Molecular mechanisms of Fas ligand-induced inflammation.

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Fas ligand (FasL) has been well characterized as a death factor. However, recent studies revealed that ectopic expression of FasL induces inflammation associated with massive neutrophil infiltration. We previously demonstrated that the neutrophil infiltration-inducing activity of FasL is partly dependent on but partly independent of IL-1β. Therefore, we investigated the cytokine profile of peritoneal lavage fluid obtained from mice that received intraperitoneal injections of FFL, a FasL-expressing tumor cell line. We found that FFL injection caused a marked increase of not only IL-1β but also IL-6, IL-17, IL-18, KC/chemokine CXC ligand 1, and macrophage inflammatory protein (MIP)-2, but not of IL-1α, IFN-γ, TGF-β, or TNF-α. Among cells transfected to express individually IL-1β, IL-6, IL-17, or IL-18, only those expressing IL-1β and IL-17 induced neutrophil infiltration. Co-administration of the anti-IL-17 antibody with FFL diminished the peritoneal KC levels and neutrophil infiltration in IL-1-deficient mice. In addition, the expression of IL-17 by the tumor cells inhibited tumor growth in wild-type and nude mice. These results suggest that IL-17 is involved in FasL-induced inflammation and tumor rejection in the absence of IL-1β.

Then, we investigated the mechanism of the FasL-induced IL-17 production. We found that the culture supernatant of mouse resident peritoneal exudate cells (PEC) cocultured with FFL cells induced IL-17 production in freshly isolated resident PEC. Anti-IL-1β Ab strongly inhibited the IL-17-inducing activity. However, recombinant IL-1β by itself induced only weak IL-17 production. Intriguingly, anti-IL-12 Ab but not an IL-15 neutralizing agent, IL15R-Fc, strongly inhibited the FasL-induced IL-17-inducing activity. IL-23, which shares the p40 subunit with IL-12, but not IL-12 itself, induced IL-17 production synergistically with IL-1β in resident PEC. FasL induced the production of IL-23 in PEC *in vivo* and *in vitro*, and IL-17 production following the i.p. injection of FFL cells was severely impaired in p40-/- mice, indicating that IL-23 plays an important role in the FasL-induced IL-17 production. FFL also induced the production of IL-23 in bone marrow- or PEC-derived dendritic cells. Finally, FasL induced only weak p40 production in a mixture of p40-/- and Fas-/- dendritic cells, indicating that FasL induces IL-23 production in dendritic cells mainly in a cell-autonomous manner.

1. Umemura, M., et al., Int. Immunol., 16:1099-108, 2004

2. Kidoya, H., et al., J. Immunol., 175:8024-31, 2005