7. Summary

Regulatory T cells are a central element for the control of the peripheral immunological self-tolerance in mammals. Based on their special characteristics they are able to control numerous immune reactions. By the interplay with other cells of the immune system like e.g. dendritic cells (DC) and natural killer T cells (NKT) they are able to specifically regulate CD4+ T cells, CD8+ T cells and B cells. CD25+ natural regulatory T cells (Treg) emerge in the thymus and seem to take a leading role in this process.

With this analysis it was shown that Treg cells represent a heterogeneous cell population contrary to past studies. Based on the expression of the chemokinereceptor CCR6, a new subpopulation can be defined as effector/memory-like Treg (T_{REM}). This Treg subpopulation shows characteristic effector/memory phenotype as well as further typical traits, that distinguishes it from CCR6 negative Treg, which show a predominantly naive phenotype. T_{REM} develop after antigen contact, most likely in the presence of additional factors from CCR6 negative Treg and seem to take an important role in the control of peripheral inflammations directly within inflamed tissues. Here they seem to be the direct counterparts of conventional effector/memory cells (T_{EM}). In addition to the typical memory phenotype, this population also differs functionally from CCR6 negative Treg. In contrast to CCR6- CD25+ T cells, T_{REM} express, after repeated antigen contact, high quantities of IL10 and are able to induce IDO (indoleamine 2,3-dioxygenase) expression of CD11c+ DC after co-cultivation with these cells.

An analogous population to the mouse CCR6+ T_{REM} can also be found in humans. Human effector/memory-like Treg can be defined additionally by a high expression of CLA (cutaneous lymphocyte antigen) and a low alpha4 Integrin (CD49d) expression. They show the highest Foxp3 protein expression of $CD25^{high}$ regulatory CD4+ T cells and therefore seem to be the most effective Treg population in humans. The differential adhesionmolecule expression enables a selective control of the Treg or effector T cell (Teff) recruitment to the inflamed tissue and seems to be therefore a decisive factor for the control of the balance between Treg and Teff.

Also in the Thymus, CCR6 can be found on CD25+ expressing T cells. The chemokinereceptor expression however seems to be transient in contrast to the peripheral CCR6 expression and marks a special step during the maturation of Treg precurser cells.

CCR6+ thymocytes still express intermediate levels of CD8 and they show an activated, premature phenotype, although they express high quantities of Foxp3 and are fully functional. Interestingly, a higher amount of CCR6 + Treg in the Thymus can be detected with increasing age. CCR6+ CD25+ thymocytes appear therefore to represent an initial stage of Treg precursers, that stands most likely in connection with a special selection mechanism of these cells in the thymus.