P141

Understanding Angiogenesis in Squamous Cell Carcinoma with Loss of Type VII Collagen

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It is not known why individuals with severe generalized recessive dystrophic epidermolysis bullosa (RDEB), a rare inherited blistering disorder caused by mutations in the COL7A1 gene, develop scarring and aggressive and sometimes fatal squamous cell carcinomas (SCC). Our group previously demonstrated that loss of type VII collagen (Col7) in SCC results in increased angiogenesis in vitro and in vivo. An angiogenesis protein array showed upregulation of Vascular Endothelial Growth Factor (VEGF), in SCC cells with knock-down (KD) of Col7, whilst RDEB SCC patient samples displayed increased VEGF expression compared to non-EB SCC controls.

To understand VEGF-mediated angiogenesis in RDEB SCC further, we compared RNAseq data from primary keratinocytes with KD of Col7 to two existing data sets in the literature using several cancer cell lines treated with the anti-VEGF antibody, bevacizumab. We identified some interesting genes in common including the novel putative phosphatase, PALD1. PALD1 encodes Paladin, a recently discovered regulator of angiogenesis. VEGF binds to and activates VEGF Receptor-1 (VEGFR-1) leading to angiogenesis, an essential requirement for tumour growth and metastasis. Stable KD of Col7 was established using shRNA and cells were used in a mouse xenograft model (n=7 per group). Protein expression levels were assessed by Western blot analysis and immunohistochemistry.

Increased VEGFR-1 and reduced Paladin expression were observed in shCol7 cells compared to shC cells using Western blot analysis. Moreover, increased VEGFR-1 expression was observed in Col7 KD xenografts compared to xenografts with Col7 present and Col7 KD xenografts with recombinant Col7 (n=7).

Our findings demonstrate that VEGFR-1 and potentially Paladin are significant to the increased angiogenesis observed in SCC with loss of Col7 and are further evidence that anti-angiogenic therapies may be beneficial to patients with RDEB SCC. (PathSoc grant funded research)