Report World Immune Regulation Meeting III - 22-25 March 2009, Davos, Swiss

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In March 2009 I visited the World Immune Regulation Meeting III, which had a special focus on regulatory and effector mechanisms. Since I work on immune inhibitory receptors, which are crucial factors for balance and regulation in the immune system, this was a particularly interesting meeting for me. Several aspects of immune regulation were dealt with: From development and characteristics of regulatory T cells and Th17 cells, via essentials of immune regulation to immune response and immune pathology. The conference consisted primarily of plenary sessions, presented by well-established scientists in the field. I will briefly discuss two personal favourites.

Jurg Tschopp discussed mechanisms of inflammation. The talk started with a short introduction on the inflammasome, an adaptor protein complex consisting of the intracellular adaptor protein ASC, a sensor protein, caspase 1 and caspase 5. Tschopps group set up an *in vitro* system in which macrophages were cultured together with inflammatory mediators. In addition, anti-CD3 and subtypes of T cells were added: either regulatory, naïve, or memory CD4+ T cells. What they found was that memory CD4+ T cells could mediate a complete inhibition of inflammation, whereas the regulatory and naïve T cells did not affect inflammation. Production of IL-1b and IL-18 is inhibited by memory T cells, whereas production of IL-12 is increased. It seems that anti-CD3 stimulated memory T cells can block activation of the inflammasome. CD40L seems to have a role in this process. Tschopp proposed the following model: If the immune system encounters the same pathogen for a second time, a memory response against pathogen is present. In this case it's better to activate this memory response than the innate immune system, because the latter is accompanied by a lot of collateral damage which should be prevented if not inevitable.

Neil Barclay discussed paired receptors. Paired receptors are receptors that bind similar ligands and are present on the same cell, but have other intracellular signalling motifs. One receptor activates the cell, the other receptor is inhibitory. Such paired receptors are abundantly present in the immune system, but what is their biological function? Barclay explained the concept that immune inhibitory receptors are attractive targets for pathogens. If a pathogen produces a protein that acts as a ligand for an inhibitory receptor, this leads to inhibition of immune cell function and hence pathogens escape killing by the immune system. To illustrate the mechanisms that have developed in the immune system to win the war against pathogens, Barclay chose the SIRP receptor family, consisting of (among others) SIRPα, which is inhibitory, and SIRPβ, which associates with DAP12 and activates the cell. The physiological ligand of SIRP is CD47, which is present on many cells in the immune system, and ligation of SIRPα prevents phagocytosis of e.g. red blood cells. Some viruses produce a protein that also ligates SIRPα, and so likewise escapes phagocytosis. In a system of co-evolution the immune system has developed mechanisms to recognise these types of pathogens. In the first place, unlike the other SIRPs, SIRPα is highly polymorphic. These polymorphisms are distant from the CD47 binding site and may have developed to prevent binding of pathogenic ligands. Secondly, SIRPα moves to the immunological synapse during the interaction with CD47, and this site is not accessible for a pathogenic ligand. Finally, although the extracellular parts of SIRPα and SIRPβ are highly homologous, SIRPβ does not recognize CD47 and has developed specifically to target and eliminate pathogens that bind SIRPα.