importance of
this enzyme
in the higher
oxygen
environment of
lung tissue

METABOLISM

Adapting to the environment

Understanding the environmental context in which tumours or metastases develop and how tumour cells adapt to survive in different conditions may point to new ways of therapeutically targeting these tumours. Alvarez, Sviderskiy *et al.* have identified a pathway that allows primary lung tumour cells or lung metastatic breast tumour cells to survive in the high oxygen concentrations present in the lung.

The authors conducted parallel short hairpin RNA (shRNA) screens for metabolic targets in a breast cancer cell line grown *in vitro*, at either tissue-level (3%) or atmospheric (21%) oxygen concentrations, or in orthotopic xenografts; through doing this, they identified cysteine desulfurase (NFS1) as being important for growth in 21% oxygen but not in 3% oxygen or *in vivo*. NFS1 is crucial for the biosynthesis of iron–sulfur clusters (ISCs), which are important oxygen-sensitive cofactors for many enzymes. In two breast cancer cell lines, shRNA-mediated knockdown of NFS1 blocked proliferation of the cells in 21% oxygen but not in 3% oxygen, an effect that required NFS1 catalytic activity. Similar effects were observed when other enzymes in the ISC biosynthesis pathway were knocked down, indicating that ISC biosynthesis is crucial for proliferation in high oxygen conditions *in vitro*.

NFS1 was not required for growth of orthotopic breast tumour xenografts, an effect that is in line with the observed hypoxic conditions in breast tumours. However, NFS1-knockdown cells were unable to colonize the lung, suggesting the importance of this enzyme in the higher oxygen environment of lung tissue. In support of this, NFS1 protein levels were increased in cells grown at 21% oxygen relative to 3% oxygen and in lung metastases compared with primary breast tumours.

The authors hypothesized that NFS1 might also be relevant in primary lung cancers. Indeed, they found increased levels of NFS1 mRNA in lung adenocarcinomas compared with normal lung in public data sets and in lung cancer cell lines compared with other lines. In addition, the NFS1 locus is amplified in many lung cancers. To analyse this pathway *in vivo*, the authors used mouse lung cancer cells that express *Kras*^{G12D} and lack *Trp53* (KP cells). KP cells expressing *Nfs1* shRNAs formed subcutaneous tumours, but they were unable to form tumours in the lungs after intratracheal instillation, again indicating the importance of this enzyme for tumour growth in the lung environment.

Several lines of evidence indicated that under conditions of high oxygen levels, ISCs have a high rate of turnover due to oxidation, and NFS1 is required to support the increased ISC biosynthesis that is necessary to replace oxidized ISCs. NFS1 suppression also activated the iron starvation response, thereby increasing cellular iron levels; this sensitized cells to undergo cell death by ferroptosis following induction of reactive oxygen species.

These data indicate the importance of the upregulation of NFS1 in high oxygen environments for protecting tumour cells from oxidative damage and cell death; this pathway might also be exploited for therapy of primary lung tumours or lung metastasis.

Sarah Seton-Rogers

ORIGINAL ARTICLE Alvarez, S. W., Sviderskiy, V. O. *et al.* NFS1 undergoes positive selection in lung tumours and protects cells from ferroptosis. *Nature* **551**, 639–643 (2017)

Macmillan Publishers Limited