ATHEROSCLEROSIS

Plexin D1 is a mechanosensor that regulates the site-specific distribution of atherosclerosis

“PLXND1 is not just a receptor for semaphorin 3E, but can also detect physical force and convert it into biochemical signals inside the cell”

Atherosclerosis is a focal disease. Areas of arteries with disturbed or turbulent flow, such as curvatures or bifurcations, are prone to develop atherosclerotic lesions, whereas areas with laminar, uniform flow, such as straight regions of the vasculature, are largely protected from the development of atherosclerosis. Endothelial cells in arteries are critical sensors of flow via mechanoreceptors that translate the mechanical forces into intracellular signalling pathways to induce atheroprotective or atherogenic responses. However, the mechanoreceptors and signalling pathways involved in these responses are incompletely understood. Now, Ellie Tzima and colleagues describe a novel mechanoreceptor in endothelial cells that regulates vascular function and the site-specific distribution of atherosclerosis. “This study reveals a hitherto unrecognized role for the receptor plexin D1 (PLXND1) in the detection of mechanical force,” says Tzima. Plexins are cell-surface receptors for semaphorins and are involved in axonal guidance, tumour progression and immune cell regulation. “We now show that PLXND1 is not just a receptor for semaphorin 3E, but can also detect physical force and convert it into biochemical signals inside the cell that will ultimately dictate the development of atherosclerotic lesions,” explains Tzima.

Several endothelial cell mechanosensors have been identified, and one of the best characterized is the PECAM1 junctional mechanosensory complex. “However, what was lacking in these studies was structural information on how the receptors carry out mechanosensation, the relevance in disease and the relationship with other known mechanosensors,” comments Tzima. Therefore, the research team set out to address these knowledge gaps.

First, using *in vitro* and *in vivo* models, the investigators demonstrate that PLXND1 is required for the response of endothelial cells to shear stress and that the PLXND1-dependent mechanotransduction is independent of its ligand semaphorin 3E. Under laminar-flow conditions, PLXND1 is required for the alignment of endothelial cells in the direction of flow, a hallmark response to atheroprotective shear stress, and the upregulation of *Klf2* and *Klf4*, which encode anti-inflammatory transcription factors. Under disturbed-flow conditions, PLXND1 is involved in the upregulation of pro-inflammatory genes, including *Ccl2* and *Vcam1*.

Next, Tzima and colleagues show that PLXND1 regulates the site-specific distribution of atherosclerotic lesions. In atheroprone mice fed a high-fat diet, PLXND1 deficiency in endothelial cells decreased the plaque burden in the whole aorta and in atheroprone regions (the aortic arch) compared with mice expressing PLXND1 in endothelial cells. PLXND1 deficiency also led to reduced levels of CCL2 and VCAM1 in the inner curvature of the aortic arch.

Finally, the researchers demonstrate that PLXND1 is a direct sensor of force that can elicit mechanical signalling in endothelial cells and they also identify the mechanism by which a single receptor can have a binary function. PLXND1 forms a complex with neuropilin 1 and VEGFR2 in response to flow. This complex acts upstream of the PECAM1 junctional complex and integrins — two mechanosensory hot spots involved in cell–cell and cell–extracellular matrix adhesions, respectively — and is sufficient for the response to shear stress. PLXND1 achieves its binary functions as a ligand receptor and a force receptor by switching between two conformational states: a ring-like conformation maintains its ligand-dependent functions, whereas flexion of the ectodomain leads to a more open conformation that is required for mechanotransduction.

“This work not only sheds light on fundamental mechanisms of mechanotransduction that could be applicable to several cell types and organ systems, but also provides answers to the century-old question on the focal distribution of atherosclerosis,” says Tzima. Tzima and colleagues are currently screening small-molecule libraries to identify inhibitors of PLXND1 and assess whether they have antiatherogenic effects. “The idea would be to repurpose known drugs to target PLXND1 signalling for the prevention of atherosclerosis,” explains Tzima.

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ORIGINAL ARTICLE Mehta, V. et al. The guidance receptor plexin D1 is a mechanosensor in endothelial cells. *Nature* **578**, 290–295 (2020)

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