Polyamine depletion limits progression of acute leukaemia

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Abstract

Cancer cells are addicted to polyamines, polycations essential for cellular function. While dual targeting of cellular polyamine biosynthesis and polyamine uptake is under clinical investigation in solid cancers, preclinical and clinical studies into its potential in haematological malignancies are lacking. Here we investigated the preclinical efficacy of polyamine depletion in acute leukaemia. The polyamine biosynthesis inhibitor difluoromethylornithine (DFMO) inhibited growth of a molecularly diverse panel of acute leukaemia cell lines, while non-malignant cells were unaffected. Responsiveness to DFMO was linked to decreased levels of its molecular target, the rate-limiting polyamine biosynthesis enzyme ODC1, and of the polyamine transporters ATP13A2 and ATP13A3. DFMO increased polyamine uptake and upregulated expression of polyamine transporters in acute leukaemia cells, a compensatory effect abolished by treatment with the polyamine transport inhibitor AMXT 1501. This drug, currently in a phase 1 clinical trial in solid tumours in combination with DFMO, potentiated the inhibitory effects of DFMO, and their combination synergistically inhibited the growth of acute leukaemia cell lines by inducing apoptosis. DFMO and AMXT 1501 limited disease progression in highly aggressive xenograft models of infant KMT2A-rearranged leukaemia, even when treatment was initiated at high disease burden. Increased expression of c-MYC was associated with enhanced sensitivity to the combination of DFMO and AMXT 1501, suggesting this oncoprotein as a potential predictive marker of response to the drug combination. In conclusion, targeting polyamine biosynthesis and polyamine uptake limits disease progression in models of acute leukaemia, supporting further preclinical and clinical investigation into this approach for acute leukaemia.

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