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Tumor Markers and Signatures

Myeloid tumor necrosis factor and heme oxygenase-1 regulate the progression of colorectal liver metastases during hepatic ischemia-reperfusion

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Abstract

The liver ischemia-reperfusion (IR) injury that occurs consequently to hepatic resection performed in patients with metastases can lead to tumor relapse for not fully understood reasons. We assessed the effects of liver IR on tumor growth

and the innate immune response in a mouse model of colorectal (CR) liver metastasis. Mice subjected to liver ischemia 2 days after intrasplenic injection of CR carcinoma cells displayed a higher metastatic load in the liver, correlating with Kupffer cells (KC) death through the activation of receptor-interating protein 3 kinase (RIPK3) and caspase-1 and a recruitment of monocytes. Interestingly, the immunoregulatory mediators, tumor necrosis factor-α (TNF-α) and heme oxygenase-1 (HO-1) were strongly upregulated in recruited monocytes and were also expressed in the surviving KC following IR. Using $TNF^{flox/flox}$ $LysM^{cre/wt}$ mice, we showed that TNF deficiency in macrophages and monocytes favors tumor progression after IR. The antitumor effect of myeloid cell-derived TNF involved direct tumor cell apoptosis and a reduced expression of immunosuppressive molecules such as transforming growth factor-β, interleukin (IL)-10, inducible nitric oxyde synthase (iNOS), IL-33 and HO-1. Conversely, a monocyte/macrophage-specific deficiency in HO-1 ($HO\text{-}1^{flox/flox}$ $LysM^{cre/wt}$) or the blockade of HO-1 function led to the control of tumor progression post-liver IR. Importantly, host cell RIPK3 deficiency maintains the KC number upon IR, inhibits the IR-induced innate cell recruitment, increases the TNF level, decreases the HO-1 level and suppresses the tumor outgrowth. In conclusion, tumor recurrence in host undergoing liver IR is associated with the death of antitumoral KC and the recruitment of monocytes endowed with immunosuppressive properties. In both of which HO-1 inhibition would reinforce their antitumoral activity.

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DATA AVAILABILITY STATEMENT

The data that support the findings of our study are available from the corresponding author upon reasonable request.

Supporting Information

Filename	Description
ijc33334-sup-0001-Supinfo.pdf PDF document, 1.2 MB	**APPENDIX S1:** Supplementary Information **TABLE S1**: Fluorochrome-conjugated antibodies for Flow cytometry. **TABLE S2**: The sequences of primers and probes. **FIGURE S1**: Features of liver IR injury in MC-38 inoculated mice. **FIGURE S2**: Liver IR-induces MC-32A outgrowth. **FIGURE S3**: Neutrophils are recruited upon IR. **FIGURE S4**: Proportion of TNF and HO-1 producing monocytes and KC upon IR **FIGURE S5**: TNF-α induces MC-38 apoptosis

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