Oiling vascular growth: adipokines can induce (pathological) angiogenesis by using the VEGF/VEGFR system

EXPERTS’ PERSPECTIVE

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This editorial refers to an article by Adya et al.9 published in Cardiovascular Research in 2008. It is accompanied by a retrospective editorial by authors of that original article, Adya et al., pp. 223–226, this issue, as part of this Spotlight on Landmark Papers in Cardiovascular Research.

Obesity is a major cardiovascular risk factor that has been associated with serious complications such as hypertension, dyslipidaemia, insulin resistance, diabetes, and the development of cardiovascular disease. Adipokines, bioactive peptides and cytokines produced by adipose tissue, play important roles in glucose and lipid metabolism, cell viability, energy homeostasis, immunity and—most importantly—in cardiovascular function. Interestingly, it was shown that the adipokine profiles of different adipose tissues are different and they are further modified depending on the pathological condition. To date, several adipokines have been identified and characterized, including adiponectin, leptin, chemerin, vaspin, and visfatin.

Visfatin has been identified as a novel adipokine that is highly expressed in visceral fat. Visfatin is also known as pre-B-cell colony-enhancing factor (PBEF, a pre-B cell colony-enhancing factor that enhances the effects of interleukin (IL)-7 and stem cell factor on pre-B-cell colony formation) and as nicotinamide phosphoribosyltransferase (NAMPT; a nicotinamide phosphoribosyltransferase, an enzyme involved in nicotinamide adenine dinucleotide biosynthesis). Visfatin was shown to be increased in obese subjects and in patients with metabolic syndrome as well as in type 2 diabetics.1–5 It was also shown that visfatin regulates insulin secretion and insulin receptor signalling in the pancreas.6 Visfatin exerts a cardioprotective effect during myocardial infarction and it has been suggested to play a protective role in non-alcoholic fatty liver disease.7,8 Visfatin exhibits direct cardioprotective effects in vivo in a murine ischaemia-reperfusion model, since the infarct size was reduced following treatment with a single intravenous dose of visfatin.8 Visfatin-induced myocardial protection was shown to be dependent upon phosphoinositide 3-kinase (PI3K) and MEK 1/2 activation. Furthermore, visfatin reduces death of murine ventricular cardiomyocytes subjected to hypoxia-reoxygenation. Based on these observations, a number of investigators have focused on the characterization of the beneficial effects of visfatin on the cardiovascular system.

One of the key papers in Cardiovascular Research during the past decade was that by Adya et al.9 This paper demonstrates that the adipokine visfatin can induce endothelial cell (EC) proliferation and angiogenesis by stimulating the vascular endothelial growth factor (VEGF) system. Adya et al. demonstrated that visfatin can induce both VEGF and VEGF receptor 2 (VEGFR2) expression and stimulate vascular function in an indirect fashion. In particular, they showed that visfatin induces VEGF and VEGFR2 expression by activating both the PI3K/Akt and the ERK1/2 signalling cascades. Enhanced VEGF signalling results in increased expression of metalloproteinases (MMP) 2 and MMP9 as well as decreased expression of TIMP1 and TIMP2 (tissue inhibitors of MMPs) (Figure 1A), resulting in enhanced EC proliferation and tube formation. Interestingly, the same group demonstrated in a follow-up study that visfatin can also induce monocyte chemotactic protein-1 (MCP-1) as well as chemokine (C-C) receptor type 2 (CCR2) expression on ECs.10 The MCP-1-CCR2 axis can induce angiogenesis either by recruiting monocytes or by increasing VEGF expression. Interestingly, visfatin-induced VEGF expression can be blocked by a MCP-1 neutralizing antibody. Moreover, MCP-1 is involved in visfatin-induced angiogenesis via nuclear factor-κB (NF-κB) and PI3K pathways.10 In analogy, another group demonstrated that visfatin can induce angiogenesis by inducing the expression of fibroblast growth factor-2 (FGF-2) in ECs by activating the extracellular signal-regulated kinase 1/2 (ERK1/2) pathway (Figure 1A).

These findings have refined novel concepts in the field of cardiovascular biology. Fat/adipose tissue not only affects cardiovascular function by the production of lipids and triglycerides, but can also influence vascular function in a paracrine fashion. In addition to the findings by Adya et al. that visfatin can induce angiogenesis by stimulating VEGF and VEGFR2 expression, others demonstrated that the...
expression of the VEGF inhibitor sFlt-1 (soluble Flt-1/VEGFR1) is reduced in an obese rat model. Moreover, clinical data show that sFlt-1 expression in women inversely correlates with BMI and directly correlates with adiponectin levels. These results imply that the reduction of the anti-angiogenic molecule sFlt-1 (leading to higher levels of available VEGF) may lead to enhanced angiogenesis and thereby to the growth of the adipose tissue mass. Indeed, overexpression of the VEGF inhibitor sFlt-1 using adenoviral gene transfer technology in a mouse model of obesity (ob/ob) resulted in reduced weight gain in the sFlt-1 group. These data further support the conclusions of Adya et al. that adipose tissue can influence vascular function (Figure 1B).

VEGF is a central modulator of EC and vascular function with an indispensable role in vasculogenesis and angiogenesis. Deletion of only one VEGFA allele results in embryonic lethality due to defects in vascularization, i.e. inability to differentiate EC in the yolk sac around Day 8.5 of embryonic development. More relevant for human pathology, VEGF is also crucially involved in the maintenance and repair of existing blood vessels. VEGF signalling is involved in physiological and pathological angiogenesis and atherosclerosis not only due its effects on ECs, but also on mononuclear cells. It has been suggested that VEGF can regulate angiogenesis by the recruitment of bone marrow-derived monocytes and macrophages, which in turn regulate angiogenesis by secreting various angiogenic growth factors. There is a baseline expression of VEGF to assure its anti-apoptotic and its anti-thrombotic actions. In addition, VEGF plays an important role in EC permeability. It has been suggested that compromised EC integrity in atherosclerotic plaques may lead to plaque destabilization and intra-plaque haemorrhage and that VEGF signalling is involved. This suggests that stabilization of the endothelium by inhibiting VEGF signalling is an attractive therapeutic approach for plaque stabilization.

Considering the fact that visfatin can induce VEGF expression in an indirect fashion, it can certainly be envisioned that visfatin, other adipokines, or their mimetics could be used to therapeutically stimulate angiogenesis. This could be beneficial for the treatment of certain pathological situations such as chronic myocardial ischaemia, where the application of VEGF itself turned out not to be efficient enough to improve myocardial perfusion in a prolonged fashion. Keeping in mind that visfatin has cardioprotective effects, visfatin could be used in cardiac and vascular repair after myocardial infarction or ischaemia-reperfusion injury. Nevertheless, the use of visfatin in therapeutic strategies must be carefully designed, since, despite its positive effects on the vascular system, visfatin might also have negative effects. Visfatin expression is increased in certain pathologies such as obesity, diabetes, and polycystic ovary syndrome that are all associated with cardiovascular complications, and this implies a potential role of visfatin in atherosclerosis, plaque growth, and plaque destabilization. Visfatin was shown to induce expression of pro-inflammatory cytokines such as IL-6 and TNF-α in peripheral blood mononuclear cells as well as MCP-1 expression in ECs. In addition, visfatin can induce VCAM-1 and ICAM-1 expression in ECs as well as in leucocytes through activation of the NF-κB pathway. This could lead to recruitment of circulating mononuclear cells, which can adhere to endothelium, infiltrate into the subendothelial space, accumulate in the intima and differentiate into macrophages. Interestingly, visfatin appeared to be localized in regions enriched in lipid-laden macrophages, suggesting that visfatin may play a role in inflammation. In addition, visfatin levels were higher in patients with coronary artery disease (CAD) when compared with control subjects. Moreover,
visfatin is increased in plaques from patients with unstable carotid and coronary atherosclerosis. Based on the results by Adya et al., it can be suggested that increased visfatin expression leads to increased VEGF expression, EC permeability, accumulation of mononuclear cells, and plaque destabilization, thus providing a novel molecular basis for the role of obesity in CAD (Figure 18).

Overall, Adya et al. provided exciting insights into the molecular mechanisms by which visfatin, through the activation of the PI3K and ERK1/2 pathways, results in the activation of the VEGF/VEGFR2 signalling pathway and promotes angiogenesis, and they highlighted the importance of investigating the role of visfatin in the vascular system. However, 4 years after publication, the article by Adya et al. still leaves some questions open: How does visfatin stimulate PI3K and ERK1/2 in ECs? Does visfatin enter the EC or does it bind to receptors on the outside of the endothelium? If it is a receptor-mediated effect, what is the biochemical nature of such a visfatin receptor? In case this receptor exists, what else does it activate within the EC? Are there other direct effects on endothelial function as well? Future studies are awaited to provide answers to these questions and important clues to help in understanding of the mechanisms of vascular pathologies and developing new opportunities for therapeutic interventions that employ the axis of visfatin/angiogenic factors.

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**References**


