Loss of CD4⁺ T cells in HCC

Derangements in lipid metabolism in NAFLD promote the loss of hepatic CD4⁺ T cells, driving development of hepatocellular carcinoma (HCC), according to a new study published in *Nature*.

NAFLD is a leading cause of HCC in developed nations. HCC is considered an inflammation-associated cancer, yet the role of the adaptive immune system in hepatocarcinogenesis has not been explored in detail. To investigate the effect of NAFLD on adaptive T-cell-mediated immune responses and the development of HCC, the researchers used mouse models of the disease. Mice with liver-specific overexpression of the *Myc* oncogene (MYC-ON mice) developed more hepatic tumours than mice lacking hepatic *Myc* overexpression (MYC-OFF mice), when both groups were fed a methionine-choline-deficient (MCD) diet to induce NAFLD.

By characterizing hepatic immune cell subtypes in MYC-ON mice using flow cytometry, the investigators showed that mice fed an MCD diet had fewer CD4⁺ T cells than mice fed a control diet. Reasoning that reduced CD4⁺ T-cell numbers might influence NAFLD-mediated HCC development, the researchers administered an anti-CD4 antibody to MYC-ON mice fed an MCD diet. Tumour development was accelerated in mice given the antibody, which depleted CD4⁺ T-cell numbers.

The investigators then questioned how NAFLD alters the numbers of CD4⁺ T cells. “We decided to use lipidomics to specifically focus on lipids and their effect on immune cells, since there is currently very little known about this topic despite the fact that obesity prevalence is increasing in the developed world,” explains author Tim Greten.

“...mice fed an MCD diet had fewer CD4⁺ T cells than mice fed a control diet”

Of the predominant hepatic free fatty acids in MYC-ON mice, only levels of linoleic acid were increased by MCD diet. Isolated mouse and human CD4⁺ T cells showed increased apoptosis, mediated by upregulated mitochondrial production of reactive oxygen species and superoxide, when cultured with linoleic but not palmitic acid. Finally, MYC-ON mice fed MCD and given the antioxidant *N*-acetylcysteine had markedly fewer microscopic tumours than untreated MCD-fed MYC-ON mice, an effect lost when *N*-acetylcysteine-treated mice were injected with anti-CD4 antibody.

In future work, Greten and colleagues plan to explore how linoleic acid induces mitochondrial dysfunction in CD4⁺ T cells, and study the effect of NAFLD on anti-tumour immunity in a therapeutic setting.

Hugh Thomas

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Laura Marshall/NPG