Clinical and Translational Studies

Cell Signaling in T cell lymphoma

Mature T cell lymphomas (TCL) comprise a rare and heterogeneous group of hematological neoplasms, characterized by the clonal proliferation of malignant post-thymic T cells. Compared to the well studied B cell lymphomas, the pathobiology of TCL is poorly understood. As a result, a lack of distinct morphological, immunophenotypic and genetic features impedes pathologic and clinical diagnosis, while prognosis remains poor in the majority of cases. Until now, no extensive studies have been made to approach TCL at the level of signaling networks. In a group of diseases lacking specific markers, the identification of dysregulated pathways could be applied for disease prognostication or even in developing novel therapeutic agents. Based on an ongoing collaborative study of M. Lia Palomba and Grégoire Altan-Bonnet on the signalosome of chronic lymphocytic leukemia, we hypothesize that specific phosphoprofiles elicited by various stimuli (cytokine and T cell receptor activation) could have a significant discriminative capacity between TCL subtypes, cell subpopulations within the same neoplasm and malignant from normal T cells. All phosphoresponses are assessed at a single-cell level through complex immunophenotyping and multiplexed phosphoflow cytometry.

A second goal of this study is to perform extensive immunological profiling of TCL subtypes. Most data in this field are based on histopathological studies or in-vitro studies with cell lines, which both have translational limitations. By taking advantage of the single-cell level approach that flow cytometry offers, we are interested in assessing T cell receptor repertoires of the malignant clones, the cellular origin and phenotypic plasticity of TCL subtypes, and finally, the role of the tumor cellular and cytokine microenvironment in disease progression and prognosis.

Cell Signaling in Waldenström's Macroglobulinemia

Waldenström's Macroglobulinemia (WM) is a rare, indolent B cell malignancy, characterized by the presence of a clonal B cell population with lymphoplasmacytic features in the bone marrow, lymph nodes and spleen, and a detectable serum paraprotein of the IgM class, often accompanied by symptoms of hyperviscosity and cytopenias. Recent genetic analysis of WM revealed that over 90% of the patients carry a MYD88 mutation leading to a leucine to proline substitution in codon 265 (L265P). MYD88 L265P promotes WM cell survival by stimulating NF-κB signaling, however it is not clear yet what is the effect of this mutation on other pathways, like the BCR and the JAK/STAT pathway. As in our T cell lymphoma studies, we are interested in assessing the phosphoprofile of WM cells, in order to clarify how networks are formed by a potential cross talk between the NF-κB pathway and other pathways. Moreover, differential signaling within the WM cell population could provide information for novel tumor subpopulations, which could have a prognostic and therapeutic significance.

Adoptive Immunotherapy with Lymphoid Precursor Cells

Culture systems utilizing Notch1 signaling can be used for the *in vitro* development of T lineage cells at various differentiation stages. The most widely used of those systems is the OP9-DL1 system, which uses a mouse bone marrow stromal cell line transduced to express the Notch1 ligand Delta-like 1 (DL1) to coculture hematopoietic stem cells in the presence of IL-7 and FLT3-ligand. This system can be modified for the generation of large numbers of lymphoid progenitors committed to the T lineage for adoptive immunotherapy. We recently demonstrated that co-transplanted allogeneic OP9-DL1 derived early T progenitors can mature in an immunosuppressed host, mediating immunity including anti-tumor activity without causing GVHD and can even be transferred in the absence of allogeneic stem cells to any immunosuppressed individual irrespective of MHC disparities for adoptive 'off-the-shelf' immunotherapy [Zakrzewski JL et al. 2008 and 2006]. Such cells also protect the thymus from atrophy which otherwise hinders future lymphopoiesis, and can be genetically modified in vitro for targeted immunotherapy. Notch-based culture systems show promise for clinically applicable therapeutic use: they can be fully humanized and human cord blood and human adult bone marrow derived CD34+ progenitor cells have been cultured in these systems to generate human T cells.

Project Members

M. Lia Palomba

Kimon Argyropoulos

PREVIOUS

CAR T Cells

NEXT

Featured News

About Us

Overview

Leadership

Administration

History

Contact Us

Research

Overview

Research programs

Research labs

Core facilities & resources

Education & Training

Overview

Postdoctoral training

Gerstner Sloan Kettering Graduate School

Joint graduate programs

Programs for college & high school students

News & Events

Overview

Seminars & events

Open Positions

Overview

Faculty positions

Postdoctoral positions