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A critical role for regulatory T cells in driving cytokine profiles of Th17 cells and their modulation of glioma microenvironment.

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Abstract

IL-17A, produced by Th17 cells, may play a dual role in antitumor immunity. Using the GL261-glioma model, we investigated the effects of Th17 cells on tumor growth and microenvironment. Th17 cells infiltrate mouse gliomas, increase significantly in a time-dependent manner similarly to Treg and do not express Foxp3. To characterize the direct effects of Th17 cells on GL261 murine gliomas and on tumor microenvironment, we isolated IL-17-producing cells enriched from splenocytes derived from naïve (nTh17) or glioma-bearing mice (gTh17) and pre-stimulated in vitro with or without TGF- β . Spleen-derived Th17 cells co-expressing IL-17, IFN- γ and IL-10, but not Treg marker Foxp3, were co-injected intracranially with GL261 in immune-competent mice. Mice co-injected with GL261 and nTh17 survived significantly longer than gTh17 ($P < 0.006$) and gliomas expressed high level of IFN- γ and TNF- α , low levels of IL-10 and TGF- β . In vitro IL-17 per se did not exert effects on GL261 proliferation; in vivo gliomas grew equally well intracranially in IL-17 deficient and wild-type mice. We further analyzed relationship between Th17 cells and Treg. Treg were significantly higher in splenocytes from glioma-bearing than naïve mice ($P = 0.01$) and gTh17 produced more IL-10 than IFN- γ ($P = 0.002$). In vitro depletion of Treg using PC61 in splenocytes from glioma-bearing mice causes increased IL-17/IFN- γ cells ($P = 0.007$) and decreased IL-17/IL-10 cells ($P = 0.03$). These results suggest that Th17 polarization may be induced by Treg and that Th17 cells in gliomas modulate tumor growth depending on locally produced cytokines.

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