HDL, PTX3, and Vascular Protection

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The superfamily of pentraxins consists of evolutionary conserved acute phase proteins characterized by the presence of a multimeric structural motif, the pentraxin domain (reviewed in1). C-reactive protein and serum amyloid P represent the short pentraxin arm of this family and are mainly produced by the liver. The long pentraxins were identified more recently as cytokine-inducible molecules expressed in a variety of tissues, and differ from the short pentraxins by the presence of a long N-terminal domain coupled to the C-terminal pentraxin domain. PTX3 was the first recognized member of this family, identified as an interleukin (IL)-1 or tumor necrosis factor (TNF)-inducible gene in several cell types but not in hepatocytes, which contrasts with the short pentraxin CRP, known to be produced in the liver and primarily induced in response to IL-6. Several cell types have been shown to produce significant amounts of PTX3 on activation, including fibroblasts, adipocytes, chondrocytes, or mononuclear phagocytes. Myeloid dendritic cells appear to produce the highest amounts of PTX3 in response to Toll-like receptor engagement and proinflammatory cytokines. In fact, PTX3 is primarily known for its ability to bind selected pathogens and the complement component C1q, and to activate the classical complement pathway, facilitating pathogen recognition by macrophages and dendritic cells, and leading to the induction of a protective immune response.1

Recent studies have also elegantly shown that PTX3 is stored in specific neutrophil granules, the neutrophil extracellular traps, is rapidly released in response to microbial challenge and inflammatory signals, and plays a critical role in microbial recognition and phagocytosis.2 Thus, the available evidence clearly points to a nonredundant role for PTX3 in the recognition of selected pathogens, locally at the site of infection, and a role in the rapid amplification of the innate immune response to resist pathogen dissemination.3

PTX3 is also highly expressed in the cardiovascular system in response to inflammatory stimuli. Vascular endothelial and smooth muscle cells produce high amounts of PTX3 in response to atherogenic inflammatory signals, including oxidized low density lipoproteins,3 which is consistent with the strong expression of PTX3 in vascular cells and macrophages of advanced human atherosclerotic lesions.4 PTX3 is rapidly induced in the heart after unstable angina or acute myocardial infarction, and its circulating levels have been shown to predict 3-month mortality in patients with MI, even after adjustment for major risk factors and other acute-phase prognostic markers.5,6 These results, coupled to those showing upregulation of endothelial cell tissue factor in response to PTX3,7,8 suggested a potential pathogenic role for PTX3 in mediating atherosclerosis progression and myocardial damage after plaque disruption and thrombosis. In this regard, the report by Norata et al in this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, showing vascular induction of PTX3 in response to HDL,9 which is well-known for its antiinflammatory, antiatherogenic, and cardiovascular protective properties, is intriguing, and will stimulate further attention to the potential pathogenic or protective role of PTX3 in cardiovascular disease.

Norata and colleagues examined the effects of HDL on the expression of acute phase proteins of the short and long pentraxin family in endothelial cells. They showed that HDL induced dose-dependent increase in PTX3 mRNA expression and protein release from HUVECs and HAECs, whereas no effect was observed on the expression of the short pentraxins CRP and SAP. The effect appeared to be dependent on the cell-type, as it was absent in a monocytic cell line, and was selective for subclasses of HDL, being much more prominent in response to HDL3 than HDL2, and undetectable in the presence of modified or native LDL. Using pharmacological inhibitors, the authors showed that HDL-induced PTX3 expression required activation of the PI3K/Akt pathway through a G-coupled lysosphingolipid receptor. More particularly, sphingosine 1 phosphate (S1P) or S1P mimetics, but not ApoA-I (lipid free or incorporated n reconstituted HDL) induced PI3K/Akt-dependent expression of PTX3, which was significantly reduced by specific silencing of S1P1 and S1P3 receptors, whereas silencing of SR-B1 had no effect. Thus, the S1P component of HDL appears to be a major inducer of PTX3 in endothelial cells, which is consistent with the greater induction of PTX3 by the small dense HDL3, rich in S1P,10 compared to HDL2. Addressing the in vivo relevance of their findings, Norata et al nicely showed that constitutive expression of PTX3 in mouse aorta, but not in plasma, was significantly lower in ApoA-I–deficient mice compared to transgenic hApoA-I mice (similar genetic background) or C57Bl/6 mice, suggesting local vascular effects of HDL.9 Finally, in vivo administration of plasma-derived HDL or a S1P mimic to C57Bl/6 mice resulted in significant upregulation of arterial PTX3 expression, without any change in CRP or SAP expression. These results show for the first time a significant physiological role for HDL-S1P in the regulation of PTX3 expression locally within the vascular wall. Given that HDL-S1P is considered a major mediator of the cardiovascular protective properties of HDL,11 including protection against endothelial cell activation and expression of adhesion

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molecules, the data may suggest a protective role for PTX3 in the vascular response to injury. However, this issue has not been addressed directly and merits further consideration. The availability of the PTX3-deficient mice should facilitate the precise determination of the direct role of PTX3, either as a mediator or inhibitor of the protective effects of HDL in endothelial cells (Figure).

There are also some issues that merit further analysis. Some of the findings reported in the study by Norata et al appear to contradict earlier findings by other groups. For example, the absence of any effect of modified LDL on PTX3 expression contrasts with the ability of oxLDL to induce PTX3 expression in vascular smooth muscle cells, and more directly with recent results showing NF-κB-dependent upregulation of PTX3 in response to oxLDL and lysophosphatidic acid in both immortalized and primary human endothelial cells. In addition, Gustin et al showed that incubation of immortalized endothelial cells with S1P did not induce PTX3 expression, in contrast with the prominent role of S1P in PTX3 expression, reported by Norata et al. The reasons for these discrepancies are unclear and remain to be determined.

The findings of Norata et al may also seem at odds with previous findings showing induction of PTX3 expression by essentially proinflammatory signals, and may appear to challenge the suggested pathogenic role for PTX3 in cardiovascular and inflammatory diseases. However, there are at least some exceptions regarding the modulation of PTX3 expression by inflammatory mediators. The Th1-related and proatherogenic cytokine IFN-γ seems to be inhibitory, whereas, surprisingly, the immunoregulatory and antiatherogenic IL-10 was found to stimulate PTX3 expression in dendritic cells and monocytes. This suggests a potential contribution of PTX3 to the regulatory arm of the innate and adaptive immune response and a potential antiatherogenic role for PTX3. Another potentially antiatherogenic pathway mediated by PTX3 may relate to its ability to clear apoptotic cells. Several studies have clearly shown that efficient apoptotic cell clearance inhibits the inflammatory response and reduces the development of atherosclerosis and the size of the necrotic core. PTX3 binds to apoptotic cells, which enhances C1q binding and complement-mediated clearance of apoptotic cells, and may therefore contribute to limit the size and the complexity of atherosclerotic lesions (Figure).

However, these issues need to be addressed directly using experimental models of atherosclerosis. Finally, contrary to previous expectations, Salio et al recently reported a nonredundant and cardioprotective role for PTX3 in acute MI using PTX3-deficient mice.

Taken together, these studies suggest a potentially important regulatory role for PTX3 in the modulation of the immunoinflammatory response associated with atherosclerosis and ischemic cardiovascular injury. Whether part of this protective effect could be mediated through local upregulation of PTX3 in vascular endothelial cells merits further consideration.

Disclosures

None.

References


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