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IMMUNOTHERAPY

Burning fences

> the generation of IgA$^+$ plasmocytes requires PDL1 activity

While it is well established that activated immune cells can eradicate established tumours, the processes involved in immune surveillance and control of cancer development are less clear. A new study published in *Nature* now demonstrates that immunoglobulin A (IgA)-producing (IgA$^+$) cells, which accumulate in the livers of patients and mice with nonalcoholic steatohepatitis (NASH) and suppress activation of cytotoxic CD8$^+$ T cells, can be therapeutically targeted with anti-programmed cell death 1 ligand 1 (PDL1) therapy to reduce progression of NASH to hepatocellular carcinoma (HCC).

Using mouse models of NASH-driven HCC, Shalapour *et al.* investigated the functional link between increased circulating IgA levels in NASH patients and the interference of IgA$^+$ cells with cytotoxic CD8$^+$ T cell activation. Transgenic mice that express urokinase-type plasminogen activator (uPA) driven by a hepatocyte-specific promoter for major urinary protein (MUP) (*MUP-uPA* mice) develop NASH and fibrosis. When fed a high-fat diet (HFD), NASH-bearing *MUP-uPA* mice had increased circulating IgA levels and liver IgA$^+$ cell infiltration than those fed a normal-fat diet. These liver IgA$^+$ cells were mainly plasma cells or plasmablasts. Interestingly, most IgA$^+$ plasmocytes in the livers of *MUP-uPA* mice and patients with NASH expressed high levels of PDL1 and interleukin-10 (IL10).

The researchers generated *MUP-uPA* mice deficient for IgA (*MUP-uPA;Iga*$^{-/-}$), in which IgA$^+$PDL1$^+$IL10$^+$ plasmocytes were abolished but steatosis was unaffected. Similarly, steatosis in *MUP-uPA* mice deficient for CD8 (*MUP-uPA;CD8a*$^{-/-}$), in which CD8$^+$ T cells were abolished, was unaffected. When fed a HFD, NASH to HCC progression in *MUP-uPA* mice occured after 7 months. Importantly, *MUP-uPA;CD8a*$^{-/-}$ mice developed HCC earlier than *MUP-uPA* mice, whereas *MUP-uPA;Iga*$^{-/-}$ mice developed HCC with significant delay, with some being tumour-free even after 11 months of a HFD. When analysing CD8$^+$ T cell infiltration in livers of *MUP-uPA;Iga*$^{-/-}$ mice, the researchers found an increasing number of activated CD8$^+$ T cells over time. By contrast, the number of activated CD8$^+$ T cells in *MUP-uPA* mice decreased over time and was consistently lower than in *MUP-uPA;Iga*$^{-/-}$ mice, indicating that IgA$^+$ plasmocytes suppress activation of CD8$^+$ T cells. When treating HFD-fed, tumour-bearing *MUP-uPA* mice with a PDL1-blocking antibody, the tumour burden was significantly reduced after 8 weeks, lymphocyte accumulation in the tumour increased and steatosis decreased. The number of IgA$^+$PDL1$^+$IL10$^+$ plasmocytes in the livers of these mice was decreased, likely due to a disrupted maturation process. By contrast, neither *MUP-uPA;Iga*$^{-/-}$ mice nor *MUP-uPA;CD8a*$^{-/-}$ mice responded to PDL1 blockade with reduced tumour growth, indicating that the generation of IgA$^+$ plasmocytes requires PDL1 activity.

Collectively, this research highlights that effective liver immunosurveillance is disrupted during chronic inflammation when IgA$^+$ plasmocyte infiltration in the liver is increased. Moreover, these findings broaden the application range of anti-PDL1 therapy, which could potentially prevent HCC progression in patients with NASH by targeting immunosuppressive IgA$^+$ cells, thereby enhancing liver cytotoxic CD8$^+$ T cell activation.

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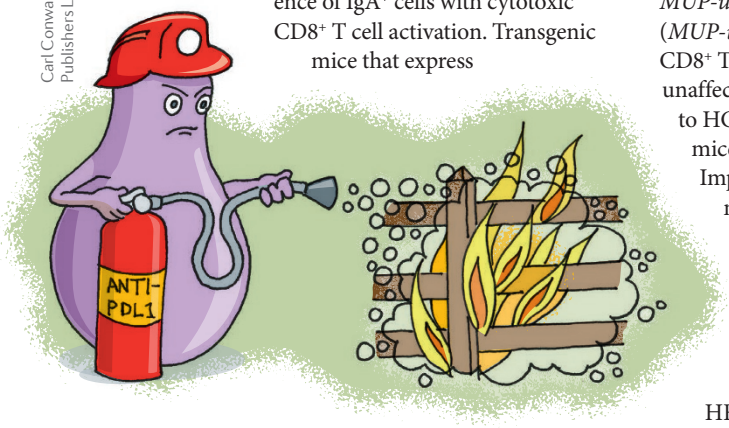

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ORIGINAL ARTICLE Shalapour, S. *et al.* Inflammation-induced IgA$^+$ cells dismantle anti-liver cancer immunity. *Nature* **551**, 340–345 (2017)