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High glucose concentrations attenuate hypoxia-inducible facter-1α expression and signalling in non-tumor cells

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Abstract:

Hypoxia-inducible factor (HIF) is the major transcription factor mediating adaption to hypoxia e.g. by enhancing glycolysis. In tumor cells, high glucose concentrations are known to increase HIF-1α expression even under normoxia, presumably by enhancing the concentration of tricarboxylic acid cycle intermediates, while reactions of non-tumor cells are not well defined. Therefore, we analyzed cellular responses to different glucose concentrations in respect to HIF activation comparing tumor to non-tumor cells. Using cells derived from non-tumor origin, we show that HIF-1α accumulation was higher under low compared to high glucose concentrations. Low glucose allowed mRNA expression of HIF-1 target genes like adrenomedullin. Transfection of C_2C_{12} cells with a HIF-1α oxygen-dependent degradation domaine-GFP fusion protein revealed that prolyl hydroxylase (PHD) activity is impaired at low glucose concentrations thus stabilizing the fusion protein. Mechanistic considerations suggested that neither O_2 redistribution nor an altered redox state explains impaired PHD activity in the absence of glucose. In order to affect PHD activity, glucose needs to be metabolized. Amino acids present in the medium also diminished HIF-1α expression, while the addition of fatty acids did not. This suggests that glucose or amino acid metabolism increases oxoglutarate concentrations, which enhances PHD activity in non-tumor cells. Tumor cells deprived of glutamine showed HIF-1α accumulation in the absence of glucose, proposing that enhanced glutaminolysis observed in many tumors enables these cells to compensate reduced oxoglutarate production in the absence of glucose.

Key-words: Prolyl hydroxylase, Glutamine, Tumor cells, Non-tumor cells