TNFR1 signaling and IFN-gamma signaling determine whether T cells induce tumor dormancy or promote multistage carcinogenesis.

Abstract:

Immune responses may arrest tumor growth by inducing tumor dormancy. The mechanisms leading to either tumor dormancy or promotion of multistage carcinogenesis by adaptive immunity are poorly characterized. Analyzing T antigen (Tag)-induced multistage carcinogenesis in pancreatic islets, we show that Tag-specific CD4+ T cells home selectively into the tumor microenvironment around the islets, where they either arrest or promote transition of dysplastic islets into islet carcinomas. Through combined TNFR1 signaling and IFN-gamma signaling, Tag-specific CD4+ T cells induce antiangiogenic chemokines and prevent alpha(v)beta(3) integrin expression, tumor angiogenesis, tumor cell proliferation, and multistage carcinogenesis, without destroying Tag-expressing islet cells. In the absence of either TNFR1 signaling or IFN-gamma signaling, the same T cells paradoxically promote angiogenesis and multistage carcinogenesis. Thus, tumor-specific T cells can directly survey multistage carcinogenesis through cytokine signaling.