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Glutamate-mediated NMDA receptor induces Ca^{2+} entry and increases growth of leukaemic megakaryoblasts

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The discovery of CALR mutations in myeloproliferative neoplasms highlighted importance of Ca^{2+} homeostasis in megakaryocytic cells. Megakaryocytes express N-methyl-D-aspartate receptors (NMDARs) known to mediate glutamate-induced Ca^{2+} entry in other cells. However, the roles of glutamate and NMDARs in normal and malignant megakaryocytes are not known. The aim of this study was to determine whether NMDARs provide a novel pathway for Ca^{2+} entry into leukaemic megakaryoblasts and if so, whether modulating NMDAR activity could influence leukaemia cell growth. Expression of NMDAR subunits was examined in human bone marrow including neoplastic and megakaryoblastic leukaemia cell lines (Meg-01, Set-2 and K-562). Well-established NMDAR modulators (agonists and antagonists) were employed to determine NMDAR effects on the levels of intracellular Ca^{2+}, cell viability, proliferation and differentiation. We found that human leukaemic cells expressed distinct combinations of the NMDAR subunits. Low concentrations of glutamate and NMDAR antagonists (riluzole, memantine, MK-801 and AP5; 5-100 μM) attenuated cell growth in culture mostly through the inhibition of cell proliferation. The use-dependent NMDAR antagonist, memantine (100 μM) reduced Meg-01 viability to 16±10% of controls (IC50 20 μM) and inhibited Meg-01 proliferation to 41±6% (IC50 36 μM). Further, after three days in the presence of NMDAR antagonists, cells acquired morphologic and immunophenotypic features of megakaryocytic differentiation. Our findings indicate that NMDARs provide a novel pathway for Ca^{2}+ entry into leukaemic megakaryoblasts that supports cell proliferation. NMDAR inhibitors counteract these effects suggesting a novel way to interrupt growth of this type of leukaemia.

Biography

Tania Kamal is a PhD student at The University of Auckland, New Zealand.

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