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Relationship between serine dipeptide lipids of commensal Bacteroidetes and atherosclerosis

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Genera such as *Porphyromonas, Prevotella, Tannerella* and *Capnocytophaga* dominate among Bacteroidetes in the mouth [1]. Microorganisms of the phylum Bacteroidetes are also prevalent in the human intestinal microbiota where members of the genus *Bacteroides* constitute approximately one-third of the cultivable bacteria [2,3]. A noteworthy feature of periodontopathogens is that they can invade endothelial cells [4–6]. Similarly, the epithelial barrier of the gut serves as an infectious foothold for many bacterial pathogens and may act as an entry port for pathogens to disseminate into deeper intestinal tissues [7]. It is recognized that normal body function may lead to transient bacteraemias from either the gut or the oral microbiomes but also passive transfer/uptake of bacterial products into the host may occur. In addition, the gut integrity can be weakened by unhealthy conditions, e.g. by high-fat intake or obesity which now is frequent in the Western world, leading to the penetration of gut microbiota or transfer of their products into the circulation [8].

Unfortunately, not much is known about the capacity of oral and intestinal organisms, such as Bacteroidetes, to promote atherosclerosis although inflammatory mechanisms acting in concert to increase systemic inflammation in periodontal disease and to promote or exacerbate atherogenesis have been reviewed [9], and 'proofs' for how periodontal bacteria can contribute to atherosclerosis have been listed [10]. An interesting study, assessing the relationship between serine dipeptide lipids of Bacteroidetes bacteria in human arteries and atherosclerosis, was recently published in the *Journal of Lipid Research* [11]. The new ideas advocated here add to our understanding of the capacity of such bacteria to contribute to atherosclerosis.

The authors found that lipid extracts from human carotid endarterectomy and carotid artery samples from young individuals consistently contained bacterial serine dipeptide classes. These lipids are produced by common oral and intestinal Bacteroidetes bacteria, e.g. by *Porphyromonas gingivalis* [12] and are known to promote inflammatory processes [13]. In *P. gingivalis*

they comprise Lipid 654, which is an agonist for human and mouse Toll-like receptor (TLR)2, but not for TLR4, and Lipid 430. The latter can be a deacylated product of Lipid 654 but is also recovered from other Bacteroidetes bacteria. Accumulation of Lipid 654 in human tissues indicated that an exogenous TLR2 ligand was present and originated from organisms either of the oral cavity or the intestinal tract. TLR2 is known to be an important immune receptor in the development of atherosclerosis [14–16], and it is upregulated in endothelial cells subjected to turbulent fluid flow [17,18].

The relative abundance of these lipids was examined in oral and intestinal bacteria from the phylum Bacteroidetes and from human serum and brain samples from healthy adults [11]. These analyses showed that the median Lipid 430/Lipid 654 ratio in carotid endarterectomy samples was significantly higher than the median lipid ratio in extracts from common oral and intestinal Bacteroidetes bacteria, as well as in extracts from serum and brain samples from healthy subjects. Even more important, the median Lipid 430/Lipid 654 ratio was increased significantly in carotid endarterectomies when compared to artery samples from controls.

The authors suggested that deacylation of Lipid 654 to Lipid 430 most likely takes place in diseased artery walls due to activity by the enzyme phospholipase A2. Expression of phospholipase A2 is increased in atherosclerotic arteries concomitant with chronic inflammation associated with the formation of atheromas [19,20]. The increased level of Lipid 430 was not seen in blood or brain tissues, suggesting that the conversion was a local process taking place in diseased arteries.

Furthermore, the results indicated that commensal Bacteroidetes bacteria from the oral cavity and the gut could contribute to the pathogenesis of TLR2-dependent atherosclerosis through deposition and metabolism of serine dipeptide lipids in the artery walls. Further, the elevated activity of lipoprotein-associated phospholipase 2 could account for the increased hydrolysis of Lipid 654 to Lipid 430 in diseased arteries. Deacylation of Lipid 654

to Lipid 430 may promote atherogenesis through engagement of TLR2. Noteworthy, serine lipids increased with formation of atheromas.

The authors concluded that oral and intestinal Bacteroidetes may be involved in atherogenesis through local deposition of serine dipeptide lipids. Lipid 654 from commensal bacteria inhabiting the gastrointestinal tract and the oral cavity is present in the systemic circulation [21]. Interestingly, serine dipeptide lipids may also promote alveolar bone loss in periodontitis by inhibiting osteoblast differentiation [22].

Although the study by Nemati et al. [11] has brought up new and interesting thoughts on the pathogenesis of atherosclerosis, other surface molecules of these bacteria may also influence this condition [23]. It should also be kept in mind that much of the pathogenicity of *P. gingivalis* is surprisingly related to its overall immunosuppression of the host [24]. Nevertheless, the study by Nemati et al. [11] has certainly extended our view on the possible pathogenesis of Bacteroidetes in atherosclerosis where serine dipeptide lipids may be hitherto unappreciated virulence factors.

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