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Dietary folic acid is responsible for maintenance of colonic regulatory T cells

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Abstract

Dietary compounds as well as commensal microbiota contribute to the generation of a unique gut environment. We report that dietary folic acid (FA) is required for the maintenance of Foxp3⁺ regulatory T (Treg) cells in the colon. Deficiency of FA in the diet resulted in marked reduction of Foxp3⁺ Treg cells selectively in the colon. Blockade of folate receptor 4 and treatment with methotrexate, which inhibits folate metabolic pathways, decreased colonic Foxp3⁺ Treg cells. Compared with splenic Treg cells, colonic Treg cells were more activated to vigorously proliferate and highly sensitive to apoptosis. In colonic Treg cells derived from mice fed with a FA-deficient diet, expression of anti-apoptotic molecules, Bcl-2 and Bcl-xL, was severely decreased. A general reduction of peripheral Treg cells was induced by a neutralizing antibody against IL-2, but a further decrease by additional FA deficiency was observed exclusively in the colon. Mice fed with a FA-deficient diet exhibited higher susceptibility to intestinal inflammation. These findings reveal the previously unappreciated role of dietary FA for promoting survival of Foxp3⁺ Treg cells that are in a highly activated state in the colon.