breast cancer target identification, validation and preclinical models

Targeting the ASCT2 glutamine uptake and metabolism pathway in triple-negative breast cancer

M. van Geldermalsen1, Q. Wang1, C.G. Bailey2, Y. Feng2, R. Nagarajah1, A. Marshall2, A. Thoeng2, S. O’Toole3, J.E.J. Rasko2, J. Holst1

1Origins of Cancer Laboratory, Centenary Institute, Sydney, Australia
2Gene and Stem Cell Therapy Program, Centenary Institute, Sydney, Australia
3Cancer Division, Garvan Institute of Medical Research, Sydney, Australia

Alanine, serine, cysteine-preferring transporter 2 (ASCT2) mediates uptake of glutamine, a conditionally essential amino acid in rapidly proliferating tumour cells. Uptake of glutamine and subsequent glutaminolysis are critical for activation of mTORC1 signalling, which regulates cell growth and protein translation in cancer cells. ASCT2 expression and glutamine dependence are increased in high-risk breast cancer subtypes and therefore present a possible axis for therapeutic intervention. Pharmacological inhibitors of ASCT2-mediated transport significantly reduced glutamine uptake in human breast cancer cell lines, leading to suppression of mTORC1 signalling, cell growth and cell cycle progression. Notably, these effects were subtype-dependent, with ASCT2 transport critical only for triple-negative breast cancer cell growth compared to minimal effects in luminal breast cancer cells. Both stable and inducible shRNA-mediated ASCT2 knockdown was sufficient to prevent cellular proliferation, deregulate intracellular metabolic pathways, and induce rapid cell death in triple-negative breast cancer cells, but not in luminal cells. Using a dual bioluminescent-fluorescent orthotopic xenograft mouse model, ASCT2 expression was then shown to be necessary for both successful engraftment and growth of HCC1806 triple-negative breast cancer cells in vivo, and that lower tumoral expression of ASCT2 conferred a significant survival advantage in these mice. These responses remained intact in primary breast cancers, where ASCT2 expression was correlated using in silico approaches with increased invasiveness, higher tumour grade at diagnosis and poor overall survival. Additionally, mRNA levels as measured by NanoString® nCounter Dx in primary samples from a cohort of 36 triple-negative tumours showed that ASCT2 expression was significantly correlated with other markers of tumour invasiveness, such as MYC, a known transcriptional regulator of ASCT2; ATF4, VEGFA and SRC.

Disclosure: All authors have declared no conflicts of interest.