Molecular Immune Regulation

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Exploring T cell regulation with patients in mind

The mammalian immune system is important to fight infections but immune cells are also involved in many other processes such as tolerance to the growing fetus, wound healing and eliminating tumors. To this end the immune system is composed of many cell types and soluble molecules. Many layers of regulation ensure proper functioning of the immune system as a whole since mistakes can lead to severe clinical disease.

In the past decade immunology has taken center stage in clinical medicine. Immune cells and inflammation are important in diseases affecting virtually any organ. Nevertheless, until recently, therapeutic interventions targeting the immune system were rather limited. Although vaccines are among the most effective (preventative) measures in medicine, only a limited number of vaccines were available and modulating the immune system therapeutically usually came at the cost of non-specific immune suppression. With the availability of "biologics", i.e. therapeutic antibodies or cytokines, this started to change. Cytokine blockade allows more specific intervention with specific pathways and is nowadays established in many different disciplines. In addition, antibody-mediated blockade of receptors on immune cells led to a long- awaited revolution in oncology. Since the turn of the century it was known that inflammation and cancer are closely linked. However, only in the last decade "cancer immunotherapy" has become clinical routine. Cancer can suppress immune responses by engaging inhibitory receptors on immune cells. Blocking such interactions with therapeutic antibodies can successfully "unleash" the immune system. Thus, in this approach, the therapeutic target are immune cells and only indirectly cancer cells. This broke a longstanding dogma that the cancer cells themselves are targeted in oncology. However, despite great success, not all patients respond. Therefore, we are investigating poorly studied molecules involved in immune regulation.

Our group has been studying small regulatory RNAs called microRNAs (miRNA) for over a decade. miRNAs inhibit specific messenger RNAs (mRNAs) by directly binding them. We previously demonstrated that a specific miRNA cluster (miR-17~92) is upregulated during T cell activation. When T cells recognize their target antigens they get activated. Two signals are required for this process: **a)** stimulation of the T cell receptor and **b)** a second signal called costimulation. The prototypical costimulatory signal is triggered by engagement of CD28. Based on the literature and our own work we hypothesized that miR-17~92 might mediate important signals during T cell activation. In the past reporting period we found that transgenic miR-17~92 can at least partially substitute for many of the functions that are defective in CD28-deficient T cells. We characterized the target genes that are bound and regulated by miR-17~92 and demonstrated that several pathways key for T cell activation and function are promoted by miR-17~92 (Doelz *et al.,* unpublished).

In parallel, we investigated if miRNAs that are relevant for T cell function could be targeted by small molecules. We identified small molecules that inhibit T cell function and proliferation of cancer cell lines. We are currently investigating the precise mode of action of these molecules (Matter & Jeker, unpublished).

Finally, cellular therapies are emerging as effective treatment modalities beside small molecules and biologics (Jeker, Trillium Immunologie). We have developed CRISPR/Cas9-based protocols to engineer the genome of T cells (Kornete, JI). More recently we have initiated projects involving more sophisticated engineering to explore cellular therapies for autoimmune diseases and transplantation. Thus, we are increasingly focusing on translating our research results to clinical practice.

Connection to Clinical Practice

Prof. Jürg Steiger
Nephrology and Transplantation Immunology

Our lab is associated with the clinical Transplantation Immunology & Nephrology at the USB. We are working together to prepare the infrastructure necessary to bring new multidisciplinary cellular therapies to patients at the USB.

Selected Publications

Doelz M, Gagnon JD, Kornete M, Marone R, Bantug G, Kageyama R, Hess C, Ansel KM, Seyres D, Roux J and Jeker LT (2020). The non-coding RNA miR-17-92 is a central mediator of T cell activation. https://www.biorxiv.org/content/10.1101/2020.10.13.336537v1.

Doelz M, Marone R and Jeker LT. Plasmid- or Ribonucleoprotein-mediated CRISPR/Cas Gene Editing in Primary Murine T Cells. Meth Mol Biol, in press.

Kornete JI, Kornete M, Marone R and Jeker LT. (2018). Highly Efficient and Versatile Plasmid-Based Gene Editing in Primary T Cells. J Immunol 200, 2489–2501.

Jeker LT. (2018). T Zellen nach Mass. Trillium Immunologie; 2(2).

Pua HH, Steiner DF, Patel S, Gonzalez JR, Ortiz-Carpena JF, Kageyama R, Chiou NT, Gallman A, de Kouchkovsky D, Jeker LT *et al.* (2016). MicroRNAs 24 and 27 Suppress Allergic Inflammation and Target a Network of Regulators of T Helper 2 Cell-Associated Cytokine Production. Immunity 44, 821–832.