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Regulatory (FOXP3+) T cells as target for immune therapy of cervical intraepithelial neoplasia and cervical cancer.

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Abstract

Regulatory (FOXP3+) T cells (Tregs) comprise a subpopulation of CD4+ T cells that suppress autoreactive immune cells, thereby protecting organs and tissues from autoimmunity. Tregs have also been detected in human malignancies and their depletion or inactivation substantially improves cellular antitumor immunity in preclinical studies. Novel therapeutic strategies for cervical cancer and precancerous cervical intraepithelial neoplasia (CIN) focus on immune-modulatory and cancer vaccination approaches. In this context, the frequency of Tregs in cervical cancer and precancerous CIN could influence therapeutic strategies. We determined the frequency of infiltrating CD4+ and CD8+ T cells as well as FOXP3+ Tregs in high-grade CIN lesions (CIN III) and cervical carcinoma compared to colon carcinoma, skin melanoma, and bronchial carcinoma. We show that human papilloma virus-derived lesions have a significantly higher number of infiltrating lymphocytes and FOXP3+ Tregs compared to three other common tumor entities. In addition we explored the therapeutic effect of agonistic anti-glucocorticoid-induced tumor necrosis factor receptor family-related protein antibodies that, by single systemic application, inactivate Tregs and induce strong intratumoral invasion of CD8+ T cells and complete tumor eradication in 70% of treated animals. The large number of Tregs in human papilloma virus-derived lesions suggests a pivotal role of Tregs for counteracting the host immune response. We therefore regard CIN and cervical cancer as prime targets for new immune-based non-invasive therapies.

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