Porphyromonas gingivalis bacteremia impairs arterial healing process in an experimental model of dissecting aneurysm

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Background: Epidemiological studies have suggested that periodontal diseases can worsen the issue of atherosclerosis complications through the iterative passage of periodontal bacteria into the circulation. However, the molecular mechanism by which circulating pathogens can impact on atherosclerosis complications remains unknown.

Objective: The aim of this study was to determine if and how Porphyromonas gingivalis (Pg, a common periodontal pathogen) bacteremia affects the healing process of experimental dissecting atherosclerotic arteries.

Methods: 28-week-old male Apolipoprotein E (apoE)-/- mice were subjected to chronic angiotensin II infusion, an experimental model of atherosclerosis complicated by acute aortic dissection. Mice received an intravenous injection of Pg (1x10⁸ CFU, n=10) once per week for 4 weeks; control mice received the vehicle only (saline, n=10).

Results: Repeated Pg experimental bacteremia dramatically increased the rate of fatal aortic rupture (23/34 in Pg vs 8/23 in controls, p<0.05). The periodontal bacteria were detected at the site of aortic dissection of Pg-injected survivors the lesions of which displayed reduced intramural hematoma resolution and decreased collagen deposition as compared to controls. The impaired aortic healing in Pg-injected mice was associated with local accumulation of CD45+ leukocytes, most of which were pro-inflammatory M1 macrophages as detected by the expression of iNOS+ and IRF-5+. A systemic inflammatory state also detected in mice subjected to experimental periodontal bacteremia, as reflected by plasma concentrations of MC-CSF, IFN-γ, and IL-12, all of which are pro-M1 factors and the addition of Pg to bone marrow-derived macrophage cultures strikingly enhanced their M1 polarization (expression of iNOS/arginase-II) whilst impairing the acquisition of the reparative M2 macrophage phenotype (arginase-I expression). Of note, the use of a gingipain-defective strain prevented the M1 polarizing effect of Pg suggesting a specific role for the Pg-associated gingipain proteases in the deleterious role of Pg bacteremia in arterial healing.

Conclusions: Recurrent Pg bacteremia, a hallmark of periodontitis, negatively impacts atherosclerosis complications by impairing the arterial healing process. This deleterious effect of Pg could be related, at least in part, to the action of gingipains which prevent the switch of lesion-associated macrophages from a pro-inflammatory M1 phenotype to a reparative M2 phenotype.