Understanding the Proteins Involved in Regenerative Angiogenesis

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Angiogenesis, the formation of new blood vessels, is key in wound healing, embryonic development, and survival of cancerous tumors. Vascular Endothelial Growth Factor (VEGF) and its binding to VEGF receptors initiate a signaling cascade. The expression of proteins involved in this pathway contribute to angiogenesis, aiding in survival and proliferation of endothelial cells that line blood vessels. The proteins downstream in the VEGF pathway like MEK (MAPK pathway) or RHEB (PI3K/Akt pathway) are also frequently increased in tumors. This study uses zebrafish and human endothelial cell lines to investigate the role of the MAPK and PI3K/Akt pathway in angiogenesis. Adult zebrafish that overexpress MEK or RHEB proteins were fin clipped to initiate angiogenesis. Tissue and vascular regeneration was assessed in the presence of an angiogenesis inhibitor PTK787. A drug dose response revealed the treatment of 200nM of PTK787 was sufficient to stop vascularization in the wildtype and MEK fish, but not the RHEB fish. When assessed for levels of VEGF ligand and VEGF receptor gene expression, there was no significant difference between the RHEB and wildtype fins. This led to the hypothesis of RHEB fish having more or bigger cells. To test this human endothelial cells (HECs) were used. Using siRNA the expression of the TSC2, a negative regulator of RHEB in the PI3K/Akt pathway, was decreased, increasing the expression of RHEB in HECs. Preliminary results show the HECs are bigger as a result of this. More experiments are underway to evaluate the effects of PTK787 on the survival and proliferation of siRNA treated HECs. The study can help decipher the role of key molecular players of the PI3K/Akt pathway in angiogenesis, assisting in the development of precise targets in cancer therapy.

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