Stimulating arteriogenesis but not atherosclerosis: IFN-α/β receptor subunit 1 as a novel therapeutic target

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This editorial refers to ‘MAb therapy against the IFN-α/β receptor subunit 1 stimulates arteriogenesis in a murine hindlimb ischaemia model without enhancing atherosclerotic burden’ by P.F.A. Teunissen et al., pp. 255–266.

In ischaemic diseases such as myocardial infarction (MI), restoration of sufficient blood supply to ischaemic areas through arteriogenesis is critical for preservation of tissue integrity and function. Although ischaemia activates natural mechanisms promoting arteriogenesis, these are often insufficient to alleviate the consequences of ischaemia in patients, prompting the need for novel therapeutic strategies. One significant hurdle, however, is that several pro-arteriogenic mechanisms and therapeutic approaches also promote atherosclerotic plaque development. Teunissen et al. now show that targeting the IFN-α/β receptor subunit 1 (IFNAR1) stimulates functional perfusion of ischaemic tissue while only minimally affecting atherosclerosis.

Arteriogenic and atherosclerotic processes often engage similar mechanisms. For example, limb ischaemia induces the mobilization of Ly6C<sup>high</sup> monocytes to the bloodstream, which then infiltrate ischaemic tissue to promote blood flow recovery in mice, but also constitutes the main precursors of atherosclerotic plaque macrophages. Myocardial or peripheral ischaemia furthermore activates the sympathetic nervous system to trigger the release of progenitor cells from the bone marrow, which, in turn, stimulate neovascularization. This, however, also promotes vascular inflammation and leads to an acceleration of atherosclerosis after MI. Conversely, some anti-atherogenic cytokines, for example IL-10, inhibit arteriogenesis. The pro-arteriogenic and pro-atherosclerotic nature of many pathways has also complicated the development of therapeutic strategies, and different pro-arteriogenic strategies such as administration of CCL2 or infusion of bone marrow-derived mononuclear cells promoted neovascularization, but simultaneously increased atherosclerosis in hypercholesterolaemic mice in pre-clinical studies (Figure 1).

Previous work had suggested that type I IFN (IFN-α and IFN-β) signalling may constitute a potential therapeutic target, as it interfered with arteriogenesis but promoted atherosclerosis. For instance, an increased IFN-β signalling was found in MI patients with poor collateral vessel networks, and IFN-β administration reduced post-ischaemic perfusion recovery. In contrast, IFN-β aggravated atherosclerosis in mice, and IFNAR1 deficiency in myeloid cells attenuated lesion formation. Teunissen et al. have now evaluated the effects of blocking IFNAR1 on arteriogenesis and atherosclerosis in hypercholesterolaemic mice. In low-density lipoprotein receptor-deficient (Ldlr<sup>−/−</sup>) mice fed a Western diet, administration of an anti-IFNAR1 mAb for 4 weeks improved blood flow recovery in ischaemic paws, but left atherosclerotic plaque size unaltered. Plaque analyses showed a mostly similar composition between groups, except for a higher proportion of macrophages and a reduction in plaque cell apoptosis in lesions of anti-IFNAR1-treated mice. In another model, apolipoprotein E-deficient mice with established plaques were treated with anti-IFNAR1 for 1 week, which again resulted in an increased perfusion after ischaemia, and was accompanied by an increased arteriolar lumen size, as well as decreased expression of CXCL-10, a downstream target of IFNAR1 blockade on neovascularization. Upon short-term treatment, IFNAR1 signalling, which had previously been proposed to either activate or inhibit tissue neovascularization. In this short-term model, IFNAR1 blockade had no effects on atherosclerotic lesions.

Investigating effects on hindlimb ischaemia in atherosclerosis-prone mice as a model of patients affected by both ischaemia and atherosclerosis, this study thus provides encouraging evidence that blocking type I IFN signalling may be a relevant therapeutic strategy for ischaemic diseases in patients. However, a number of questions remain. The mechanisms underlying improved perfusion recovery upon anti-IFNAR1 treatment are still unclear. In particular, it remains to be determined, which cell type(s) is/are responsible for the effects of IFNAR1 blockade on neovascularization. Upon short-term treatment, macrophage infiltration, M1/M2 macrophage polarization, and expression of arteriogenic cytokines were not altered. Discrete local changes in macrophage phenotype and cytokine expression, however, may have gone unnoticed in these analyses. Effects of IFNAR1 blockade may also depend on smooth muscle cells, as previously proposed. Anti-IFNAR1 treatment resulted in only small changes in vessel density and size in ischaemic tissues, except for an increased arteriolar lumen size upon short-term treatment; alternative mechanisms, such as an
improved endothelial-dependent vasorelaxation following IFNAR1 blockade could thus also be underlying ameliorated perfusion recovery. Deciphering the cell type-specific effects of IFNAR1 signalling in arteriogenesis and atherosclerosis, for example by using mice with a conditional deficiency of IFNAR1, as well as dissecting potential effects of the IFNAR1 ligands IFN-α and IFN-β would clearly be of interest. One other important aspect that deserves attention in future studies is the increased macrophage content of atherosclerotic plaques of Ldlr^−/− mice. Although this was observed in experiments of early lesion development after 4 weeks of diet, effects of longer-term anti-IFNAR1 treatment in mice with established plaques await to be evaluated. Given the increased IFN-β signalling in patients with MI, it will also be important to study whether anti-IFNAR1 treatment functions to ameliorate neovascularization after MI, and to analyse whether it has an impact on MI-triggered acceleration of atherosclerosis.

In conclusion, findings by Teunissen et al. open up new possibilities to tackle what was once coined the ‘Janus phenomenon’, indicating that pro-arteriogenic therapeutic strategies tend to promote atherosclerotic lesion growth. Targeting type I IFN signalling appears as a promising therapeutic strategy for promoting arteriogenesis without affecting atherosclerosis, and calls for further research in this area.

References


