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Depletion of Myeloid Cells Reduces Tumorigenesis Driven by a High-Protein Diet in a Colitis-Associated Cancer Model

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Abstract

Diet shapes the tumor microenvironment in colorectal cancer by modulating the reactivity of the immune system. We investigated the immunomodulatory properties of increased dietary protein intake in the early phase of tumorigenesis in a mouse model of colitis-associated cancer.

BALB/c mice were fed a synthetic control diet (CD) or a high-protein diet (HPD) and subsequently treated with azoxymethane and dextran sodium sulfate to induce colitis-associated cancer. The involvement of macrophages in tumorigenesis was examined by depleting them with clodronate-loaded liposomes. Immunophenotyping was performed by flow cytometry, and cytokine production in Peyer's patches (PPs) was measured by ELISA. Colonoscopic screening was performed to assess tumor characteristics.

HPD-fed mice developed more numerous and larger tumors and had a lower proportion of systemic CD8+ T cells. However, clodronate-mediated depletion of macrophages during early tumorigenesis significantly reduced tumor incidence and restored CD8+ T cells. In the spleens of clodronate-treated mice, a proinflammatory macrophage subpopulation was partially depleted, along with a significant reduction in neutrophils, while NK, NKT and DC cells increased. In addition, HPD-fed mice had elevated proinflammatory TNFα, IL-17, IL-1β and S100A8 in PPs, with TNFα and IL-17 even higher in clodronate-untreated mice.

Our findings demonstrated that HPD contributes to intestinal inflammation and exacerbates tumor development driven either by macrophage or neutrophil stimulation.