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EDITORIAL

Elastin degradation and ensuing inflammation as emerging keys to atherosclerosis

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This editorial refers to 'Elastin-derived peptides potentiate atherosclerosis through the immune Neu1–PI3Kγ pathway' by S. Gayral *et al.*, pp. 118–127, this issue.

In atherosclerosis, remodelling of extracellular matrix (ECM) has long been considered a critical step in disease development/progression, but the multitude of cell types and molecular mechanisms involved is only now starting to emerge. In arteriosclerotic vascular disease, infiltrating leucocytes are known to release proteases, degrade the ECM, and lead to environmental changes allowing smooth muscle growth and plaque evolution. Among the enzymes secreted by leucocytes, a major role is played by elastases, which promote degradation of the elastin ring of arterial walls. This process triggers a tissue rearrangement that is more extensive than simple ECM destruction, because it triggers the production of elastin-derived peptides (EPs) that are not only degradation products, but also bioactive moieties evoking reactions in the surrounding tissues.[1] EPs, also known as elastokines, are a family of matrix fragments that possess cytokine-like functions and primarily signal via binding to a unusual cell surface receptor, the elastin receptor complex (ERC). The ERC is a heterotrimeric structure that includes an elastin binding protein, which binds elastin peptides, the protease cathepsin A and the membrane-bound neuraminidase, Neu-1. Upon elastin binding, different cell types, including those that actively participate to atherosclerosis development, organize an ERC complex that engages diverse signalling pathways, eventually converging on ERK1/2 activation. For instance, EPs control smooth muscle cell migration and proliferation, key determinants of plaque de/stabilization, via an ERC-dependent initiation of a Raf-1/MEK1/2/ERK1/2 cascade. EPs also affect fibroblast function and endothelial nitric oxide production, which limit atheromatous plaque formation.[2] Nonetheless, how ERC specifically triggers these signals has largely remained unknown. Recently, ERC has been reported to trigger the G protein-coupled receptor-activated phosphoinositide 3-kinase γ (PI3Kγ).[3] Given the ability of this lipid kinase to interact with Ras and promote MEK phosphorylation,[4] the activation of PI3Kγ has been suspected as a key link between EP and MAPK pathway activation. In principle, activation of PI3Kγ and its downstream targets, like Akt, MEK, and the small GTPases of the Rac family, could also explain the ability of EPs to elicit a strong chemotactic response as well as production of reactive oxygen species that oxidize low-density lipoproteins (LDL) and exacerbate plaque development. Although EPs have been shown to orchestrate this variety of cellular functions that are central to atherogenesis, the current knowledge of the biological effects of EPs mainly relies on *in vitro* studies in isolated cells, exposed to synthetic EPs. Conversely, a direct evidence of a key role of EPs in disease development *in vivo* has not been observed so far.

Gayral *et al.* show that EPs serve as enhancers of atherosclerosis development *in vivo,* as exogenous administration of EPs to two distinct murine models of atherosclerosis, ApoE$^{-/-}$ and LDLR$^{-/-}$, accelerates atheromatous plaque formation. The study also provides a strong indication of the cell types involved, an issue that has remained guesswork for long. Gayral *et al.* now elegantly demonstrate that the target cells of EPs, triggering the exacerbation of atherosclerotic plaque development, consist of monocytes. By the use of mouse bone marrow chimeras, with donor haematopoietic stem cells and recipient individuals carrying different mutations, they conclusively show that the pro-atherosclerotic effect of EPs stems from selective activation of ERC signalling in infiltrating monocytes, which in turn promote enhanced cell migration and ROS production.[5]

Gayral *et al.* extend their study to show that this process strictly relies on the activity of PI3Kγ within leucocytes, as EPs fail to potentiate atherosclerosis development in chimeric ApoE$^{-/-}$ and LDLR$^{-/-}$ mice transplanted with PI3Kγ$^{-/-}$ bone marrow. Intriguingly, PI3Kγ-dependent chemotaxis and oxidative stress require neuraminidase activity, as evidenced by reduced disease severity of atherosclerotic mice carrying cathepsinA/neuroaminidase 1-deficient haematopoietic cells.[5] Although PI3Kγ is proposed to provide the direct link between ERC and atherosclerosis development, the mechanism whereby this kinase is engaged remains to be elucidated. A plausible hypothesis posits that Neu-1-dependent glycosphingolipid production, a key event in ERC signalling, mediates activation of a selective G_i-coupled receptor, which is typically involved in PI3Kγ activation.[6] While EP-dependent triggering of Neu-1/PI3Kγ signalling was found pivotal to atherogenesis in artificial models of exogenous EP administration, it is conceivable that the same mechanisms apply to contexts of endogenous EP production. Further studies will clarify whether GPCR signalling is involved and whether inhibition of EPs-mediated signalling events might function *in vivo*.

Overall, Gayral *et al.* provide evidence of a pro-atherogenic role of EPs in *in vivo* models of atherosclerosis and place the Neu-1/PI3Kγ signalling

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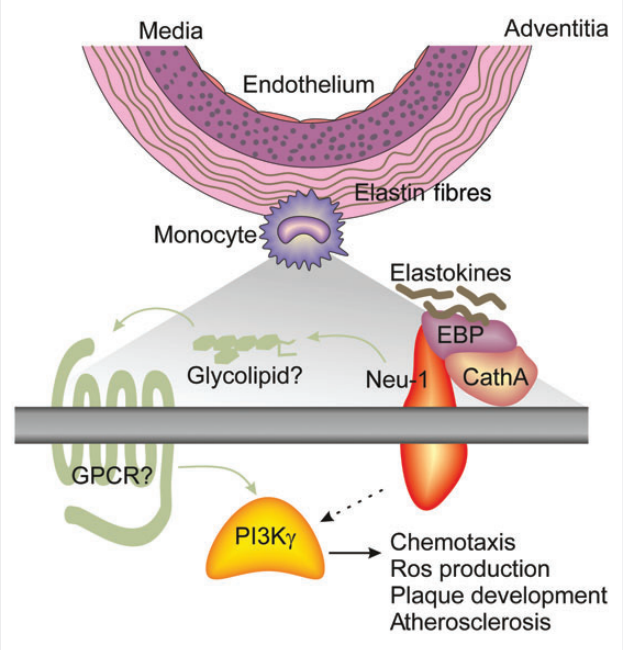

Figure 1 Schematic representation of ERC signalling to PI3Kγ in leucocytes in response to the degradation of elastin fibres of arteries into bioactive peptides.

module downstream leucocyte ERC activation during atherogenesis (*Figure 1*). In humans, EP blood concentration increases during atherosclerosis and correlates with the degree and progression of vascular disease.[7] Therefore, targeting the ERC signal transduction machinery with Neu-1/PI3Kγ inhibitors could be envisaged as a novel way of preventing the onset or limiting the progression of arterial diseases.

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