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## Glutamine metabolism drives breast cancer invasion by providing a source of extracellular glutamate to activate the GRM3 metabotropic glutamate receptor

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Glutamine metabolism is well-established to contribute to cancer cell growth and proliferation by providing a source of nitrogen for nucleotide and amino acid biosynthesis as well as TCA cycle intermediates. There is also accumulating evidence that glutamine metabolism may contribute to metastasis although mechanistic links to tumour cell migration and invasion remain unclear. We have generated a number of highly invasive primary cell lines from the polyoma middle-T genetically engineered mouse model of breast cancer (MMTV-PyMT) and found that withdrawal of glutamine from these cells reduces not only their proliferation, but also their invasive migration into 'stroma-like' preparations of fibroblast-derived extracellular matrix. Our metabolomic analyses indicate that invasive MMTV-PyMT cells actively secrete glutamate, a product of glutamine metabolism, into the extracellular milieu. Moreover, addition of glutamate is sufficient to restore invasiveness (but not cell growth or proliferation) to glutamine-starved MMTV-PyMT cells. We have pursued these findings by investigating the role played by plasma membrane receptors for glutamate in cell migration and invasion in PyMT cells and in MDA-MB-231 triple negative breast cancer cells. We provide evidence that glutamate generated within the cell by deamidation of glutamine leaves the cell via the xCT antiporter to activate the GRM3 metabotropic glutamate receptor at the cell surface. This, in turn, suppresses adenylate cyclase activity to prevent protein kinase A activation and to drive an invasive programme. Indeed, knocking out GRM3 with CRISPR technology or inhibition using a selective GRM3 antagonist (LY341495) is sufficient to oppose invasiveness without compromising proliferation. Conversely, a specific GRM3 agonist (LY354740) drives invasiveness without increasing proliferation. Consistently, treatment with LY341495 was sufficient to abrogate lung colonisation following tail vein injection whilst tumour growth after orthotopic injection was unaffected. Our results provide a mechanistic link between glutamine metabolism and invasion and identify GRM3 as a potential therapeutic target in breast cancer.