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Invited commentary

Biglycan: Unpuzzling the causal links between tobacco-smoking and atherosclerosis?

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Tobacco smoking is the major cause of preventable death worldwide, resulting in almost 6 million deaths per year. Up to 10 per cent of all deaths are accredited to cardiovascular diseases (CVD), with the prevalence of fatal CVD events being highest among young adults below the age of 45. In fact, fatal CVD events are the leading cause of premature deaths in young smokers [1]. This suggests that smoking rapidly leads to modifications within the cardiovascular system with potentially pathological consequences. In line with this observation, several studies have demonstrated tobacco-smoke induced alterations, like increased aortic and carotid intima media thickness (a- and c-IMT) and endothelial dysfunction – all key features of CVD – in healthy and young passive smokers [2–5].

Epidemiological studies suggest that atherosclerosis, the underlying cause of most CVDs, is initiated with a diffuse intimal thickening by accumulating extracellular matrix (ECM)-containing proteoglycans like biglycan (BGN) or decorin [6]. In this issue of Atherosclerosis, Mandraffino and colleagues analysed a large number ($n > 250$) of healthy young current smokers and found increased monocytic BGN expression, which highly correlated with arterial stiffness and c-IMT [7]. Their findings are of special relevance regarding CVDs as they provide strong evidence for the early onset and accelerated atherogenesis in young cigarette smokers.

According to the "response-to-retention hypothesis", atherosclerosis develops as a consequence of cumulating lipoproteins in the arterial wall [8]. Actually, all proteoglycans are able to bind lipoproteins due to ionic interactions *in vitro*, however Apolipoprotein B, the major lipoprotein of atherogenic LDLs, was found in human lesions to preferentially co-localize with BGN. In line with this observation, mounting evidence supports BGN as a major player in the initiation and development of atherosclerosis. For example, overexpression of human BGN in $LDLR^{-/-}$ mice resulted in increased lesions [9], while mice expressing proteoglycan-binding-defective apoB demonstrated lower degree of atherosclerosis [10].

Whether smoking increases the BGN concentration in the ECM of the artery wall, initiating atherosclerosis as proposed in the "response-of-retention hypothesis", still needs definite proof, but at least seems plausible. For instance, BGN expression is induced by transforming growth factor beta-1 (TGFb), which is linked to the occurrence and severity of CVD, and found to be increased in the small airway epithelium of tobacco smokers [11]. Furthermore, increased oxidative stress and hypertension, both consequences of heavy smoking, have been demonstrated to promote BGN expression [12,13]. However, *in-vitro* studies, i.e. smoke-extract treatment of smooth muscle and/or endothelial cells, might shed more light into the causal link between smoking, increased intimal BGN expression and atherogenesis.

Increased monocytic BGN expression and release could also potentially accelerate atherosclerosis. Additionally to the secretion of BGN, monocytes/macrophage-derived matrix metallo-proteases, i.e. MMP-2, MMP-3 and MMP13, proteolytically cleave BGN from ECM and increase BGN concentrations in the blood [14]. In this context, soluble BGN has been identified as an endogenous danger signal capable of inducing the sterile inflammation response of macrophages and dentritic cells via simultaneous stimulation of TLR2/4 and P2X7/P2X4 receptors [15]. Consequently, activated immune cells secrete mediators like TNF and IL-1 beta, resulting in the pro-inflammatory state that can also be observed in smokers.

Large scale studies, like that presented by Mandraffino and colleagues, are highly valuable for the identification of smoking induced alterations, which can have large variations due to several different factors. Cigarette smoke contains more than 4500 different chemical compounds, oxidants, and metals, and their

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concentrations may vary due to tobacco breed and additives. Further, smoking behaviour, including inhalation intensity and duration, could influence the results. Indeed, existing data indicates that smoking is an enormous health risk for both the active and passive smokers. Passive smoking or moderate smoking has been shown to rapidly lead to changes in blood markers, which are linked with development of different pathologies [16]. Some of the noxious effects triggered by smoking may return to baseline after smoking cessation, but others are non-reversible or may need decades to become negligible, resulting for example in an elevated risk for developing CVDs also for smoking quitters [17].

Smoking is a critical contributor for the initiation and acceleration of atherosclerosis and CVD mortality. Despite the fact that the smoking-related mechanisms of action are not yet fully understood, the report by Mandraffino et al. reveals substantial insights towards a better understating of its causal relation. This may finally lead to measures of early detection of smoke induced pathologies, when treatment has the highest probability of success.

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