Potential adverse effects to the retina of cancer therapy targeting pyruvate kinase M2

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To the Editor,

The Warburg effect was first observed in 1920s when Otto Warburg and his team demonstrated that cancer cells make lactate from glycolysis despite the presence of oxygen [1]. His team also noted that normal mammalian retinal explants displayed aerobic glycolysis, but the finding was dismissed as experimental artefact because it did not fit neatly with Warburg's beliefs about cancer pathogenesis [1]. However, subsequent studies have confirmed that the mammalian retina does, in fact, display a strong Warburg effect [2].

The presence of the Warburg effect in cancer and normal embryonic tissue can be explained by the cellular biosynthetic demands [3]. When energy supply (in the form of glucose) is sufficient, proliferating cells direct the metabolic pathways away from oxidative phosphorylation towards biomass synthesis via aerobic glycolysis [3]. Cancer cells have the ability to oscillate between biosynthesis and energy production to meet the metabolic requirements. In adult mammalian retina, such biosynthetic demands exist due to the constant prodigious photoreceptor turnover in the rod outer segments [4].

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(Received 19 April 2014; accepted 3 May 2014)

ISSN 0284-186X print/ISSN 1651-226X online
DOI: 10.3109/0284186X.2014.922217

Pyruvate kinase is a glycolytic enzyme which catalyses the conversion of phosphoenolpyruvate into pyruvate in the final step of glycolysis [3]. However, hypoxia-inducible factor 1 alpha (HIF-1α) is a master regulator of transcription processes in response to hypoxia [3]. Both pyruvate kinase M2 isoform (PKM2) and HIF-1α are established key mediators of the Warburg effect in cancer, with PKM2 reportedly coactivates HIF-1α to promote the reprogramming of glucose metabolism [3]. A greater understanding of the molecular underpinnings of the Warburg effect in recent years has motivated attempts to modulate PKM2 as a novel cancer therapy [5].

Goldberg et al. identified several small interfering RNAs (siRNAs) namely si25, si155 and si156 which specifically silenced PKM2 mRNA to induce apoptosis in cancer cells in vitro [6]. Interestingly, intratumoural delivery of si156 into xenograft tumour in mice demonstrated tumour regression [6]. In a high-throughput screen, Vander Heiden et al. identified Compound 3 as an inhibitor of PKM2, postulated to target the allosteric regulatory site of PKM2 [6]. More potent shikonin and alkannin were subsequently shown to inhibit PKM2 selectively and downregulate glycolysis [7]. Conversely, small-molecule activators of PKM2 such as DASA-58 and TEPP-46 also illustrated inhibitory effect on tumour xenograft growth in mice, possibly by interfering with the anabolic biosynthesis [8]. All the aforementioned agents are currently still in the preclinical development phase with in vitro and in vivo animal studies.

Although the mechanism of the Warburg effect in the retina has not been elucidated, it is likely that key aspects of the molecular mechanism are conserved between the retina and cancer. Recent evidence indicates that both PKM2 and HIF-1α are present in normal physiological mammalian retina [9,10]. Hughes et al. demonstrated the presence of stabilised HIF-1α in physiological human and rat retinas [9]. Morohoshi et al. demonstrated the presence of PKM2 in physiological mouse retina [10], and we have recently demonstrated the presence of PKM2 and constitutive expression of low level of HIF-1α in the rat retina (unpublished data).

Adult human retina has one of the highest metabolic requirements of any tissue and is susceptible to energy compromise. Hence, disruption to a key metabolic pathway essential for physiological maintenance of continuous photoreceptor renewal and energy production may result in significant cellular disturbance or irreversible cell death. The notion of modulating PKM2 as a therapeutic strategy for cancer should therefore proceed cautiously with current and future studies to particularly investigate for adverse effects on the mammalian retina and visual function. This potential blinding consequence represents a major obstacle to be elucidated and overcome before such therapy can be safely introduced in human clinical studies.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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