Endothelial FGF receptor signaling: angiogenic versus atherogenic effects

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MEMBERS OF the fibroblast growth factor (FGF) family have been shown experimentally to stimulate angiogenesis through their mitotic and migratory effects on endothelial cells and by promoting endothelial integrity (2, 8). As such, they have been explored as a potential treatment of ischemic disease in several clinical trials (6). In their article in the issue of the American Journal of Physiology-Heart and Circulatory Physiology, Che et al. (2) report that an overexpression of FGF receptor (FGFR) accelerates the development of atherosclerosis in a transgenic mouse model, casting doubt on using this treatment in patients with preexisting atheromatous disease.

In the study by Che et al. (2), FGFR2-overexpressing mice were crossed with atherosclerosis-prone apolipoprotein E (ApoE)-deficient mice. The mice were fed a Western diet, and the vascular end points were compared with those of ApoE-deficient mice (as the control group). After 8 wk of consuming the diet, the FGFR2 mice had double the amount of atherosclerosis compared with the ApoE-deficient mice. This was associated with an increased arterial expression of adhesion molecules and smooth muscle cell proliferation, with associated concurrent increased PDGF-B and early growth response (Egr)-1 expression. Additionally, an overexpression of FGFR2 was associated with increased serum and in vitro measures of oxidation and inflammation. Interestingly, the knockdown of p21cip1 (a cell cycle-dependent kinase inhibitor) reversed these effects of FGFR2 expression, implicating FGFR2 in atherogenesis through a p21cip1 mechanism. The authors then concluded that the clinical use of FGFR2 therapy in promoting angiogenesis for ischemic diseases may be suspect in the presence of atherosclerosis.

That FGFR2 may affect atherogenesis has been previously reported. Probably the most direct correlation between FGFR2 and atherogenesis was reported by Raj et al. (9). In this study, ApoE-knockout mice were fed an FGF-2 tyrosine kinase inhibitor SU-5402. These mice had less atherosclerosis than control ApoE-knockout mice receiving no inhibitor. Unlike the study of Che et al. (2), the study by Raj et al. (9) included evidence that FGFR2 affects plaque inflammation and oxidation processes. This was illustrated by a reduced number of macrophages, a reduced expression of monocyte chemotactic protein-1, and a reduced expression of cyclooxygenase and CD36 in the SU-5402-treated mice.

If FGFR2 modulates plaque inflammation (not just serum measures of inflammation and oxidation), it may have important implications for plaque stability/instability and risk of plaque rupture. FGFR2 has also been implicated in further (but associated) inflammatory pathways. Chan et al. (1) reported that FGF-2 modulates pathways associated with NF-κB production (9), such as VCAM and ICAM. An interesting pathway by which FGFR2 may affect atherogenesis and plaque stability is through its effects on heparin sulfate and perlecan-induced cell proliferation and inflammation (3–5). It has also been reported that VEGF indirectly simulates smooth muscle cell proliferation and migration through the stimulation of FGF-2 and TGF-β1 (7), thus involving further inflammatory processes.

A potential interesting aspect of the FGFR2 effects on both atherogenesis and angiogenesis is its effects on the proliferation of aorta vasorum in the atherosclerotic artery wall. Proliferation of aortic into the intima-media of atherosclerotic arteries is viewed as both a good thing (provides nutrition to a thickened artery) and a bad thing [may predispose to intra-arterial hemorrhage and plaque rupture (11)]. Important to the FGFR2 story, plaque size and cell proliferation are not the sole stimulant of neovascularization within the atheroma (11). In relation to the studies reporting the marked effects of FGFR2 on inflammatory processes (1, 3–5, 7, 9), it is probably more important that FGFR2 affects oxidation processes and possibly oxidative stress in the lesions, which are probably the most potent stimulus for angiogenesis (11).

Therefore, the significance of the study by Che et al. (2) is not so much that FGFR2 is associated with atherosclerosis, which has been previously reported (9), but that it more precisely identifies the signaling processes by which FGFR2 affects atherogenesis. This then elegantly constructs a working model of how FGFR2 may affect atherogenesis. Even more importantly, the studies confirm the role of FGFR2 in regulating the inflammatory processes that may change a stable atherosclerotic lesion to a more unstable lesion capable of rupture. This information, in the face of FGFR2 being used to promote angiogenesis clinically, warrants the caution of using this approach to promote angiogenesis in the presence of atherosclerotic disease.

While great strides in medicine are made by developing a specific target for therapy, this study is a good lesson in how affecting one single molecule can be beneficial for one disease process (treatment of ischemic disease) but harmful to another (atherosclerotic disease). As with all therapeutic approaches, one needs to weigh the cost-to-benefit ratio to each individual patient.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author(s).

REFERENCES

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