Lipids produced within the thymus give immune cells the initial boost they need to fight off infection

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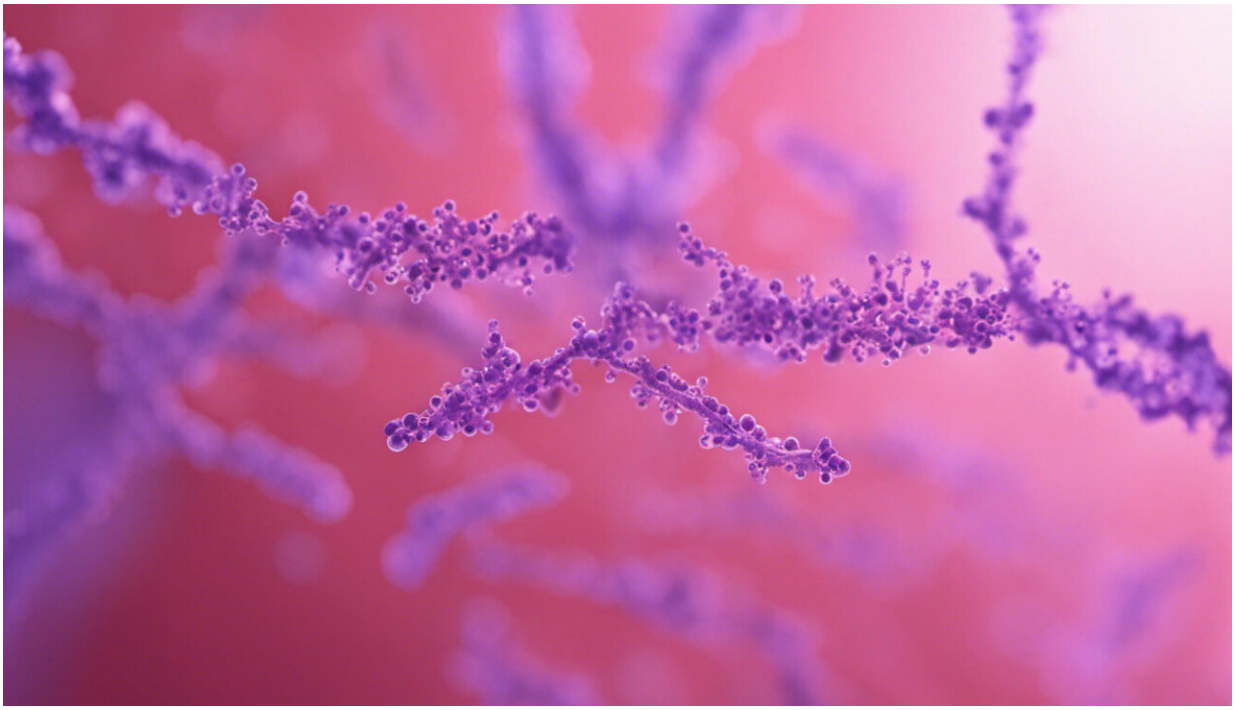

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Semi-invariant natural killer T (iNKT) cells wage war against infectious threats, attacking microbial cells and generating signals that enable other immune cells also to respond aggressively. iNKT cells initially undergo activation in the thymus; after being 'switched on' via interaction with

certain antigens, they undergo an initial population expansion and then migrate to peripheral immune sites where they proliferate further so they can mount an effective defense.

Some of these activating triggers are foreign in origin, such as bacterial membrane components. However, iNKT cells can also be activated by lipids produced within the thymus itself, as demonstrated in new research from a team led by Gennaro De Libero of the A*STAR Singapore Immunology Network. Previous research had indicated that such 'self' lipids might be an important stimulus. De Libero's team therefore began by treating cultured mouse iNKT cells with lipids isolated from thymic cells and looking for biological signatures of activation. "We found that unusual lipids are important for thymic selection, and that these lipids are produced within unique organelles called peroxisomes," he says.

A peroxisomal enzyme called glyceronephosphate O-acyltransferase (GNPAT) plays a central role in producing these particular lipids. Accordingly, the researchers observed that iNKT cell maturation tended to stall in mice lacking GNPAT, and these animals had considerably fewer functional iNKT cells than normal mice. Subsequent transplantation experiments demonstrated that immature iNKT cells from wild-type mice are less likely to reach full maturity when grafted into thymuses of GNPAT-deficient mice. Collectively, these experiments demonstrate that a substantial subset of developing iNKT cells is dependent on interactions with peroxisomally produced lipids in the thymus in order to undergo full activation.

Despite the team's revelation of insightful details about the development of these important immune cells, a number of mysteries remain—for example, how mature iNKTs learn to stop targeting the antigens that switched them on in the first place. "Now that we know the stimulatory self lipids, we can address the mechanisms which reduce iNKT

reactivity against them in the periphery," explains De Libero. This would provide a means to avoid autoimmune attacks.

In parallel, he and his colleagues intend to determine whether foreign lipids also trigger immune cell maturation via a similar mechanism. "For example, T cells that recognize mycobacterial lipids are important in protecting people from tuberculosis," he says, "and it will be important to study how these cells are selected and mature within the thymus."

More information: Facciotti, F., Ramanjaneyulu, G. S., Lepore, M., Sansano, S., Cavallari, M., et al. Peroxisome-derived lipids are self antigens that stimulate invariant natural killer T cells in the thymus. *Nature Immunology* 13, 474–480 (2012). www.nature.com/ni/journal/v13/n5/abs/ni.2245.html

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