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METASTASIS

Metabolic reprogramming in disseminated cells

Tumour cells undergo considerable metabolic reprogramming to survive and proliferate within the hostile environment and limited nutrient supply of solid tumours. But the metabolic profile of invasive and disseminated tumour cells is unknown.

LeBleu *et al.* isolated green fluorescent protein (GFP)-positive primary, circulating and metastatic tumour cells from mice implanted with GFP-labelled 4T1 mammary epithelial cancer cells that form tumours and metastasize to the lung. Gene expression profiling revealed that oxidative phosphorylation pathway genes were the most differentially regulated in circulating tumour cells (CTCs) compared with primary tumour cells. Further analyses revealed that certain genes were specifically upregulated in the CTCs, especially those associated with mitochondrial biogenesis and oxidative phosphorylation. Peroxisome proliferator-activated receptor-γ co-activator 1α (*PPARGC1A*; also known as *PGC1A*) encodes a transcriptional co-activator that promotes mitochondrial biogenesis, ATP production and metabolic reprogramming during stress and its expression was the highest among all genes in the CTCs. Consistently, the authors found that CTCs from 4T1 tumours, as well as CTCs from GFP-labelled B16F10 mouse melanomas and MDA-MB-231 human breast xenograft tumours, had increased amounts of mitochondrial DNA and ATP, as well as increased basal respiration rate and mitochondrial oxygen consumption rate, compared with matched primary tumour cells.

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Lara Crow / NPG

Interestingly, comparing primary and metastatic tumour cells from the 4T1 mouse model revealed limited differences in the expression of genes associated with mitochondria biogenesis and oxidative phosphorylation, indicating that the changes in CTCs are reversible. The metabolic gene expression changes in CTCs occurred concomitantly with epithelial–mesenchymal transition (EMT); gene expression in metastatic tumour cells (which have presumably undergone mesenchymal–epithelial transition (MET)) partially returned to that of primary tumour cells. This indicated that the metabolic changes of CTCs were coupled with a mesenchymal phenotype. Indeed, the authors found that cancer cells with a mesenchymal phenotype had significantly higher levels of PPARGC1α than cancer cells without mesenchymal markers. Moreover, PPARGC1α expression was induced as tumour cells were moved into an oxygenated environment from hypoxia — as occurs when cells become migratory — and in parallel, the expression of *Twist1* (which encodes an EMT transcription factor) was induced. However, knockdown of either TWIST1 or PPARGC1α expression had no effect on the other or on the transcriptional programmes they induce, indicating that EMT and PPARGC1α-mediated metabolic reprogramming occur independently in response to the same microenvironmental conditions.

What is the role of PPARGC1α in metastasis? Knockdown of PPARGC1α expression in 4T1, B16F10 and MDA-MB-231 cells led to significant downregulation of genes associated with mitochondrial biogenesis and oxidative phosphorylation, and mitochondrial DNA and ATP levels were also reduced in these cells. However, glycolysis was unaffected, indicating that PPARGC1α drives mitochondrial respiration to increase ATP levels. Knockdown of PPARGC1α also reduced cell invasion and migration *in vitro*. Moreover, PPARGC1α knockdown did not affect the growth of 4T1, MDA-MB-231 or B16F10 cells *in vivo*, but the number of CTCs and metastases was significantly reduced. The authors found that anchorage-independent survival was unchanged when PPARGC1α was knocked down. Together, these data indicate that PPARGC1α-mediated increases in mitochondrial respiration promote tumour cell migration and intravasation. Finally, using 161 invasive ductal breast carcinoma (IDC) samples, the authors found that high PPARGC1α expression in the invasive front correlated with metastasis and poor survival, and that PPARGC1α was expressed in >80% of CTCs derived from patients with IDC and lung metastases.

This study suggests that metabolic reprogramming that favours ATP generation, rather than anapleurosis, is important for the invasive properties of disseminating tumour cells.

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ORIGINAL RESEARCH PAPER LeBleu, V. S. *et al.* PGC-1α mediates mitochondrial biogenesis and oxidative phosphorylation in cancer cells to promote metastasis. *Nature Cell Biol.* http://dx.doi.org/10.1038/ncb3039 (2014)