tumors (49,50). In fact, the presence of Tregs in a tumor (tumor-infiltrating Tregs) serves as a prognostic factor for the survival of the patient (51). Where the tumor mass is infiltrated with a great number of Tregs, this means that the patient has a poorer chance of survival.

Cyclophosphamide is a common oncology drug that inhibits Tregs (52). By inhibiting Tregs, this drug releases normal physiological braking mechanisms that set upper limits on the immune system, thereby enabling a more vigorous immune response against tumors. Fluorouracil may also inhibit Tregs (53). Moreover, an anti-GITR antibody targets Tregs and blocks the immunosuppressive activity of Tregs (54,55). GITR, which may be pronounced as *guitar*, stands for glucocorticoid-induced tumor necrosis factor receptor. Anti-GITR antibodies, such as MK-4166 and TRX518, are being tested for treating cancer (56). "MK" and "TRX" stand for the pharmaceutical companies that sponsor the antibodies, Merck, Inc. and Tolerx, Inc.

GITR, a membrane-bound protein on Tregs, transmits a signal to the Treg that blocks the immunosuppressive activity of the Treg. Therefore, when anti-GITR antibody is used as an anticancer drug, the antibody must be one that provokes GITR-mediated cell signaling. In other words, the antibody must be an activating antibody, and not an inhibitory antibody (Fig. 27.2).

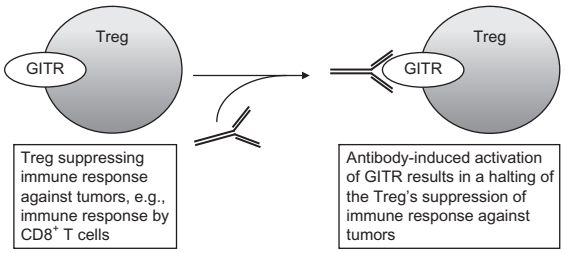

FIGURE 27.2 T-regulatory cell. Tregs have the useful effect of preventing indiscriminate inflammatory diseases in healthy people. However, Tregs can have the undesirable effect of preventing effective immune response in cancer, and in chronic infections such as hepatitis C virus infections. Drugs such as anti-GITR antibody may block the immune-suppressing effects of Tregs.

[49]Heier I, Hofgaard PO, Brandtzaeg P, Jahnsen FL, Karlsson M. Depletion of CD4 + CD25 + regulatory T cells inhibits local tumour growth in a mouse model of B cell lymphoma. Clin. Exp. Immunol. 2008;152:381–7.

[50]Kobayashi N, Hiraoka N, Yamagami W, et al. FOXP3 + regulatory T cells affect the development and progression of hepatocarcinogenesis. Clin. Cancer Res. 2007;13:902–11.

[51]Yakirevich E, Resnick MB. Regulatory T lymphocytes: pivotal components of the host antitumor response. J. Clin. Oncol. 2007;25:2506–8.

[52]Leao IC, Ganesan P, Armstrong TD, Jaffee EM. Effective depletion of regulatory T cells allows the recruitment of mesothelin-specific CD8 T cells to the antitumor immune response against a mesothelin-expressing mouse pancreatic adenocarcinoma. Clin. Transl. Sci. 2008;1:228–39.

[53]Vincent J, Mignot G, Chalmin F, et al. 5-Fluorouracil selectively kills tumor-associated myeloid-derived suppressor cells resulting in enhanced T cell-dependent antitumor immunity. Cancer Res. 2010;70:3052–61.

[54]Placke T, Kopp HG, Salih HR. Glucocorticoid-induced TNFR-related (GITR) protein and its ligand in antitumor immunity: functional role and therapeutic modulation. Clin. Dev. Immunol. 2010;2010:239083.

[55]Cohen AD, Schaer DA, Liu C, Li Y, et al. Agonist anti-GITR monoclonal antibody induces melanoma tumor immunity in mice by altering regulatory T cell stability and intra-tumor accumulation. PLoS One 2010;5:e10436.

[56]Berman D, et al. The development of immunomodulatory monoclonal antibodies as a new therapeutic modality for cancer: the Bristol-Myers Squibb experience. Pharmacol. Therap. 2015;148:132–53.