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Is there a Common Mechanism that Explains the Links between Inflammation and Coronary Artery Disease; Calcification of Atheromas

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Much research has been done to demonstrate and understand the putative links between periodontitis and coronary artery disease (CAD); in particular calcification of atheromatous plaques. To be sure, there are numerous studies including cross-sectional, retrospective, interventional and now Meta analyses that have confirmed the association between periodontitis and CAD. However, the mechanisms underlying this linkage remain unclear. Therefore there is no proof of a causal relationship between these conditions.

Indeed it is not only periodontitis that has been shown to be related statistically to the onset and/or development of CAD. Other conditions shown to be related statistically to CAD include inflammatory disorders such as osteoarthritis (OA), rheumatoid arthritis (RA) and even psoriasis. Given these widespread associations, there has been much research dedicated to the understanding of these links and whether the relationships are causal, merely statistical correlations, or a combination of the two. In relation to the associations between periodontitis and CAD, most of the focus has been on the potential for periodontal pathogenic microorganisms to play a causal role. The putative microbial mechanisms that are being used to explain the associations between periodontitis and CAD/atheroma calcification are compelling and biologically plausible. However we suggest that they cannot be used to explain the statistical connections that have also been shown to exist between psoriasis, OA, or RA and CAD/atheroma calcification.

If there are causal relationships between disparate inflammatory diseases with CAD, then it would seem unlikely that the mechanisms responsible for these linkages are microbiological. As noted above, CAD is characterized not only by accumulation in arteries and arterioles of cholesterol-filled plaques, but also by calcification of those plaques, a development that is suggested to be a significant risk factor for the development of thromboembolic phenomena as well as vascular stiffening, and ultimately for acute myocardial infarction and ischaemic stroke. Perhaps factors that regulate inflammation, and in relation to this Editorial, the calcification of atheromatous plaques, should also be considered in more detail. In this regard, collaboration of our laboratory with the laboratories of Dr. James Dennis and Dr. Christopher McCulloch as well as studies carried out by Dr. W. Jahnen-Dechent has led to a potentially unifying hypothesis that might explain why inflammatory diseases in vastly different systems could increase the risk for the development of CAD/calcifying atheroma formation. This is based on the two main processes involved in the development of vascular calcification. Vascular calcification includes not only dystrophic calcification but also osteogenic cell-differentiation and formation of mineralized bone within the intimal layers of involved arteries and arterioles (both detectable radiographically as vascular calcification). Therefore, anything that might modulate these regulatory mechanisms could also play an important role regarding the associations described between inflammatory diseases and CAD as will be described below.

Studies by Dr. W Jahnen-Dechent demonstrated that Alpha-2 Heremans Schmid glycoprotein (Ahsg or fetuin-A) acts as an inhibitor of mineralization. It was suggested that Ahsg, being a ubiquitous serum glycoprotein, could thus play an important inhibitory or regulatory role in vascular calcification. Indeed it has been demonstrated that in patients with increases in vascular calcification, lower levels of Ahsg was observed. Studies by Dr. Dennis, reported that Ahsg contained a transforming growth factor-beta (TGFβ) receptor-like region in its structure can act as a decoy receptor for TGF as well as for related proteins, the bone morphogenetic proteins (BMPs). Given these findings, it was thought reasonable that Ahsg should also inhibit osteo-differentiation by sequestration of BMPs. Therefore, in collaboration with Dr. Dennis our laboratory demonstrated, using both *in vivo* and *in vitro* studies, that it inhibits differentiation of osteoblasts and formation of mineralized tissue; i.e. bone. These findings also led to the concept that Ahsg might also play an important role in the regulation of BMP-induced ectopic mineralization and the ankylosis that occurs in some cases following total joint arthroplasty (joint replacement). In relation to this it is thought that particles of bone created during joint replacement surgery induce *de novo* osteogenesis that leads to ankylosis in certain patients. It was hypothesized that perhaps patients who were susceptible to ectopic osteogenesis and/or who had severe osteoarthritis (hence needing joint replacement) might have reduced serum levels of Ahsg in comparison to a healthy age and sex matched control group and this was in fact shown to be the case. Taken together then, this line of research led to the notion that Ahsg might have the potential to regulate ectopic ossification and/or mineralization, and that when its levels are reduced, there are increases in atheroma calcification that could lead to the end-stage sequelae of CAD. Hence the reduced levels of serum-Ahsg measured in patients with inflammatory diseases could explain the links seen between those diseases and CAD.

Given Ahsg's possibly important role in the development of inflammation associated CAD it was still not known what mechanisms could explain how the actual reductions in this serum glycoprotein develop. In relation to this it came to our attention that the matrix metalloproteinases (MMPs) proteolytic enzymes known to be up regulated in inflammatory diseases (for our initial purposes, periodontitis), might be responsible for reducing the levels of serum Ahsg. This then led to a series of experiments showing that MMPs hydrolyze Ahsg. Moreover, once hydrolyzed, Ahsg lost its ability to inhibit mineralization. By extension, if enough degradation of Ahsg

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could be caused by MMPs leaked into serum from inflamed tissues (no matter the source), the loss of function caused by its (Ahsg) degradation could increase the risk for the formation of calcified atheromas.

At this point, further investigations are underway to determine whether Ahsg retains or loses the structure in its TGFβ receptor-like region after MMP-mediated hydrolysis. It is predicted that this structure is lost following hydrolysis, therefore causing Ahsg to lose its ability to interfere with BMP-induced osteogenesis. This would then complete the circle of evidence relating to Ahsg and MMPs in their putative roles in the regulation of calcified atherogenesis. We suggest that these preliminary findings could help to explain how inflammation is linked to vascular calcification, and this is mediated in large part by MMP-mediated degradation of Ahsg caused by higher than normal levels of inflammation associated MMPs released into the serum of patients with inflammatory diseases; a mechanism that could be applied to virtually all inflammatory diseases that are linked to CAD, including of course, periodontitis.