Targeting glutamine transport in triple-negative breast cancer

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Although a nonessential amino acid in normal cell growth, the demand for glutamine is dramatically increased throughout malignant transformation to provide catabolic substrates for ATP production and anabolic substrates for macromolecule biosynthesis. To maintain glutamine availability for these metabolic processes, cancer cells overexpress cell surface transporters that function to exchange amino acids across the plasma membrane. Cancer cells also increase enzyme expression to facilitate both the catabolic and anabolic usage of these substrates that fuel cell growth. A number of transporters, such as the SNAT family and ASCT2, are increased in a variety of cancers, thereby facilitating high levels of glutamine uptake.

We and others have recently shown that in breast cancer, although ASCT2 and SNAT2 are highly expressed in most tumour subtypes, only aggressive triple-negative breast cancer (TNBC) cells require transporter-mediated uptake of glutamine to sustain cell growth *in vitro* and *in vivo*. Gene expression analysis of TNBC patient samples suggested coordinated regulation of ASCT2 and other glutamine metabolism-related genes, such as glutaminase and glutamate–ammonia ligase, indicating a global activation of glutaminolytic energy production pathways in these tumours. The metabolism-regulating transcription factor MYC was significantly correlated with these genes, suggesting a dynamic MYC-driven transcriptional programme in TNBC. We therefore hypothesize that highly proliferative TNBC that are sensitive to glutamine restriction (*e.g.* transporter inhibitor or glutaminase inhibitor CB-839 in clinical trials) may have unique metabolic signatures that could be targeted for therapeutic purposes.