Delta/Notch signaling pathway mediates in skeletal muscle intussusceptive angiogenesis induced by the over-expression of VEGF\textsuperscript{164}.

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The overexpression of Vascular Endothelial Growth Factor (VEGF\textsuperscript{164}) in skeletal muscle can induce either normal or aberrant angiogenesis depending strictly on its dose in the microenvironment around each producing cell \textit{in vivo} (Ozawa 2004).

We recently found that in non-ischemic skeletal muscle the initial response to VEGF was the homogeneous enlargement of pre-existing microvessels into transient structures termed “mother” vessels (MV) (Sundberg 2001). MV remodelled into networks of normal capillaries with low VEGF levels or into bulbous angioma-like vascular structures with high VEGF levels. Furthermore MV showed several tiny holes in the vascular casts typical of intussusceptive angiogenesis (Gianni-Barrera, submitted).

Aim of this study was to investigate the role of Notch1 signaling pathway in MV formation induced by VEGF\textsuperscript{164}. MV showed continuous stretches of several contiguous endothelial cells, which all expressed Dll-4 and at the same time had activated Notch-1 intracellular domain (NICD) localized in the nucleus. After remodeling, neither the normal nor the aberrant vascular structures generated showed Dll4 expression or intra-nuclear activated NICD. Intriguingly the pharmacological inhibition of the Notch1 pathway by DAPT, led to a disruption of MV, which were substituted by a disorganized and irregularly shaped network of ECs.

In sum, Notch1 activation is necessary to induce the proper formation of MV. The switch between normal and aberrant angiogenesis by different VEGF doses in skeletal muscle appears to be regulated by mechanisms independent of Notch1 signaling.