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Integrated stress response couples mitochondrial fitness with lineage reprogramming to drive cancer evolution

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Tumour progression towards dedifferentiated cell clusters plays a critical role in intratumor heterogeneity and therapy resistance. While tumour microenvironmental stress has been implicated, the underlying mechanisms remain poorly defined. In particular, although the integrated stress response (ISR)'s role in stem cell phenotypes is established², its function in lineage reprogramming, the process by which cells dynamically transition into distinct phenotypic states in a stressful microenvironment in vivo, remains unclear.

Using mouse models of lung adenocarcinoma, we demonstrate that activation of the integrated stress response (ISR)-marked by phosphorylation of eIF2 (p-eIF2) and ATF4 induction-drives tumour heterogeneity. ISR activation facilitates the emergence of high-plasticity, undifferentiated and pre-epithelial-to-mesenchymal transition clusters characterized by elevated ATF4 and MYC activity. This process is MYC dependent and involves ISR-mediated repression of NKX2-1, a key determinant of alveolar identity, and induction of CHCHD10, a regulator of mitochondrial integrity and metabolic fitness. Disruption of the p-eIF2-ATF4 axis induces mitochondrial dysfunction, limits dedifferentiation and suppresses tumour growth.

In human lung adenocarcinoma, ISR-driven dedifferentiation correlates with advanced disease and poor prognosis, identifying the ISR as a central driver of lineage reprogramming and metabolic fitness in tumour progression.