

Functional control of regulatory T cells by TLR signaling

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Many groups have tried to develop a vaccine for the treatment of cancer, but the data from 10 years of clinical trials suggest that cancer-specific immune responses can be induced, but such responses are too weak and transient to eradicate tumor cells. The answer may lie in a group of cells called CD4+ regulatory T (Treg) cells. Regulatory T cells form a vital arm of the immune system, which is responsible for controlling rogue immune responses and autoimmunity. However, we recently reported the existence of tumor-specific Treg cells at tumor sites (1, 2). Thus, the tumor cells use these Treg cells to suppress desired antitumor immune responses and to protect themselves from immune attack. More importantly, we found that the majority tumor samples obtained from many types of cancer, including breast and prostate cancer, harbored increased proportions of Treg cells. To overcome immune suppression mediated by Treg cells, we recently identified a set of ligands (a special stretch of guanosine-containing oligonucleotides) that can bind specifically to human Toll-like receptor 8 (TLR8) and then turn off the suppressive function of Treg cells (3). Treatment of Treg cells with TLR8 ligands reverse the suppressive activity of these cells in culture as well as in a mouse tumor model, thus enhancing antitumor immunity. These results link TLR signaling to the functional control of Treg cells. By shifting the functional balance between Treg and effector T cells through TLR8 signaling, it is conceivable that polyG oligonucleotides or similar ligands might be utilized in clinical settings to enhance the efficacy of immunotherapy directed to cancer and infectious diseases.

References

1. Wang HY, Lee DA, Peng G, Guo Z, Li Y, Kiniwa Y, Shevach EM, Wang RF. Tumor-specific human CD4+ regulatory T cells and their ligands: implication for immunotherapy. *Immunity* 2004; **20**: 107-18. (PMID: 14738769)
2. Wang HY, Peng G, Guo Z, Shevach EM, Wang RF. Recognition of a new ARTC1 peptide ligand uniquely expressed in tumor cells by antigen-specific CD4+ regulatory T cells. *J Immunol* 2005; **174**: 2661-70. (PMID: 15728473)
3. Peng G, Guo Z, Kiniwa Y, Voo KS, Peng W, Fu T, Wang DY, Li Y, Wang HY, Wang RF. Toll-like receptor 8 mediated-reversal of CD4+ regulatory T cell function. *Science* 2005; **309**: 1380-4. (PMID: 16123302)

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