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The ABC of Adaptive Immunity in Liver Cancer

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Although from a clinical perspective the role of the adaptive immune system seems to be clear and straightforward in hepatocellular carcinoma (HCC) and activation of adaptive immune effector cells has become a therapeutic option, animal studies using different tumor models speak a different language. A very recent study from the Karin lab looked at adaptive immunity in the context of nonalcoholic steatohepatitis (NASH) and HCC.⁽¹⁾ Using different murine NASH models, the authors observed an accumulation of immunoglobulin A–positive (IgA⁺) as well as cluster of differentiation 8–positive (CD8⁺) T cells in the liver. Similar results were obtained when serum samples from patients with NASH were tested for IgA concentration and CD8⁺ T cells were analyzed in liver samples. While the exact mechanism of how fatty liver disease causes an accumulation of IgA⁺ cells in the liver of mice with NASH and HCC has not been described yet, the authors focus their studies on the effector mechanisms of these cells in the context of NASH and HCC. IgA-ablated mice (as well as other B cell–deficient mice) showed reduced tumor burden and HCC growth. In contrast, CD8 depletion restored HCC growth in IgA-deficient mice. IgA⁺ cells found in the livers of tumor-bearing mice with NASH expressed high levels of interleukin-10 (IL-10) and programmed death ligand 1 (PD-L1). Functional *in vitro* and *in vivo* studies showed that IgA⁺ cells suppressed activation, proliferation, and cytotoxic function of CD8⁺ T cells, which was dependent on PD-L1 expression and IgA specific for tumor antigens. Based on these results, the authors studied the effect of PDL1 blockade on already established tumors in 7-month-old mice. Anti-PD-L1 treatment decreased liver IgA⁺IL10⁺ cells, increased CD8⁺ T-cell tumor infiltration, and reduced tumor growth. In contrast, PD-L1 blockade had no effect on tumor growth in tumor-bearing IgA^{−/−} or Cd8^{−/−} mice. In summary, the authors provide very compelling evidence that IgA⁺PD-L1⁺IL-10⁺ cells are associated with liver fibrosis and NASH and impair CD8 effector function, ultimately leading to accelerated growth of HCC. Anti-PD-L1 therapy successfully eliminates IgA⁺ cells, thereby improving CD8⁺ T-cell function, leading to impaired tumor growth.

This is the second paper coming from the Karin lab describing an immunosuppressive function of IgA⁺ cells. In an earlier study, Shalapour et al. showed that IgA-expressing plasma cells, which infiltrate human therapy-resistant prostate cancer, prevent cytotoxic T lymphocyte–dependent eradication of oxaliplatin-treated tumors.⁽²⁾ So what are these IgA-producing cells? In the context of prostate cancer, these cells have been described as CD19⁺B220^{low}CD138⁺PD-L1⁺IL10⁺ plasma cells, of which between 40% and 80% express IgA. It is not clear if these are exactly the same type of cells as those found in the liver of

mice with NASH, which are described as IgA⁺B220^{neg}CD138⁺ cells and can be further divided into major histocompatibility complex II^{hi} plasmablasts and major histocompatibility complex II^{low} plasma cells. Further studies on this cell population are clearly needed, and it will be important to better understand how these cells are induced. Also, it is not clear how they actually suppress CD8 T-cell function, what role IgA has in this setting, and if it really has to bind to a tumor-associated antigen.

For many years it has been difficult to understand how chronic inflammation can induce tumor development on one side, whereas current immune-based treatment approaches using immune checkpoint inhibitors aim to enhance antitumor immune responses. As a matter of fact, there are three very interesting publications demonstrating that adaptive immune responses can actually promote HCC tumor development.

A paper by Faggioli and colleagues has recently been published in HEPATOLOGY looking at the role of B cells in inflammation and HCC.⁽³⁾ The authors used an α Mdr2^{-/-} mouse, a model of inflammation-associated cancer, and B cell-deficient μ Mt-Mdr2^{-/-} mice. The authors describe that B-cell ablation reduced tumor formation. In addition, the authors report results from the analysis of human tumor samples. They demonstrate that the presence of infiltrating B cells correlated with increased tumor aggressiveness and reduced disease-free survival in human HCC.

A second paper reported on NASH and HCC. Unlike in the model used by Shalapour et al., CD8⁺ T cells actually promoted liver damage, NASH, and HCC in a mouse model using a choline-deficient, high-fat diet.⁽⁴⁾ Here, the authors suggest that efficient reduction in the number of hepatic CD8⁺ T and/or natural killer T cells will minimize the risk of HCC development in NASH-dependent HCC. It is not entirely clear why CD8⁺ T cells show opposite functions in two different NASH/HCC models, but this may be explained by the different animal models used in the two labs.

Another study suggesting a potentially negative effect of adaptive immune responses in the context of HCC comes from Pikarsky's group. They studied ectopic lymphoid structures (ELSs). ELSs often develop at sites of chronic inflammation and are characterized by aggregates of T and B cells, often showing T/B segregation. Although ELSs signify good prognosis in certain malignancies, in HCC they indicated poor prognosis.⁽⁵⁾ Interestingly, ablation of ELSs attenuated liver tumorigenesis in murine HCC models.

In contrast, we recently described that CD4⁺ T cells are depleted in NASH liver, leading to accelerated tumor growth.⁽⁶⁾ Linoleic acid, which was found to accumulate in mice with fatty liver disease, led to increased reactive oxygen species production in CD4⁺ T cells causing CD4⁺ T-cell death and, as a consequence, more tumors in mice. Reactive oxygen species blockade rescued CD4⁺ T cells in the liver and impaired tumor growth, indicating a tumor protective effect of the adaptive immune response. Another example of the antitumor effect of adaptive immune responses comes from a study in mice with diethylnitrosamine-induced HCC. More or larger tumors were found in diethylnitrosamine-injected Rag1^{-/-} mice (which lack B and T cells) and B cell-deficient Igh6^{-/-} and major histocompatibility complex II^{-/-} mice.⁽⁷⁾

Apart from the interesting studies on the role of immunosurveillance and adaptive immune responses, the paper by Shalapour and colleagues also touches upon a different topic, namely the use of immune checkpoint inhibitors in HCC, which clinically may be even more relevant. Most clinical investigators evaluate the efficacy of anti-PD1 antibodies in HCC, and it is not clear if anti-PD-L1 and anti-PD1 are very different in terms of efficacy. As a matter of fact, PD-L1 not only is found on IgA⁺ cells but also has been shown to be expressed on tumor cells in HCC tissue as well as antigen-presenting cells including CD45⁺BDCA1⁺CD19⁻ myeloid dendritic cells, CD45⁺CD14⁺ monocytes, and CD45⁺CD19⁺ B cells. Interestingly PD-L1 expression has even been shown to be higher in tumor-infiltrating antigen-presenting cells compared to antigen-presenting cells derived from nontumor tissue.⁽⁸⁾ *Ex vivo* studies using lymphocytes isolated from human HCC samples have shown that anti-PD-L1 treatment can activate the proliferation and interferon- γ secretion of CD4⁺ and CD8⁺ tumor-infiltrating lymphocytes,⁽⁸⁾ and it is not clear whether this mechanism was dependent on the presence of IgA⁺ cells because all B cells expressed PD-L1.

In summary, the study by Shalapour et al. describes a novel concept of how IgA⁺ cells impact adaptive immune responses and CD8⁺ T-cell function. Results from this study are different from those of earlier studies. Some of the discordant results may be explained by the fact that adaptive immune responses may play a different role during the induction of liver damage, maintaining liver damage, tumor initiation, promotion, and metastasis formation. Obviously not all mouse models are ideal to address all of these questions at the same time, and the data published clearly support the notion that murine models need to be recognized as a tool to study the biology of liver cancer but can never reflect the entire spectrum seen in patients.

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