SUMMARY

1. Explore the pro-survival metabolic processes of leukemic cells upon ASNase treatment in the BM microenvironment.

In the main project, I have elucidated the metabolic mechanism by which MSCs increase the survival of leukemic cells. Using a BM model, we have demonstrated that MSCs restore the biosynthetic pathways of leukemia cells after ASNase treatment. The restored pathway sustained the leukemic cells' survival, which retrieved the intrinsic resistant mechanisms in leukemic cells. The latter mechanism counteracts the cytotoxicity of the drug.

2. Study of the basal metabolic profile of leukemic cells in the cellular response to ASNase treatment.

This study investigated the connection between basal metabolic profile and the sensitivity to ASNase treatment in acute leukemia. The metabolic profile was assessed by measuring glycolysis parameters, mitochondrial respiration activity, and MMP in leukemic cell lines (19) and primary cells from both ALL and AML patients (26). Higher glycolytic flux was strongly associated with lower ASNase sensitivity. Moreover, we demonstrated a correlation between lower ASNase sensitivity with higher ATP-linked respiration and basal MMP.

3. Investigate PTEN mutations or aberrant PI3K/Akt pathway in T-ALL in the ASNase sensitivity and glucose metabolism.

This study focused on the link between PTEN deletion, glucose metabolism and the sensitivity of T-ALL to ASNase treatment. T-ALL with lower ASNase sensitivity displayed higher glycolysis, upregulated by the aberrant activation of the PI3K/Akt pathway. PTEN is a negative regulator of PI3K/Akt pathway, which we found was functionally lost in T-ALL cells which were resistant to ASNase. Pharmacological inhibition of Akt kinase enhanced the sensitivity to ASNase, and led to the inhibition of glycolytic flux.

4. Characterize the role of metabolic rewiring in malignant transformation driven by mutated JAK2 kinases identified in *BCR-ABL*-like ALL subgroup.

This study compared the metabolic rewiring during leukemogenesis induced by *JAK2* translocations with different fusion partners. We demonstrated that the translocations with altered JAK/STAT signaling displayed different metabolic phenotypes. As a result, we confirmed metabolic heterogeneity within leukemia subtypes, implying different metabolic vulnerabilities.