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Editorial

Molecular Signaling Pathways in Infantile Hemangiomas

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INTRODUCTION

Infantile hemangiomas are the most common type of vascular anomalies in children, occurring shortly after birth in about 5% of Caucasian infants [1], with more females affected than males. Many hemangiomas are well-circumscribed single lesions, but some are segmental and diffuse, often involving large areas of the extremities or the head and neck. Increased incidence of hemangiomas has been observed in preterm babies, and the vast majority of hemangiomas occur sporadically without a hereditary component. Infantile hemangiomas have a distinctive proliferative phase characterized by a rapid proliferation of capillaries within the first year of life, followed by an involuting phase characterized by spontaneous regression of the lesion with gradual replacement of vascular tissue with fibrofatty tissue [1].

VEGF Signaling

Pro-angiogenic growth factors are important regulators of hemangioma growth. Insulin-like growth factor-2 (IGF-2) and vascular endothelial growth factor-A (VEGF-A) are highly expressed in proliferating hemangioma tissues [2]. Interestingly, corticosteroids, which are a standard treatment for infantile hemangiomas, have been shown to reduce VEGF-A levels, suggesting a role for this potent angiogenic factor in hemangiogenesis [3]. Somatic mutations in VEGF receptors (VEGFR) have been found in some hemangiomas, and may lead to abnormal endothelial cell proliferation as a result of dysregulated VEGF signaling. Hemangioma endothelial cells have been shown to have low vascular endothelial growth factor receptor-1 (VEGFR-1) expression, but constitutively activated vascular endothelial growth factor receptor-2 (VEGFR-2) signaling caused by defects in a complex of VEGFR-2, TEM8 and β1-integrin in hemangioma endothelial cells that compromise the ability of the complex to stimulate the nuclear translocation of nuclear-factor-of-activated T cells (NFAT) and the transcription of VEGFR-1 [4]. VEGFR-1 appears to be required for the differentiation of hemangioma stem cells into mature endothelial cells, and this process is mediated by VEGF-A and VEGF-B by stimulating ERK-1/2 phosphorylation though VEGFR-1 [5].

VEGFR-2 activates a number of downstream effector pathways, including the Akt and mammalian target of rapamycin (mTOR) pathways. Recent studies have shown that the mTOR inhibitor rapamycin (sirolimus) reduces the self-renewal capacity of hemangioma stem cells, and diminishes their differentiation potential [6]. There is an on-going Phase II clinical trial with rapamycin for the treatment of complicated vascular anomalies in children (NCT00975819). Early results from the study showed that in a series of 6 patients with complicated and life-threatening vascular anomalies who were treated with rapamycin had significant disease improvement with tolerable side effects [7]. Since systemic rapamycin is an immunosuppressant, topical application of rapamycin has been shown to be effective in the treatment of cutaneous vascular tumors in animal models, with limited systemic drug absorption [8].

Beta-Adrenergic Signaling

Since the initial report of the use of propranolol, a nonselective beta-adrenergic receptor blocker, in infantile hemangiomas by Léauté-Labrèze et al. [9], propranolol has rapidly become the first-line medical therapy for these lesions. The efficacy of propranolol points to the potential regulatory role of the beta-adrenergic signaling pathway in hemangioma development. Propranolol controls vascular tone by vasoconstriction through inhibition of nitric oxide synthesis and release. By inhibiting the beta-adrenergic receptors, propranolol blocks receptor-mediated activation of the ERK/MAPK signaling pathway that stimulates endothelial cell proliferation and migration [10]. Propranolol can also affect angiogenesis by inhibiting VEGF expression. Moreover, propranolol induces major alterations in the gene expression of cyclins and cyclin-dependent kinase inhibitors, lipid/sterol metabolism, cell cycle regulation, angiogenesis and ubiquitination [11].

Notch Signaling

Genome-wide transcriptional profiling of proliferating hemangiomas showed an increase in the expression of genes involved in endothelial-pericyte interactions, such as Jagged-1 and Notch-4 [12]. Notch signaling is involved in embryonal vascular development and in the determination of vascular differentiation, and is an anti-angiogenic therapeutic target. The differentiation of hemangioma stem cells to pericytes has been found to be regulated by the Notch ligand Jagged-1 in an animal model of infantile hemangiomas [13], and loss of Notch1 causes widespread vascular tumors in mice [14]. These findings point to the important role of Notch in the vasculature and hemangiomas.

Other Signaling Pathways

Large-scale gene expression analysis of proliferating hemangiomas revealed increased expression of genes involved in endothelial-pericyte interactions, such as angiopoietin-2 [12]. Analysis of the angiopoietin-2 receptor Tie2 mRNA expression revealed elevated Tie2 in cultured hemangioma endothelial cells as compared with normal endothelial cells [15]. Platelet-derived growth factor (PDGF) signaling has been shown to be an intrinsic negative regulator of hemangioma involution [16]. PDGF is elevated during the proliferating phase, and may inhibit adipocyte differentiation. Inhibition of PDGF receptor signaling resulted in enhanced adipogenesis in hemangioma stem cells, and increased the expression of adipocyte-specific transcription factors [16].

Promising New Molecular Therapy

A better understanding of key molecular pathways driving hemangioma growth will provide a strong impetus for the development of novel targeted molecular therapy. The finding of constitutive activation of VEGFR-2 in hemangioma endothelial cells may lead to new therapeutic options with VEGFR-2 inhibitors to prevent receptor activation in these lesions. The mTOR inhibitor rapamycin has been shown to have good efficacy in preclinical studies and early clinical trials of complex vascular anomalies [6-8]. Blockade of the beta-adrenergic signaling pathway has already been shown to be highly efficacious in the treatment of infantile hemangiomas. Further research to understand the mechanism of how propranolol inhibits hemangioma growth and the specific growth regulatory role of the beta-adrenergic receptor pathway in hemangioma is needed in order to develop more effective and safer therapy targeting these pathways.

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