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Shall we blame CD4 T cells for everything?

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Persistent inflammatory conditions in the liver promote chronic liver damage and liver fibrosis ultimately leading to hepatocellular carcinoma (HCC). Multiple cytokines have been investigated in the context of acute and chronic liver damage. Interleukin 17 (IL-17) is a proinflammatory cytokine produced by a subset of CD4 T cells (T helper 17 (Th17) cells). IL-17 recruits other immune cells such as monocytes and neutrophils to the site of inflammation in response to invasion by pathogens. It can promote inflammation and has been linked to various auto-immune disorders.¹ In the liver, Th17 responses have been shown in non-alcoholic steatohepatitis, cholestatic liver diseases, liver fibrosis and antimicrobial defences.² In this issue, Nadine Kuttkat from the Trautwein group investigated Th17 cells in a murine model of liver injury and HCC development.³ Following a previous report on the role of nuclear factor-kappa B (NF- κ B) signalling events in hepatocytes using liver parenchymal cell-specific Nemo knockout (Nemo^{LPC-KO} or Nemo^{Hep}) mice that develop steatohepatitis followed by HCC,⁴ the investigators now crossed these mice with CD2-cyclic AMP-responsive element modulator α isoform (CREM α) transgenic mice. CD2-CREM α mice express the CREM- α in T cells, which are characterised by decreased IL-2 production and T cell proliferation as well as an unexpected production of IL-17 and the TH17 lineage transcription factor ROR γ t. Of note, no change in CD4⁺CD25⁺Foxp3⁺ regulatory T cells (Tregs) has been described in CD2-CREM α mice.⁵

Based on prior studies in CD2-CREM α and Nemo^{Hep} mice, the authors expected that inflammation in the liver would be more severe, and mice would develop more rapidly liver damage ultimately resulting in pronounced tumour growth. However, the opposite was seen. Eight-week-old Nemo^{Hep}/CD2-CREM α mice showed less extensive liver damage than Nemo^{Hep} mice. Immune profiling of Nemo^{Hep}/CD2-CREM α mice demonstrated fewer CD11b⁺, CD8⁺ T and natural killer T cells as well as monocytes and granulocytes. In addition, Nemo^{Hep} mice showed more profound signs of hepatic fibrogenesis than Nemo^{Hep}/CD2-CREM α mice. And finally, 1-year-old Nemo^{Hep}/CD2-CREM α mice showed fewer and smaller HCC than Nemo^{Hep} mice. The authors conducted a number of in vitro as well as in vivo transfer experiments to study the underlying mechanisms. An increased number of hepatic Foxp3⁺ regulatory T helper cells were found in Nemo^{Hep}/

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CD2-CREMa mice and fewer Th17 cells compared with Nemo^{Hep} mice. Induction of a Foxp3⁺ regulatory T helper subset was probably caused by activated hepatic stellate cells in the liver producing retinoic acid (figure 1). It is known that retinoic acid can shift the T helper subset from a Th17 type to Tregs. We have previously made a similar observation studying the effect of different myeloid cell subsets on CD4 T cells.⁶ More in-depth analysis of CD4 T cells from Nemo^{Hep}/CD2-CREMa mice lead to some very interesting, but also very provocative findings: CD4 T cells augmented the transformation potential of a murine HCC cell in vitro and led to molecular changes in murine HCC responsible for tumour progression. How can (regulatory) T cells do this? Tregs are a subpopulation of T cells that maintain tolerance to self-antigens and prevent autoimmune diseases.⁷ They have been shown to impair effector T cell function with the help of IL-10 and transforming growth factor β . Depletion of Tregs or genetic knock-down has been shown to cause severe autoimmune diseases and in the context of cancer, Tregs suppress anti-tumour immunity. In line with this observation, patients with HCC have increased numbers of Tregs, which correlate with worse outcome.⁸⁹

Thus, while it is easy to understand that more Tregs in Nemo^{Hep}/CD2-CREMa mice can ameliorate hepatitis and chronic liver damage, leading to tumour development, it is an unexpected finding to see that they may also have direct effects on hepatocytes and/or tumour cells? Is this a direct cytokine-dependent effect or are other cells involved? Our own group has recently shown that CD4⁺ T are eliminated in the context of fatty liver disease leading to enhanced tumour development.¹⁰ While we did not observe specific changes in Tregs, Th17 cells were actually increased in mice with fatty liver disease. In conclusion, it seems that CD4 T cells can play good or bad role in the liver. One may blame them for many different phenotypes, but one thing is certainly true: More interesting studies on CD4 T cells in chronic inflammation, liver inflammation and liver cancer shall be expected. Stay tuned!

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Figure 1.

HSCs block the induction of Th17 cells from CREM- α transgenic T cells and induce CD4⁺ Tregs, which block inflammation, fibrosis and cancer development. CREM- α , cyclic AMP-responsive element modulator α isoform; HSC, hepatic stellate cell; RA, retinoid acid; Th17 cell, T helper 17; Treg, regulatory T cells.