TNF-RIPK3 axis is crucial for the Kupffer cell reduction associated with tumoral progression following partial hepatectomy

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Introduction: Partial hepatectomy (PH) is the best treatment for hepatocellular carcinoma since the liver shows the unique ability to regenerate. However, a significant amount of patients undergoes recursion of the disease. Liver resident macrophages (Kupffer cells) drive the early response to liver partial ablation by producing tumor necrosis factor (TNF) and IL-6 that in turn stimulate hepatocyte proliferation. Studies in other liver disease model have also pointed some monocyte-derived cells as potent remodelers of the liver. It is thus likely that tumoral cells would use this TNF and IL-6 signaling to favor their own proliferation. Of note, TNF is also a potent cell-death inducer. Its signaling can lead to the formation of a protein complex containing RIPK3, which induces necroptosis.

Materials and Methods: C57BL/6, RIPK3KO and TNFM-KO innate immune cells were analyzed by flow cytometry following PH in both Hepa1.6 hepatocellular carcinoma injected liver and non-tumor bearing context. An in-vivo follow-up of the tumor progression was also performed using bioluminescence imaging.

Results: We showed that PH induces a TNF-RIPK3 dependent reduction of the number of KC shortly after surgery. This reduction was concomitant with an important Ly6Clowmonocyte increase in the organ. The same drop was observed in wild-type tumor bearing animals following surgery as well as a long-term increase of Ly6Clowmonocytes. Bioluminescence imaging reported that while non-resected wild-type animals were able to control and reject Hepa1.6 cells, resected liver had an increased tumoral proliferation. Both RIPK3KO and TNFM-KO mice restored tumor rejection following PH, suggesting a crucial role of KC in controlling tumor proliferation. Interestingly, while TNFM-KO mice bearing tumor didn't show any decrease in KC number, RIPK3KO mice bearing tumor had the same drop in KC number as the wild-type mice, but lacked long-term increase of Ly6Clowmonocytes suggesting a differential cell-death pathway activation in KC upon tumor encounter and a possible pro-tumoral role of Ly6Clowmonocytes in this model.

Conclusions: Taken together, these data suggest an important role of the TNF-RIPK3 dependent cell death in the observed tumoral progression following PH.

Keywords : Macrophages, Liver regeneration, Necroptosis, Partial hepatectomy
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