Cancer metabolism and its role in the sensitivity of leukemic cells to L-asparaginase

ABSTRACT

No ultimate treatment strategy exists for relapsed or non-responsive (15-20%) children with acute lymphoblastic leukemia (ALL). In this study, we aimed to elucidate the impact of metabolic rewiring in leukemic cells on poor therapy response and the emergence of resistance. This dissertation focuses on l-asparaginase (ASNase), a crucial chemotherapeutic agent and its effect on leukemia, using models of leukemic cell lines and primary cells of ALL patients. Cell metabolism was assessed by measuring metabolic pathways and nutrient influx using a Seahorse analyzer and stable isotope tracing. Main findings of the study demonstrated that the ASNase-therapy response was mitigated by the activity of the mechanistic target of rapamycin (mTOR)-regulated biosynthetic pathways. This phenomenon was induced by the bone marrow environment, which enabled the activation of the resistant mechanism in leukemic cells. We next found a correlation between the following metabolic features and lower sensitivity to ASNase: low ATP-linked respiration, high mitochondrial membrane potential and high glycolytic flux before therapy. The latter was shown to have prognostic implications. Moreover, high glycolytic flux was detected in T-ALL to be responsible for ASNase resistance and modulated by the phosphoinositide 3-kinase (PI3K)/Akt pathway. Further, we demonstrated metabolic rewiring plays a role in leukemogenic process driven by deregulated JAK/STAT signaling. In conclusion, we identified several metabolic features implicated in resistance, presenting novel therapeutic targets. Moreover, we have proposed a re-evaluation of patient stratification using cellular metabolism.

Keywords

Asparagine, PI3K/Akt pathway, cellular metabolism, childhood acute lymphoblastic leukemia, glutamine, l-asparaginase, mesenchymal stromal cells, metabolic profile, mTOR signaling pathway.