On the link between periodontitis and atherosclerosis

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Chronic oral infection with the periodontal disease pathogen, *Porphyromonas gingivalis*, not only causes local inflammation of the gums leading to tooth loss but also is associated with an increased risk of atherosclerosis. A study published on July 10th in *PLOS Pathogens* now reveals how the pathogen evades the immune system to induce inflammation beyond the oral cavity.

Like other gram-negative bacteria, *P. gingivalis* has an outer layer that consists of sugars and lipids. The mammalian immune system has evolved to recognize parts of this bacterial coating, which then triggers a multi-pronged immune reaction. As part of the "arms race" between pathogens and their hosts, several types of gram-negative bacteria, including *P. gingivalis*, employ strategies by which they alter their outer coats to avoid the host immune defense.

Caroline Attardo Genco, from Boston University School of Medicine, USA, in collaboration with Richard Darveau, at the University of Washington School of Dentistry, USA, and colleagues focused on the role of a specific lipid expressed on the outer surface of *P. gingivalis*, called lipid A, which is known to interact with a key regulator of the host's immune system called TLR4. *P. gingivalis* can produce a number of different lipid A versions, and the researchers wanted to clarify how these modify the immune response and contribute to the ability of the pathogen to survive and cause inflammation—both locally, resulting in oral bone loss, and systemically, in distant blood vessels.

They constructed genetically modified strains of *P. gingivalis* with two distinct lipid A versions. The resulting bacteria produced either lipid A that activated TLR4 (called "agonist") or lipid A that interacted with TLR4 but blocked activation ("antagonist"). Utilizing these strains, they demonstrate that *P. gingivalis* production of antagonist lipid A renders the pathogen resistant to host bacterial killing responses. This facilitates bacterial survival in macrophages, specific immune cells that normally not only gobble up the bacteria but also "digest" and kill them.

When the researchers infected atherosclerosis-prone mice with the *P. gingivalis* TLR4 antagonist strain, they found that this exacerbates inflammation in the blood vessels and promotes atherosclerosis. In contrast, the ability of *P. gingivalis* to induce local inflammatory bone loss was independent of lipid A variations, which demonstrates that there are distinct mechanisms for induction of local versus systemic inflammation.

The researchers conclude, "*P. gingivalis* modifies its lipid A structure in order to evade host defenses and establish chronic infection leading to persistent systemic low-grade inflammation". They go on to state that "uniquely among gram-negative pathogens, *P. gingivalis* evasion of TLR4-mediated host immunity results in progression of inflammation at a site that is distant from local infection by gaining access to the vasculature."

More information: Slocum C, Coats SR, Hua N, Kramer C, Papadopoulos G, et al. (2014) Distinct Lipid A Moieties Contribute to Pathogen-Induced Site-Specific Vascular Inflammation. *PLoS Pathog* 10(7): e1004215. DOI: 10.1371/journal.ppat.1004215

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