The role of the brain-derived neurotrophic factor in the neuro-immune control of acute myeloid leukemia

Project

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Summary and strategic objectives of the project

The immune system and the peripheral nervous system are present throughout the body and cooperate to ensure vital organs maintain tissue homeostasis and the overall health of the host. However, it is still poorly understood how this cooperation is modified or lost in cancer, in particular in leukemia, and more thorough investigation is needed to ideally identify targetable determinants able to restore the correct crosstalk. Leukemia is a group of blood cancers originating in the bone marrow (BM), a highly innervated tissue.

In this project, I will focus on acute myeloid leukemia (AML), a disease that urgently requires a more complete understanding, the overall survival rate being below 20% due to drug resistance and disease relapse. The main cause of treatment failure in AML are leukemic stem cells (LSC) that are resistant to chemotherapy, that survive and give rise to other leukemic clones that proliferate and engraft in the patients. LSCs reside in the BM and are sustained by cells and soluble factors, including neural-derived factors, that constitute the BM microenvironment, also called the BM niche. Previously published findings from the host laboratory show that innate lymphoid cells (ILC), a recently described family of immune cells involved in tissue homeostasis, inflammatory diseases and cancer, are present but functionally dysregulated in the BM of AML patients at disease onset and only partially restored after chemotherapy. However, how ILCs interact with malignant cells including LSCs and whether this interaction is modulated by neurotrophic factors is yet to be discovered. Among the nerve-derived factors, I will focus on the role of the brain-derived neurotrophic factor (BDNF) in this project, since it has been associated with a favorable outcome in chronic lymphocytic leukemia (CLL) and was found to be dramatically reduced in the peripheral blood (PB) and BM of AML patients in my preliminary experiments. The aim of this project will be to understand whether its loss affects ILC anti-tumoral functions, promotes LSC survival and/or modulates their interactions.

Therefore, I plan to dissect the role of BDNF in the neuro-immune control of AML by: 1) identifying cellular and molecular players involved in BDNF-tropomyosin receptor kinase B (TrkB) signaling (Aim 1); 2) dissecting the tumor/stroma-immune cell crosstalk involving BDNF (Aim 2); and 3) assessing the impact of BDNF on leukemia clearance *in vivo* (Aim 3). Overall, I expect to shed light on a new layer of tumor immunity, i.e., the neuro-immune circuit in leukemia, a potential key contributor to disease progression and response to therapy.

Schematic representation of the proposed project