André de Almeida

Publications

Myb drives B-cell neoplasms and myeloid malignancies in vivo
Pieters & Almeida *et al.* Blood Advances, 2022

Myb overexpression synergizes with loss of *Pten* and is a dependency factor and therapeutic target in T-ALL
Almeida *et al.* Under revision.

SOX11 gain interferes with normal T-cell development and cooperates with LMO2 in T-ALL development
Almeida *et al.* Under preparation

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Functional evaluation of transcription factors in T-ALL: MYB and SOX11

André de Almeida

Dissertation submitted to obtain the degree Doctor of Health Sciences

Promotors Prof. Dr. Pieter Van Vlierberghe
Prof. Dr. Steven Goossens
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Leukemia

Leukemia is a cancer resulting from the uncontrolled proliferation of blood-forming cells in the bone marrow. Leukemic overgrowth impairs the production of healthy blood cells, thus weakening the immune defenses and causing anemia, which in turn can result in symptoms such as fatigue, weakness, and fever.

Lymphocytes are a subset of white blood cells responsible for the establishment and management of immune reactions. When lymphocyte precursors become malignant and proliferate rapidly in the bone marrow and blood of the patients, they originate acute lymphoblastic leukemia. These lymphoblastic leukemias are the most common pediatric cancer, peaking in children around 5 years of age. However, a second wave of lymphoid leukemia occurs in adults older than 65 years of age.

T-cells are a subtype of lymphocytes which regulates other immune cells and ensures an adequate immune reaction against specific pathogens. T-cell acute lymphoblastic leukemia (T-ALL) accounts for 15% of pediatric and 25% of adult acute lymphoblastic leukemias. The current treatment for T-ALL relies heavily on chemotherapy, and the improvement in therapeutic regimens has brought the 5-year survival rate of children close to 90%, and that of adults close to 50%. Unfortunately, patients who suffer from therapy-resistant or relapsed T-ALL have few therapeutic options, and most of these people end up dying from the disease. Additionally, T-ALL survivors suffer from short- and long-term side-effects due to therapy. Therefore, there is a continued need for the identification of novel therapeutic targets and alternative therapeutic approaches.

MYB

A century ago, a rapidly fatal infectious leukemia was identified in chicken. This was one of the first pieces of evidence showing cancers can be caused by specific pathogenic agents. Decades later, this pathogen was identified as a retrovirus that forces the infected cells to express an overactive viral *Myb* gene, thus promoting the formation of leukemia in hens (viral *Myb* = oncogene). Under physiological conditions, the MYB protein is considered an important regulator of differentiation, proliferation, and survival of progenitors that originate the blood cells. However, some T-ALLs express abnormally high levels of *MYB*, which is partially due to an increases number of copies of the *MYB* gene. We found that this increased copy number of *MYB* can be associated with a worse prognosis for T-ALL patients. With the aim of better understanding leukemia biology, we generated several mouse models with non-viral MYB overexpression.

In the first part of this work, we found that the overexpression of this MYB protein on its own causes myeloid tumors and B-cell proliferative diseases in mice. However, no T-cell tumors were formed in these mice, which suggests that other specific genetic lesions are necessary for the formation of T-ALL. We then combined the MYB overexpression in two distinct mouse models that spontaneously develop T-cell malignancies. This occurs by either overexpressing the LMO2 oncogene, or by losing the tumor suppressor PTEN. In these models we observed that MYB did not affect malignancy formation driven by LMO2, but that it accelerated the onset of disease in cooperation with PTEN loss, thus showing that non-viral MYB is also oncogenic in T-ALL.

Finally, we investigated the potential of targeting MYB as a therapy for T-ALL, both in mouse and human tumor cells, and we observed that the absence of MYB makes the cancer cells stop proliferating and die. Therefore, MYB can be a good target for T-ALL.

SOX11

SOX11 is found in multiple embryonic tissues, and it regulates cell maturation, organ remodeling, and the normal development of neurons. Under physiological conditions SOX11 is not found in T-cells, and there is no know function for it in this lineage. However, some T-ALLs express SOX11, which could indicate that its expression is associated with a malignant role promoting T-ALL. To study the impact of SOX11 on T-cells we used mouse and human models, and we observed that SOX11 interferes with the normal T-cell development. Furthermore, our results indicate that SOX11 cooperates with LMO2 to expand a fraction of immature T-cell precursors. Consequently, SOX11 facilitates the formation of T-ALL driven by LMO2. On the other hand, SOX11 reduced the number of more mature T-cell precursors and delayed the onset of leukemia resulting from loss of PTEN.

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