Mar 10th 2026 | 3:00PM CET VIRTUAL

iPSZÜRICH

A Lecture Series Focused on Induced Pluripotent Stem Cells

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INTESTINAL INTERACTIONS OF INNATE LYMPHOID CELLS IN HEALTH AND DISEASE

Intestinal homeostasis relies on coordinated interactions among immune, mesenchymal, neural, epithelial, and microbial compartments. Disruption of these interactions contributes to the development of several diseases including Inflammatory Bowel Disease (IBD). Innate Lymphoid Cells (ILCs) are central regulators of these networks. In healthy intestine, type 3 ILCs (ILC3) predominate, whereas inflamed IBD tissue exhibits an accumulation of type 1 ILCs (ILC1) with a concomitant reduction of ILC3. Our work focus on dissecting the mechanisms that govern the interaction between ILCs and intestinal epithelial cells in health and in IBD.

Using human co-culture models of ILCs with intestinal organoids, we show that ILC1 drive epithelial and extracellular matrix remodelling, implicating them in the development of fibrosis and cancer—two major IBD sequelae.

Conversely, we show that ILC3 promote epithelial regeneration and induce regulatory FoxP3+ T cells via TGF-β1 production and activation. Importantly, TGF-β1 signalling remains intact in ILC3 from IBD tissue, suggesting this pathway is functional and therapeutically targetable.

Given the protective role of ILC3 and their depletion in IBD, we propose restoring ILC3 populations as a therapeutic strategy. To this end, we developed a protocol to generate large numbers of functional human intestinal ILC3 by co-culturing blood-derived ILC precursors with intestinal organoids.

In conclusion, ILCs are pivotal regulators of intestinal homeostasis whose dysregulation is linked to IBD pathology. Our findings support therapeutic approaches aimed at restoring ILC balance to reinstate intestinal homeostasis.