Crosstalk of lipids and inflammation in atherosclerosis: the PRO of PGRN?

Saskia C.A. de Jager and Gerard Pasterkamp*

Laboratory of Experimental Cardiology, University Medical Center Utrecht, Utrecht, The Netherlands

This editorial refers to ‘Deletion of progranulin exacerbates atherosclerosis in ApoE knockout mice’ by R. Kawase et al., pp. 125–133, this issue.

Atherosclerosis is recognized as a chronic inflammatory process that accelerates in the context of high cholesterol levels.1 The unique aspect of atherosclerosis, over other inflammatory diseases, is the major effect of the cholesterol environment. There is accumulating evidence that lipids can influence inflammatory responses and vice versa, but so far the lipid and inflammatory components that initiate atherosclerotic disease have mainly been studied as two separate pathogenic entities. Elucidation of the functional determinants that link immune activation and derailed cholesterol metabolism may facilitate the development of novel therapeutic strategies to treat atherosclerosis.

Evidence is accumulating that supports the relevance of cross-talk of lipid metabolism and the immune responses in vascular pathology. For instance lipid loading induces a distinct, unique gene expression profile in macrophages within the atherosclerotic lesion.2 It also was shown that cholesterol crystals (consequence of extreme cholesterol loading) that are present in early atherosclerotic lesions, can induce inflammasome activation and may thus be considered as a novel initiators of inflammation.3,4

In this issue of cardiovascular research, Kawase et al.5 describe a role for the growth factor progranulin (PGRN) in the pathogenesis of atherosclerosis. Data are presented suggesting that PGRN is a glycoprotein that strongly influences and inhibits detrimental immune responses. PGRN is a protein that may exert a role in the cross-talk of immunity and lipid turnover, as it has both immunomodulatory and lipoprotein-like properties. PGRN is expressed and secreted from several cell types, including endothelial cells, macrophages, T cells, dendritic cells, and neuronal cells. Once secreted, PGRN can be cleaved into granulin by various proteases, including matrix metalloproteinase and elastase. Interestingly, PGRN and granulin have many distinctive and opposing functions in which PGRN is generally acknowledged as inducing an anti-inflammatory response, whereas granulin acts pro-inflammatory.6

A key determinant for inflammation is TNFα as it often is the first responder in the inflammation cascade. PGRN is a ligand for the TNFα-receptor and can block TNFα-mediated responses. The observation that PGRN can interfere at the top of the inflammation cascade suggests that it has multiple and complex functions in immune-related diseases and the maintenance of a balanced immune response. Indeed, PGRN has been implicated in a variety of immune-related disorders, such as rheumatoid arthritis (RA), inflammatory bowel disease, diabetes, and obesity, but also in response to injury or infection. Interestingly, PGRN is also a key player in neurodegenerative disorders, a disease type that has also been linked to alterations in lipoprotein metabolism.7–9

The immune-modulatory properties of PGRN in inflammatory diseases is quite delicate and very much depend on the stage and determinants of the inflammatory response (Figure 1). For instance, PGRN can improve tissue repair by active recruitment of leucocytes and increasing local blood circulation after acute injury, while in acute infection it dampens LPS-induced inflammation in macrophages. The cytokine network induced by inflammation is tightly regulated and disturbance of the immune-balance can result in a chronic inflammatory state. RA is a chronic inflammatory disorder that has many similarities with atherosclerosis and one of the major constituents in RA is TNFα. Via its interaction with TNF-R1, TNFα leads to caspase-induced cell death and NF-κB-mediated inflammation, this culminates in chronic inflammation and eventual progressive damage to the joint. PGRN-deficient mice are more susceptible to collagen-induced arthritis while administration of PGRN attenuates the development of inflammatory arthritis.10 In contrast to these anti-inflammatory properties, PGRN has pro-inflammatory effects in insulin resistance in diabetes and obesity.11 Circulating PGRN levels are significantly higher in insulin resistant subjects and correlate to the body mass index, Hb1Ac, and total cholesterol levels. In experimental models, a high-fat diet up-regulated PGRN and induced insulin resistance and appeared to be dependent on IL-6, while PGRN-deficient mice were less sensitive for insulin resistance.

PGRN is a relatively new player in the pathobiology of atherosclerosis and was first observed in human carotid endoatherectomy specimens <5 years ago.12 A functional implication for PGRN in atherosclerosis was also reported, as it mildly inhibits MCP-1-mediated monocyte migration, while it strengthens TNFα-mediated human aortic smooth muscle cell migration.12 Additionally, PGRN inhibits TNFα induced IL8 release, while in the presence of elastin (thereby forming granulin) IL8 release from human aortic smooth muscle cells is enhanced. These initial findings clearly suggest a functional, and most likely complex, role for PGRN in atherosclerosis. From a more translational aspect, it was very recently established that PGRN has prognostic value for subclinical
atherosclerosis (carotid artery intima media thickening), independent of other cardiovascular risk factors. 

Apart from its broad functions in inflammation, PGRN has also been suggested to possess the properties of a lipoprotein. It was initially postulated that PGRN is a component of HDL; however, these findings are debatable as Nguyen et al. showed that PGRN circulates as a homodimer and not as a part of HDL. Nevertheless, the observation that HDL and Apolipoprotein-A1 may directly inhibit the conversion of PGRN into granulin remains interesting, specifically for atherosclerosis-associated research. In this issue Kawase et al. show that PGRN impacts both the inflammatory as well as the lipid component of the disease. In the absence of PGRN, atherosclerotic lesion formation in ApoE knock-out mice is accelerated, despite the moderately declined cholesterol levels. The absence of PGRN enhances local inflammation, migratory responses to the atherosclerotic aorta, and negatively affects the atherogenic properties of HDL. It must be noted that the atherosclerotic lesions found in this experiment are relatively small, with only 2% coverage in the whole aorta after 12 weeks of a high-fat diet. The authors used a high-fat diet (containing Lard fat and low cholesterol) rather than a Western type diet (containing milk fat and high cholesterol), which may very well explain the modest atherosclerotic lesions formation. It would be of interest to study the effect of PGRN on plaque characteristics, specifically in advanced atherosclerotic lesions since these lesions normally express higher levels of granulin. In future studies, it would be interesting to follow-up on the current observations either by overexpressing circulating PGRN levels, or inhibiting its pro-inflammatory counterpart granulin.

The current study by Kawase et al. provides the reader with an intriguing novel target that functions at the junction of lipid metabolism and inflammation in atherosclerosis again stressing the importance of cross-talk of lipid metabolism and immunity in vascular pathology.

Conflicts of interest: none declared.

References


