SIgN Immunology Seminar



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Unexpected Targets and Triggers of Autoimmunity

Host
Prof Paola Castagnoli
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Date
Tuesday,
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Time
3pm – 4pm

Venue
SIgN Seminar Room,
Immunos Building.
Level 4
Biopolis

Upon activation, T cells undergo distinct developmental pathways, attaining specialized properties and effector functions. T-helper (T_H) cells are traditionally thought to differentiate into T_H1 and T_H2 cell subsets. Recently, a subset of interleukin (IL)-17-producing T cells (T_H17) distinct from T_H1 or T_H2 cells was described and shown to have a crucial role in the induction of autoimmune tissue injury. In contrast to the effector T cells, $CD4^+CD25^+$, $Fox\text{-}P3^+$ regulatory T cells (T-regs) inhibit autoimmunity and protect against tissue inflammation. TGF-b is a critical differentiation factor for the generation of T-regs and using Foxp3-GFP "knock-in" mice we have shown that IL-6, an acute phase protein induced during inflammation, inhibits the generation of $Foxp3^+$ T-reg cells and induces proinflammatory Th17 cells. Our data therefore suggests a reciprocal relationship in the generation of pathogenic (Th17) T cells that induce autoimmunity and regulatory ($Foxp3^+$) T cells that inhibit autoimmune tissue injury. Accumulating data suggests that there are three distinct steps in Th17 differentiation: Induction, Amplification and Stabilization mediated by distinct cytokines and loss of any of the cytokines (TGF-b, IL-6, IL-21 or IL-23) in the pathway results in a defect in generation of Th17. It has been suggested that Th17 cells are not always proinflammatory or pathogenic and in fact some Th17 cells may have been shown to have regulatory properties. We have defined experimental conditions that induce differentiation of highly pathogenic Th17 cells. Naive TcR transgenic mice with specificity for myelin antigens when differentiated under these defined conditions induce very severe Experimental Autoimmune Encephalomyelitis (EAE). However not all Th17 cells are pathogenic to induce EAE, IL-23 is a key cytokine that induces pathogenicity in Th17 cells. Using expression profiling and systems biology approaches, we have identified Serum Glucocorticoid Kinase-1 (SGK-1) a key kinase induced during IL-23R signaling. High concentration of NaCl also induces SGK-1 and promotes Th17 differentiation, therefore supporting the possibility that high salt diet promotes Th17 differentiation and provides a trigger for inducing autoimmune disease on a genetically susceptible background.