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On the relationship of LDL and VEGFR1: not just a family affair

In this issue of *EMBO reports*, Usui *et al* (2007) report their findings of ligand-independent activation of vascular endothelial growth factor (VEGF) receptor 1 (VEGFR1) by low-density lipoprotein (LDL). Thus far, VEGFR1 has been shown to be activated only by members of the VEGF ligand family, including VEGF-A, VEGF-B and placenta growth factor (PlGF). The new finding indicates indirect activation by a ligand that lies outside this family and suggests a connection between lipoprotein metabolism and vascular signalling through the VEGFR1 pathway. The findings are unexpected, but they could shed light on some previously unexplained findings regarding LDL-receptor-mediated signalling and modes of VEGFR1 activation. It is not surprising that researchers in such different fields as lipoprotein metabolism and angiogenesis have not considered the possibility that VEGFRs and LDL receptors might have something in common. Several questions have remained unanswered for decades: How do proliferating endothelial cells obtain enough cholesterol for membrane synthesis during active phases of angiogenesis? How is it possible that, during the progression of atherosclerosis, LDL-derived lipids never accumulate in endothelial cells but do so only in the underlying smooth muscle cells and macrophages? How do normal blood vessels transport LDL and cholesterol from the vessel lumen to the parenchymal cells? It is remarkable that, in most cell types, LDL uptake leads to lysosomal degradation of LDL components and release of cholesterol into the cytoplasmic compartment. However, although endothelial cells face high plasma cholesterol levels and take up LDL particles, they somehow avoid excessive lysosomal degradation of LDL. So far, this had been at least partly explained by transcytosis of LDL through the endothelial layer and downregulation of LDL receptors by high intracellular cholesterol content and oxysterols (Brown & Goldstein, 1986), but now there are other possible scenarios.

VEGFR1 is indispensable for embryonic development (Fong *et al*, 1995), whereas LDL-receptor deficiency is well tolerated during embryogenesis and growth (Ishibashi *et al*, 1994). Usui *et al* (2007) now suggest that LDL—by binding to its cognate receptor—induces autophosphorylation of VEGFR1 and its internalization with LDL receptors through a pathway that is clathrin-independent, but probably dependent on adaptor proteins known to affect the cellular uptake of LDL (Garuti *et al*, 2005). Such stimulation could mediate important intracellular actions in a VEGF-independent but VEGFR1-dependent manner. Usui *et al* (2007) also show that knockdown of LDL-receptor expression abrogated the LDL-induced VEGFR1 phosphorylation. As macrophages express VEGFR1, these findings might explain why LDL can induce migration of monocytes and/or macrophages (Hara *et al*, 1992).

While the presence of the VEGF co-receptor neuropilin-1 (Soker *et al*, 1998) in these complexes has not yet been assessed, it has been recently reported that oxidized phospholipids might stimulate the function of VEGFR2 (Zimman *et al*, 2007). Indeed, oxidized LDL that accumulates during atherogenesis (Ylä-Herttuala *et al*, 1989) contains significant amounts of oxidized phospholipids. Thus, connections between LDL metabolism, cholesterol-carrying lipoproteins and VEGFRs might be more widespread than originally thought. The cardiovascular and thrombotic side effects in patients treated with the VEGF monoclonal antibody Avastin (Ratner, 2004) have already indicated some links between VEGF biology and cardiovascular diseases. The findings of Usui *et al* (2007) suggest new potential mechanisms whereby VEGFR1 might modify the risk of coronary heart disease.

However, the exciting findings of Usui *et al* (2007) warrant further studies. They used stably transduced cells that overexpress large quantities of VEGFR1 in most of their experiments, and it is known that markedly enhanced receptor expression can lead to interactions that might be irrelevant in normal physiology. It will be important to extend these findings to *in vivo* models, in which other aspects of LDL metabolism and VEGF biology can be evaluated simultaneously. This is especially important in the case of coronary heart disease in which multiple risk factors and deviations of lipoprotein metabolism have already been implicated. More information is needed about the stoichiometry and inhibitors of LDL, VEGFR1 and LDL-receptor interactions. This information is relevant because the concentration of LDL particles in blood vessels is relatively high. Potential signalling through the LDL receptor remains enigmatic.

Whether the current findings ultimately establish a new atherogenic mechanism for the effects of LDL remains to be seen. However, there is no doubt that the paper by Usui *et al* (2007) connects two unrelated families of receptors in a fascinating way that could potentially be exploited for the prevention and treatment of cholesterol-related vascular diseases.

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