Regulatory T cells

The aim of the immune system is to fight foreign organisms and to protect the host. This means that the immune systems needs to distinguish between foreign and self-proteins. Many different mechanism that prevent the inadvertent activation of self reactive T cells have been described, e.g. depletion of self-reactive T cells in the thymus, anergy induction in the periphery, ignorance of self-proteins and the dominant suppression of effector T cells by $CD4^+CD25^+$ regulatory T cells (Treg) . The latter cells were discovered by their virtue of preventing autoimmune gastritis, throiditis and oophoritis. These $CD4^+CD25^+$ cells present 5-10% of the CD4 cells of mice and they are further characterized by the constitutive expression of GITR, CD122, intracellular CD154 (CTLA-4). As these cell surface markers are also expressed on activated conventional T cells the best Treg marker to date is the transcription-repressor scurfin (*Foxp3*). Further studies in various mouse models have demonstrated that Treg are also instrumental in achieving transplantation tolerance and in preventing overwhelming pathology in infections. Unfortunately for cancer patients these cells also prevent an effective immune-response to tumour cells. These $CD4^+CD25^+$ Treg have also been demonstrated in humans where they display the identical phenotype and function as in mice, however only 1-3% of the peripheral blood CD4 cells qualify as Treg which makes their purification difficult.

As mentioned before the function of Treg is to suppress the activation of autoreactive T cells *in vivo*. The mechanism by which this occurs is difficult to study *in vivo* and may also depend on the animal model used. For instance TGF and IL-10 are instrumental in the control of bacterially driven inflammatory bowel disease, while both of these cytokines are dispensable for the suppression of autoimmune gastritis. In order to study the molecular terms of suppression *in vitro* assays have been established. $CD4^+CD25^+$ Treg do not proliferate upon stimulation in cell culture, but when added to other CD4 or CD8 T cells they suppress the proliferation and cytokine production of these effector T cells (Teff). The suppression can be overcome by either adding growth factors (Interleukin -2) or by supplying the Teff with a very strong stimulus. The stimulation of the Treg and a cell contract between the Treg and Teff cell are needed for suppression to occur, supernatants of Treg cultures cannot inhibit Teff cells. The molecular mechanism of suppression and possible cell surface markers involved in this function are not known and part of our research.

As mice develop autoimmune diseases in the absence of Treg it has been hypothesized that Treg might be missing or functionally impaired in human autoimmune disease. In collaboration with the Clinic of Neurology, University of Heidelberg we are analyzing the function of Treg in patients with Multiple Sclerosis. While we and others have not seen a difference in the number of $CD25^{hi}$ Treg in MS patients, the *in vitro* proliferation assay indicates a reduced suppressive capacity of Treg obtained from the blood of MS patients compared to healthy individuals. In evaluating this defect we are analyzing the factors that induce survival and death of Treg.

As the treatment of cancer is one of the main problems in medicine there is a tremendous effort to boost the function of the immune system to attack the tumour. Seminal studies in mice showed that many tumors could be rejected by the immune system in the absence of Treg. Furthermore, recent work in patients indicates that Treg reside in the tumour and that $CD25^+$ cells are increased in the blood of cancer patients. It might thus be that one strategy of the tumour to evade the immune system is to activate Treg which then suppress the immune response to the cancer. Therefore a joined project between the Division of Immungenetics and the Clinic for Dermatology, University of Heidelberg, analyzes Treg in tumour-bearing mice and melanoma patients and determines their impact on immunizations with tumour-specific antigens.