Phospholipase C gamma 1 as a key regulator in human and animal hemangiosarcomas

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Objectives: Although alterations in the PLCG1 gene have been previously reported in angiosarcomas, very littler is known about their role as drivers or therapeutic targets in angiosarcomas. This study aimed to investigate the functional impact of the D1165H variant in endothelial cell-derived tumours in both humans and dogs, using a comparative oncology approach.

Materials and Methods: Human whole-exome sequencing (WES) was analysed to identify recurrent mutations in PLCG1. Functional characterization of the D1165H variant was conducted using in vitro endothelial cell models and in vivo mouse xenografts. Cellular proliferation, morphological alterations, and downstream signalling activation were assessed. Drug response assays were carried out using tyrosine kinase inhibitors, including sunitinib.

Results: The PLCG1 D1165H mutation was identified in a subset of human angiosarcomas. In vitro, the mutation induced increased proliferation, spindle-shaped morphological changes, and enhanced activation of MAPK and PI3K/AKT pathways. In vivo, D1165H-expressing cells showed increased tumour growth. Notably, the mutation conferred resistance to tyrosine kinase inhibitors such as sunitinib, indicating a bypass of upstream receptor-mediated signalling.

Conclusions: These findings suggest that the PLCG1 D1165H mutation contributes to endothelial tumorigenesis through increased proliferation, morphological transformation and drug resistance. While further studies are needed to fully elucidate its mechanisms, animal models are essential to validate the human functional effects found.

Keywords: Angiosarcoma; PLCG1; D1165H; endothelial tumours; tyrosine kinase inhibitor resistance; comparative oncology.