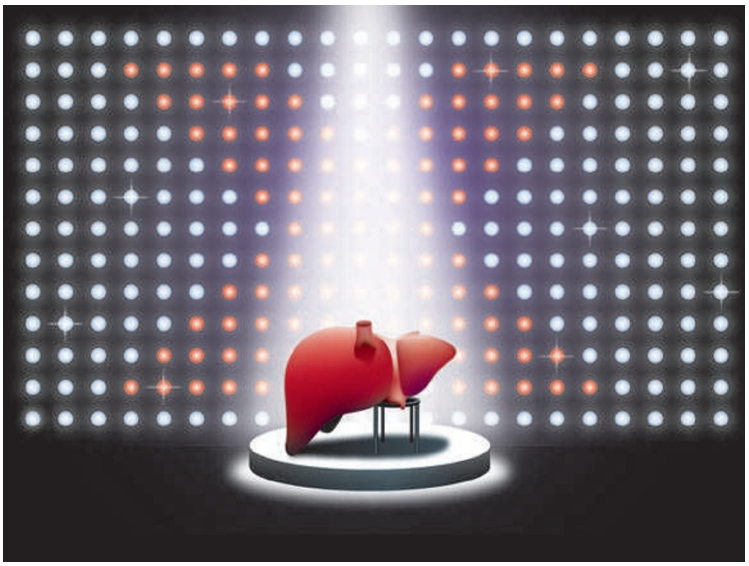
TUMOUR IMMUNOLOGY

Liver X factor helps tumours escape

The liver X receptors (LXRα and LXRβ) are transcription factors that are important for lipid and cholesterol homeostasis. Recent work has suggested that LXR signalling can also regulate innate and adaptive immune responses. Now, a study published in *Nature Medicine* shows that tumour cells can exploit LXRs to inhibit dendritic cell (DC) functions, enabling escape from immune detection.

The authors began their study by investigating the effects of tumour-derived factors on DC maturation. Immature monocyte-derived human DCs that were activated in the presence of conditioned medium from a tumour cell line showed normal upregulation of co-stimulatory and MHC class II molecules. However, treatment with tumour media inhibited DC expression of the lymphoid-homing receptor CC-chemokine receptor 7 (CCR7) and reduced their migratory responses to the CCR7 ligand CCL19. Previous studies suggested that agonism of certain nuclear receptors could inhibit DC chemokine receptor expression. Using a luciferase-based detection assay, the authors showed that media from the CCR7-inhibitory tumours, but not media from a non-inhibitory tumour cell line, induced activation of LXRα. DCs expressed transcripts for LXRs, and treatment of DCs with natural or synthetic LXR ligands prevented CCR7 upregulation. Furthermore, tumour-conditioned media was less efficient at preventing CCR7 upregulation following blockade of LXR signalling in DCs.

To assess whether the activation of LXRs can affect the ability of DCs to prime T cell responses, mice were injected with antigen-pulsed DCs that had been cultured in the presence of tumour media or LXR ligands. In keeping with a key role for CCR7 in promoting DC trafficking, LXR ligand-exposed DCs had an impaired ability to enter draining lymph nodes and prime antigen-specific T cells. Next, the authors investigated whether targeting of LXRs could promote anti-tumour immune responses *in vivo*. When LXR signalling was blocked in tumour-bearing mice, these animals showed less tumour growth and improved survival compared with controls. However, inhibiting LXRs had no effect on tumour growth in immuno-deficient mice, suggesting that the effects of LXR signalling depend on an intact immune system and are not due to direct effects on the tumour itself. By doing a series of experiments in which DCs were conditionally depleted from tumour-bearing mice, the authors showed that DCs inhibit tumour growth and seem to be a target of tumour-derived LXR ligands, as blocking LXR signalling did not inhibit tumorigenesis in DC-depleted animals.



Taken together, the data suggest that production of LXR ligands may be a strategy by which tumour cells can evade the immune system. Furthermore, these findings suggest that drugs interfering with sterol metabolism or LXR signalling could be a used as a cancer therapy.

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Nature Reviews Immunology

ORIGINAL RESEARCH PAPER Villablanca, E. J. *et al.* Tumor-mediated liver X receptor-α activation inhibits CC chemokine receptor-7 expression on dendritic cells and dampens antitumor responses. *Nature Med.* **16**, 98–105 (2010)