inflammatory bone loss in humans and animal models of arthritis or periodontitis [33–35]. The dysregulation of the IL-23/IL-17 response is consistent with the disruption of a major neutrophil homeostatic mechanism, known as the 'neutrostat'. This mechanism senses neutrophil recruitment and clearance in peripheral tissues and regulates neutrophil production through a granulopoietic cytokine cascade involving IL-23, IL-17, and granulocyte

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