Cardiovascular disease is the leading cause of death globally, accounting for over 17 million deaths per year. The major underlying cause of lethal cardiovascular events is the sudden occlusion of blood vessels related to atherosclerosis. Over the years, several hypotheses have been proposed to explain the underlying mechanism of atherogenesis, but it is now well established that plasma low-density lipoprotein (LDL) is causatively linked to cardiovascular disease and that subendothelial retention of atherogenic lipoproteins initiates atherogenesis. Use of both statins and the nonstatin drugs ezetimibe has proven that lowering LDL concentrations reduces cardiovascular events in humans. These drugs are based on the principle that reducing the number of circulating atherogenic lipoproteins decreases the probability that they will enter and be retained in the subendothelium.

Lipoproteins normally flux into and out of the arterial wall. The transport of LDL across endothelial cells has previously not attracted much attention, but recent studies have shown that SR-BI and possibly caveolin-1 mediate LDL transcytosis and that this process is responsive to LDL levels in the blood. The retention of LDL is mediated by positively charged amino acids in apolipoprotein B (the main protein moiety on LDL) that interact with negatively charged artery wall proteoglycans. Once in the artery wall, LDL has been shown to undergo several modifications with important biological consequences. Aggregated or modified LDL is avidly taken up by macrophages or vascular smooth muscle cells (VSMCs), leading to foam cell formation. The conversion of macrophages and VSMCs to foam cells stimulates the release of potentially atherogenic factors and has been shown to induce synthesis of proteoglycans with enhanced affinity for atherogenic lipoproteins. Thus, retained lipoproteins can provoke all known features of early atherosclerotic lesions and, by stimulating local synthesis of proteoglycans and proatherogenic factors, accelerate further lipoprotein retention and aggregation.

Until recently, most attention has focused on the role of proteoglycans in atherogenesis. The role of VSMCs in this process is less clear, but they are likely crucial for the initiation of atherogenesis by being the major producers of proteoglycan-rich extracellular matrix that binds and retains lipoproteins within the arterial wall. In experimental studies, several proteoglycans have been shown to be important for arterial lipoprotein retention and atherosclerosis, most notably the matrix-associated proteoglycans biglycan, perlecán, versican, and decorin.

In this issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, She et al focus on a less well-known proteoglycan in the vasculature, the neural/glial antigen 2 (NG2) proteoglycan (in humans known as melanoma proteoglycan or chondroitin sulfate proteoglycan 4). NG2 is a transmembrane chondroitin sulfate proteoglycan that is highly expressed by immature progenitor cells. In blood vessels, NG2 is expressed during early development but is barely detected in healthy mature vessels. Despite this, She et al found that NG2-deficient mice develop less atherosclerotic lesions compared with control mice. This was unexpected also because NG2 deficiency impairs the formation of brown fat, leading to increased blood lipoprotein levels and increased white fat formation.

Although NG2 is rarely expressed in the vasculature, She et al show that VSMCs during atherogenesis in *apoE*-deficient mice start to express NG2 (Figure). The authors could locate the NG2 expression to VSMCs positive for platelet-derived growth factor receptor-beta, indicating that NG2 is primarily expressed by immature synthetic VSMCs in atherosclerotic lesions. Thus, the atherogenic effects of NG2 seem to emerge with accumulation of synthetic VSMCs in the vasculature, which in human occurs during the formation of diffuse intimal thickening. Diffuse intimal thickening occurs naturally in many vascular beds, such as coronary arteries, and its formation is closely associated with the subsequent formation of atherosclerotic lesions.

She et al also demonstrate using cultured cells that NG2 on VSMCs enhances lipoprotein uptake in macrophages. They show that cultured NG2-positive VSMCs dramatically increase the uptake of LDL by macrophages, whereas NG2-deficient VSMCs reduce this LDL uptake. Surprisingly, they found that the NG2 glycosaminoglycan chains were not required for the binding of LDL to NG2. Furthermore, NG2 also bound acetylated LDL, indicating that NG2 has the capacity to bind LDL through hydrophobic interactions. These features make NG2 unique among LDL-binding proteoglycans. NG2 can therefore mediate the interaction between LDL and proteoglycans independently of the physical state of apolipoprotein B and thus of the affinity between apolipoprotein B and proteoglycans. This is important because this interaction is partly diminished in oxidized LDL.

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Although the study demonstrates an interesting and potentially important role of NG2 in atherogenesis, some caution must be used in interpretation of the data. First, is the NG2 expression in mouse atherosclerotic vessels similar to the chondroitin sulfate proteoglycan expression in human atherosclerotic vessels? Second, what is the relative contribution of NG2 to arterial LDL retention compared with other vascular proteoglycans? Finally, the study by She et al is based on mice with a global deficiency of NG2. Because NG2 has important functions in many tissues, it will be important to verify the results in mice with a VSMC-specific NG2 deletion.

Disclosures

None.

References

Catch and Release: NG2-Coated Vascular Smooth Muscle Cells Capture Lipoproteins for Macrophages
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