Title: Deciphering the molecular pathways governing TCR-induced cell death and anti-leukemic activity in T-ALL

Project

T cell acute lymphoblastic leukemia (T-ALL) is characterized by the expansion of immature T cells blocked in differentiation. Despite considerable progress in T-ALL treatment in the last 30 years, about 40% of adult cases relapse. Improvement of patient survival and discovery of novel therapeutic approaches entails a more profound understanding of T-ALL at the cellular and molecular levels.

Using mouse models of T-ALL and human T-ALL cases xenografted in NSG mice (T-ALL PDX), the laboratory recently demonstrated that CXCR4, a cell surface receptor for the chemokine CXCL12, is critical to the migration, survival and proliferation of T-ALL cells and the activity of the leukemia stem/propagating cell. CXCL12 is not expressed in T-ALL cells but is abundantly produced by several cell types in the tumor microenvironment, enlightening the critical role of the dialog that leukemic establish with their microenvironmental niche(s) in disease initiation, progression and resistance to treatment (Passaro et al 2015).

During normal T cell development the T cell receptor (TCR) is essential to educate mature T cells to distinguish between self and non-self antigens to ultimately establish an efficient immune response. We found that strong and persistent activation of the TCR by e.g. monoclonal antibodies to TCR components (anti-CD3 mAb) rapidly induces T-ALL cell death and strong anti-leukemic effects in vivo (Trinquand, dos Santos, Tran Quang et al 2016). This opens new therapeutic options through the use of either such antibodies, or compounds targeting molecular pathways critical to enforcement of the TCR-induced cell death program.

We identified the global transcriptome associated with anti-CD3-induced cell death in T-ALL cells (unpubl obs), which pointed to the activation of known and novel cell death pathways. The first objective of the proposed PhD Thesis is thus to persue the identification of essential cell death effectors in TCR-induced death of T-ALL cells and to investigate the therapeutic value of targeting these effectors alone or in combination with anti-CD3 treatment or chemotherapy. In T-ALL CXCR4 forms a complex with the TCR, which is rapidly internalized upon anti-CD3 treatment (unpubl obs). The second objective is to investigate if and how CXCR4 is involved in anti-CD3-induced cell death of T-ALL cells. The third objective is to investigate whether TCR-induced signaling deregulates translation of mRNAs critical to TCR-induced cell death in T-ALL and whether this level of genetic deregulation is therapeutically targetable.

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Cancer Discov **6 (9):972-985.** **Equal first authors . §Co-seniors authors*.