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Increased frequency of CTLA4+ TGFβ+ CD4+ CD25+ T cells in peripheral blood of patients with chronic lymphatic leukemia and multiple myeloma

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A globally suppressed T cell function has been described for cancer patients including patients with chronic lymphatic leukemia (CLL) or multiple myeloma (MM). This has been mainly associated with inhibitory factors released by the tumor cells, while the role of recently characterized regulatory immune cells is not understood. Several different regulatory T cells such as $CD4^+$ $CD25^+$ T cells (T_{reg}), TGFβ producing TH3 or IL-10 producing TR1 cells have been described in murine models, and T_{reg} cells have also been implicated in the control of graft versus host disease after allogeneic transplantation in humans. In contrast, little is known about frequencies and function of regulatory cells in leukemias and lymphomas. To address this issue we have analyzed 82 peripheral blood samples from 24 CLL patients, 18 MM patients and 26 healthy individuals. By assessing $CD4^+$ $CD25^+$ T cells we established a strongly significant increase of this subpopulation in both CLL (13 ± 7% mean ± SD, $p < 0.01$) and MM (13 ± 9%, $p < 0.01$) when compared to healthy individuals (3.5 ± 1.5%). While $CDC4^+$ $CD25^+$ T cells could also comprise previously activated T cells, the expression of CTLA4 has been associated with T_{reg} cells. In fact, 80± 14% respectively 67± 26% of $CD4^+$ $CD25^+$ T cells in CLL resp. MM were also $CTLA4^+$, while only 30 ± 22% were found to be positive in healthy individuals strongly suggesting that these cells are mainly T_{reg} cells. In contrast, using the BDCA-4 specific antibody for Neuropilin-1, we were unable to detect this molecule recently described on murine T_{reg} cells on any of our samples. Interestingly, a significant proportion of $CD4^+$ $CD25^+$ T cells in CLL 28 ± 13% and MM 22 ± 12% also expressed intracellular TGFβ, which was only found in 6 ± 4% of these T cells in healthy individuals. Whether TGFβ production reflects a particular activation status of T_{reg} cells or whether these cells are a defined subpopulation requires further investigation. By analyzing co-expression of CCR7 and CD45RA we established that the fraction of $CD4^+$ $CD25^+$ T cells was particularly increased in the naïve and the central memory pool in peripheral blood of CLL and MM patients. Next we assessed T cell activation as a function of T_{reg} cells. As expected, there was already a significantly decreased proliferative response of $CD4^+$ T cells in many CLL patients even when $CD25^+$ cells were depleted. These findings are most likely explained by chronic exposure to inhibitory cytokines as well as T_{reg} cells. However, even under these conditions, coculture experiments of $CD4^+$ $CD25^-$ and $CD4^+$ $CD25^+$ T_{reg} cells supported the inhibitory role of T_{reg} cells in CLL. We therefore propose that immunotherapy in any malignancy including CLL and MM characterized by an increase of regulatory factors and cells will significantly benefit from strategies inhibiting immune repression.