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Commentary

FAM3A – A mitochondrial route to the stimulation of angiogenesis?

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Cells die after prolonged ischaemia, and the only way to prevent this is by the restoration of blood flow [1]. The body achieves this by the process of angiogenesis. Ischaemic tissue releases angiogenic growth factors such as Vascular Endothelial Growth Factor (VEGF), Fibroblast Growth Factor and angiopoietins to stimulate the co-ordinated sprouting of new vessels from pre-existing blood vessels [2]. New methods of stimulating angiogenesis are eagerly sought as treatments for various diseases that involve ischaemia, including ischaemic heart disease, ischaemic stroke, peripheral artery disease and wound healing, but to date, efforts to develop a drug to stimulate neovascularization, for example via the administration of VEGF or other growth factors, have seen limited success [2]. Although VEGF stimulates vessel growth in animal models, it also increases vascular permeability, which can be detrimental [2]. It may be that a different approach is needed. In this regard, a new study by Xu et al. in this issue of *EBioMedicine* shows that the protein FAM3A stimulates angiogenesis in a mouse hind limb ischaemia model, via an intriguing signalling pathway that originates in the mitochondria, and leads to an increase in local VEGF production via purinergic signalling [3].

FAM3A is one of a family of four, cytokine-like proteins including FAM3B, FAM3C, and FAM3D [4]. While FAM3A and FAM3B are ubiquitously expressed, FAM3B and FAM3D have more localized expression in the pancreas and placenta, respectively [4]. FAM3A is highly expressed in vascular endothelium, but is also present in other cell types. Expression of FAM3A has previously been detected in the tunica media of rat arteries, where it promotes neointima formation after balloon injury via the PI3K/AKT pathway [5]. Curiously, despite FAM3A containing a predicted signal peptide for cellular secretion, it is mainly found localized to mitochondria within cells [5], where changes in its expression levels modulate mitochondrial respiratory activity [5]. When overexpressed, it enhances ATP production, contributing to an overall increase in the cellular release of ATP. This extracellular ATP then binds and stimulates purinergic receptors such as $P2Y_1$, leading to the activation of downstream, protein-kinase signalling pathways including PI3K/AKT [5].

A similar mechanism for FAM3A has been identified in the liver, where it may contribute to the regulation of glucose and lipid metabolism [6]. Interestingly, a marked reduction of FAM3A expression was found in the livers of diabetic mice [6]. Hepatic overexpression of FAM3A was able to attenuate different measures of diabetes by activating the PI3K-AKT signalling pathway [6]. In a pathway similar to that described above, an increase in mitochondrial ATP production in hepatocytes overexpressing FAM3A led to an increase in the synthesis and release of extracellular ATP, thereby activating PI3K/AKT signalling via P2 ATP receptors in the plasma membrane [6]. Since insulin also acts via PI3K/AKT, these results demonstrate a potentially important insulin-sensitizing role for FAM3A in the liver [6]. Conversely, obesity may contribute to the progression of type 2 diabetes by repressing FAM3A-ATP-AKT signalling [7].

Returning to the new publication by Xu et al., the localization of FAM3A in endothelial cells was first confirmed as being mitochondrial by immunostaining and subcellular fractionation [3]. Despite the fact that endothelial cells are usually primarily glycolytic, they contain mitochondria which have important functions in various aspects of cell physiology, from the regulation of Ca^{2+} signalling dynamics, to the control of cell death pathways such as apoptosis [8]. When endothelial FAM3A expression was increased, this caused an increase in ATP production and secretion, which was then able to bind to and activate plasma membrane P2 receptors, causing an increase in cytosolic Ca^{2+} levels [3]. This stimulated the transcription of VEGF-A, leading to an increase in endothelial angiogenesis [3]. An increase in the expression of FAM3A was found to promote endothelial tube formation, proliferation and migration, and also improved blood perfusion and capillary density in a mouse, hind limb ischaemia model [3]. Silencing of FAM3A had the opposite effect, decreasing mitochondrial respiration and ATP production and impairing angiogenesis [3]. Together, these data show that endothelial FAM3A positively regulates post-ischaemic angiogenesis [3]. Since it appears to work via an autocrine stimulation of endogenous VEGF release, it may overcome some of the problems seen with the stimulation of angiogenesis by the addition of exogenous VEGF.

How FAM3A modulates mitochondrial respiration remains an important, but unanswered question. Interestingly, endothelial mitochondria have also been implicated in the anti-ischaemic signalling pathway of other proangiogenic ligands such as SDF-1α [9]. Since mitochondrial dynamics and morphology is affected by mitochondrial respiration, it would be interesting to look more closely at mitochondrial morphology in cells with altered expression of FAM3A.

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If there is prospect for FAM3A regulation as a future pro-angiogenic therapy in patients, a simple and convenient means of increasing FAM3A expression without gene therapy would be preferable. Interestingly, rosiglitazone, an agonist of peroxisome proliferator-activated receptor gamma (PPARγ), has been shown to upregulate FAM3A expression in mouse hepatocytes [10]. Via this mechanism, in vivo administration of rosiglitazone increases FAM3A and, consequently, AKT activity, in liver cells [10]. However, it could be problematic if rosiglitazone increased FAM3A expression in all cells, since, as mentioned, its expression in smooth muscle can lead to neointima formation [5]. In any case, rosiglitazone is not a suitable drug itself, as it was withdrawn from the market due to cardiotoxicity. Future studies are also necessary to confirm that FAM3A upregulation is effective as a pro-angiogenic therapy in animal models with co-morbidities such as diabetes and obesity, since these often impair angiogenic pathways in patients [2].

Author disclosure

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