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### Protective genes as T-cell antigens

Protective proteins are expressed in the late phase of inflammatory reactions and contribute in a critical manner to inhibit or terminate inflammation. In the present study we analyzed if protective proteins serve as targets for T-cells in cancer patients.

The deficiency or altered function of regulatory T cells (Tregs) is associated with autoimmunity. In the context of malignancies accumulation of Tregs occurs in the tumor microenvironment and has been associated with prevention of antitumor immunity and anti-cancer immunotherapy. While CD4<sup>+</sup> Tregs have received much attention over the past years, less is known about CD8<sup>+</sup> Tregs; moreover, antigens recognized by these cells remain unknown. In the present study we describe the first natural target for CD8<sup>+</sup> Tregs. HO-1 specific CD8<sup>+</sup> T cells were detected *ex vivo* and *in situ* among T cells from cancer patients. Directly isolated from cancer patient PBL these HO-1 specific T cells were able to inhibit cytokine release, proliferation and cytotoxicity of other immune cells thereby supporting the anti-inflammatory function of HO-1. Hence, HO-1 specific Tregs seem to be immune suppressive per se. The first identification of antigen specific CD8<sup>+</sup> Tregs and especially the potency of these cells open new avenues for therapeutic interventions both in autoimmune diseases and cancer.

The enzyme indoleamine 2,3-dioxygenase (IDO) exerts an well established immunosuppressive function in cancer. IDO is expressed within the tumor itself as well as in antigen-presenting cells in tumor-draining lymph nodes, where it promotes the establishment of peripheral immune tolerance to tumor antigens. In the present study, we tested the notion whether IDO itself may be subject to immune responses. The study unveiled spontaneous cytotoxic T-cell reactivity against IDO in peripheral blood as well as in the tumor microenvironment of different cancer patients. We demonstrate that these IDO reactive T cells are indeed peptide specific, cytotoxic effector cells. Hence, IDO reactive T cells are able to recognize and kill tumor cells as well as IDO-expressing dendritic cells, i.e. one of the major immune suppressive cell populations. Consequently, IDO may serve as an important and widely applicable target for anti-cancer immunotherapeutic strategies. Furthermore, as emerging evidence suggests that IDO constitutes a significant counter-regulatory mechanism induced by pro-inflammatory signals, IDO-based immunotherapy holds the promise to boost anti-cancer immunotherapy in general.

In conclusion, although both HO-1 and IDO have an immunosuppressive function, IDO specific CD8 T cells apparently seem to be traditional cytotoxic effector cells, whereas HO-1 specific CD8 T cells seem to be Tregs, which exert immune suppression.