VEGF receptor switching in heart development and disease

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This editorial refers to 'Copper-induced regression of cardiomyocyte hypertrophy is associated with enhanced vascular endothelial growth factor receptor-1 signalling pathway' by Y. Zhou et al., pp. 54–63, this issue.

Vascular endothelial growth factor (VEGF), also known as VEGF-A to distinguish it from other isofoms (B–D) that are mainly involved in lymphangiogenesis, is an endothelial cell mitogen that has an essential role in both vasculogenesis and angiogenesis.1 VEGF regulates the development of endoderm-derived tissues, such as the vascular endothelium and the endocardium, by inducing multiple angiogenic cellular responses, including promotion of survival, migration, and differentiation, through the activation of Akt signalling in endothelial cells.2 VEGF exerts its biological actions by interacting with two main tyrosine kinase receptors, known as VEGFR-1 [or FMS-like tyrosine kinase-1 (Flt-1)] and VEGFR-2 [alternative names: foetal liver kinase-1 and kinase insert domain receptor (KDR)] (Figure 1).3

Intriguingly, based on work done predominantly using the mouse and the zebrafish as models, it now appears that there may be a role of VEGF and its receptors in many different aspects of cardiovascular development, including stem cell differentiation into cardiomyocytes, stem cell migration and survival, and heart development.4–6 On the premise that cardiomyocytes express VEGF receptors7 and that VEGF triggers the activation of mitogen-activated protein kinases,8 a role for VEGF has also been shown in inducing the adult cardiomyocyte to re-enter the cell cycle, thus promoting cell division in the heart and determining the appearance of cardiac hypertrophy in response to pathological (pressure overload) and physiological (exercise) stimuli.9 Finally, it has been shown that VEGF, even without pressure overload, can induce cardiomyocyte caryokinesis (increased number of cardiomyocyte nuclei) in vivo, e.g. after direct intramyocardial injection of a plasmid encoding human recombinant VEGF in a pig model of chronic myocardial ischaemia, in the absence of cytokinesis (increased number of cell divisions, leading to increased number of cardiomyocytes).10 These observations suggest a role for VEGF in determining the physiological growth of the post-natal heart, even without the induction of true cardiomyocyte regeneration.

Despite the growing number of observations on putative roles for VEGF as a cardiac transcriptional regulator, a highly relevant issue in this area is to decipher VEGF pathway(s) that control pathological and physiological hypertrophy, aiming at inhibiting the former and augmenting the latter. Understanding how VEGF may actually reverse—not induce—hypertrophic cardiomyopathy, a disease condition characterized by pathological myocardial hypertrophy secondary to pressure overload or to a large number of gene mutations affecting the cardiac contractile apparatus, and restore cardiac contractile function that is impaired in this condition has been the focus of the research by Zhou et al.11

Although it was originally thought that in the heart VEGF-R-2, or KDR, is expressed predominantly in endocardial cells, more recent studies suggest that VEGF/KDR signalling also influences the embryonic development of cardiac muscle.12 Cell fate lineage-marking experiments with the Rosa26-LacZ reporter mouse strain and a Cre (causes recombination) recombinase gene targeted to the KDR locus (i.e. a transgenic mouse strain expressing Cre recombinase in endothelial cells under the transcriptional control of the gene encoding KDR, cross-bred with the Rosa26 reporter strain, which expresses LacZ following Cre-mediated recombination) have demonstrated that KDR+ progenitor cells give rise to both cardiomyocytes and skeletal myocytes.13 Furthermore, studies in the mouse embryo and mouse embryonic stem cell differentiation models have provided evidence that three lineages—endothelial cells, smooth muscle cells, and cardiomyocytes—develop from a common KDR+ cardiovascular progenitor.14 The essential role of VEGF/KDR signalling in the initial stages of cardiovascular development is also suggested by the observation that KDR null embryos die at the stage of 6–8 somite pairs, even earlier than VEGF−/− embryos.15 The death in these animals is the result of a failure of mesodermal and endodermal progenitors to differentiate into the vascular endothelium, the endocardium, and the myocardium.15

Contrary to KDR, the role of Flt-1 has been more controversial, as it has been debated whether this latter VEGF receptor acts as a major transducer of VEGF signals or

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and UO126 are selective ERK1/2 inhibitors. M mice. Here, copper addition at a physiologically relevant density, but markedly reduced KDR density in hypertrophic cardiomyocytes. Gene silencing of Flt-1, conversely, blocked copper-induced regression of cell hypertrophy. The effect of Flt-1 on cardiac hypertrophy was mediated by the activation of a cGMP-dependent protein kinase-1 signalling pathway. Copper did not cause any change in VEGF production, but—through the changes described—altered VEGF pathway. Copper did not cause any change in VEGF protein expression, yielding one of the first demonstrations of an active signalling role for Flt-1, which acts not only—
as previously mostly believed—as a VEGF scavenger averting KDR signalling in cardiomyocytes. From this standpoint, it would also be of interest to identify additional cofactors for VEGF receptors and to investigate their potential roles in cardiomyocyte development and in disease conditions. Secondly, and more practically relevant, it might lead to the development of novel therapies against cardiac hypertrophy through pharmacological (e.g. dietary copper supplementation at doses that can be found in conventional multiple mineral supplements) or molecular biological strategies. Should similar effects of copper supplementation be found in controlled studies in patients, this might pave the road to a simple, non-toxic, and cheap therapy for hypertrophic cardiomyopathy.

**References**


