HIF-1α and HIF-2α Differently Regulate Tumour Development, Metabolism and Inflammation of Clear Cell Renal Cell Carcinoma in Mice

Ian Frew

Department of Medicine, Centre for Translational Cell Research, BIOSS Centre for Biological Signalling, Albert-Ludwigs-Universität Freiburg, Freiburg, Germany

Mutational inactivation of *VHL* is the earliest genetic event in the majority of clear cell renal cell carcinomas (ccRCC), leading to accumulation of the HIF-1a and HIF-2a transcription factors. While correlative studies of human ccRCC and functional studies using human ccRCC cell lines have implicated HIF-1a as an inhibitor and HIF-2a as a promoter of aggressive tumour behaviours, their roles in tumour onset have not been functionally addressed. We now show using an autochthonous ccRCC model that *Hif1a* is essential for tumour formation whereas *Hif2a* deletion has only minor effects on tumour initiation and growth. Both HIF-1a and HIF-2a are required for the clear cell phenotype. Transcriptomic and proteomic analyses reveal that HIF-1a regulates glycolysis while HIF-2a regulates genes associated with lipoprotein metabolism, ribosome biogenesis and E2F and MYC transcriptional activities. HIF-2a-deficient tumours are characterised by increased antigen presentation, interferon signalling and $CD8^+$ T cell infiltration and activation. Single copy loss of *HIF1A* or high levels of *HIF2A* mRNA expression correlate with altered immune microenvironments in human ccRCC. These studies reveal an oncogenic role of HIF-1a in ccRCC initiation and suggest that alterations in the balance of HIF-1a and HIF-2a activities can affect different aspects of ccRCC biology and disease aggressiveness. We are currently investigating the therapeutic implications of these findings by testing a number of different inhibitors of HIF-1a and HIF-2a in our autochthonous model.