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Regulation of p53 tumor specific immune responses in colorectal cancer patients

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Anti-tumor specific immune responses are modulated during tumor development via different escape mechanisms abrogating the process of effective immunological tumor destruction. In this study we analyzed the p53 specific immune response in colorectal cancer patients (n = 24) depending on their UICC stage and characterized their regulatory T cell functions independent of the p53 mutational status.

Peripheral blood lymphocytes (PBMCs) from patients (UICC-stage I-IV) were stimulated with 10 pools of synthetic overlapping p53 peptides encompassing the full length wild-type (wt) p53 sequence and Il-10 and IFN-γ expression was assessed (ELISA and ELISPOT). PBMCs and tumor specific cells as well as tumor specimens of those patients were further characterized (cytospins, immunofluorescence/histology) and the expression of the following gene classes were analyzed: CD4, CD25, Foxp3, GITR, and GATA-3. After stimulation of the lymphocytes with the peptide pools distinct residues were found that induced a Th2 (IL-10, n = 24) or Th1 (IFN-γ, n = 10) type response. T cells from patients in UICC III (n = 7) and IV (n = 7) expressed higher IL-10 levels in response to p53 peptide (residues 291–330) than patients in UICC I and II (n = 6) (26 and 62 spots/10^5 cells versus 14 spots/10^5 cells, respectively), indicating that the UICC stage may play a crucial role in IL-10 production in response to p53 peptides. In contrast, other p53 peptides (residues 331–370) led to IFN-γ production but no correlation was observed between the UICC stage and the Th1 response. Markedly elevated amounts of CD4+ CD25+ cells in the PBMCs, as well as intensified staining for p53 (clone DO-7) within the tumor were observed in patients expressing higher levels of IL-10. Comparison of all tumor tissues using hierarchical clustering analysis showed a Th2 gene pattern. Dissimilarity between the tissues was due to differences in the tumor stage. Within the whole p53 protein sequence comparably more determinants inducing a Th2 type immune response were observed suggesting that the type of the tumor specific immune response to p53 depends on presentation and recognition of specific wt p53 residues. Furthermore, the level of IL-10 production seems to overweigh the IFN-γ production indicating that specific p53 epitopes may directly influence the outcome of immunological surveillance in colorectal cancer patients. This study offers new insights in a possible mechanism facilitating the tumor to escape immune surveillance by inducing rather a Th2 type (tolerance) than Th1 type response (destruction) through p53 overexpression.