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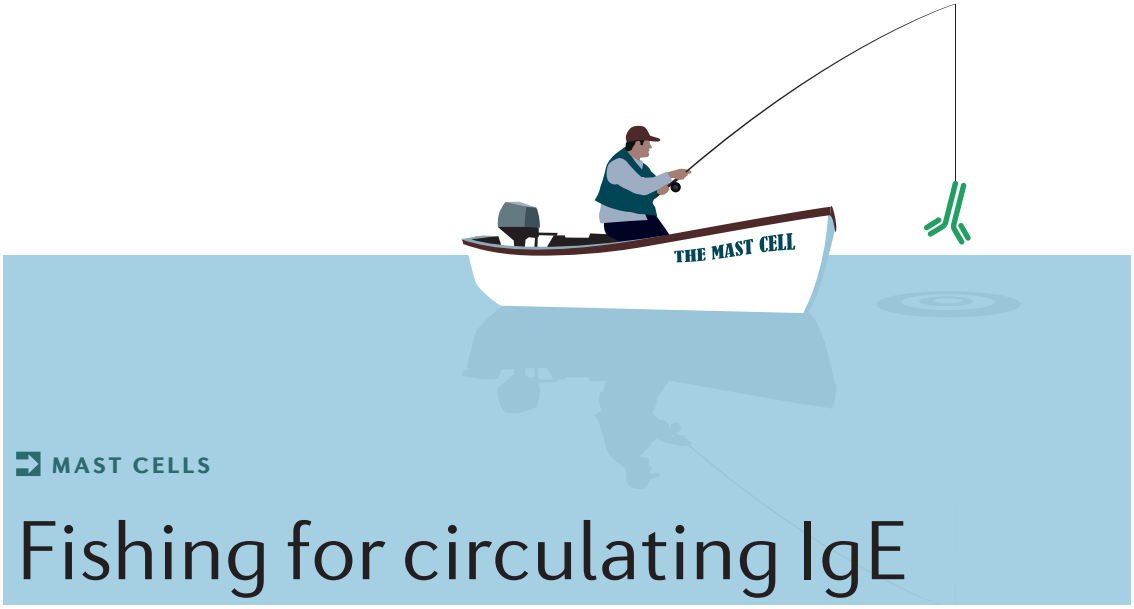

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MAST CELLS

Fishing for circulating IgE

Perivascular mast cells actively acquire IgE from blood vessels in a selective manner, according to new research published in *Immunity*. The demonstration that mast cells extend processes into the vascular lumen to 'fish' for IgE closes a gap in our understanding of the IgE–mast cell axis in allergic disease.

Mast cells capture monomeric IgE on their surface using the high-affinity Fc receptor for IgE (FcεRI); antigen-mediated crosslinking of FcεRI-bound IgE then leads to mast cell activation and the release of allergic mediators. However, IgE is produced by plasma cells in the bone marrow, spleen and lymph nodes, whereas mast cells mainly acquire IgE in the tissues. Thus, the blood is the primary reservoir for unbound IgE, but few data have addressed how tissue mast cells acquire free IgE from the blood.

This study showed that ear skin mast cells in mice have heterogeneous levels of surface-bound IgE (~50% of them have high levels), whereas peritoneal mast cells have uniform levels of IgE. In IgE-deficient mice infused intravenously with supraphysiological levels of IgE, only some of the ear skin mast cells had taken up IgE after 1 hour, whereas IgE was acquired by all of the mast cells in the peritoneum, which has a more permeable vasculature. This could not be accounted for by differences in FcεRI expression, which indicates that mast cell populations in the skin have differential access to vascular contents.

The authors constructed a reporter IgE molecule — consisting of red fluorescent protein fused to the Fc domain of IgE (RFP–Fcε) — that has similar binding and distribution properties to native IgE. Confocal microscopy of ear tissue mounts obtained 24 hours after intravenous infusion of RFP–Fcε into mast cell-reporter mice showed binding of RFP–Fcε to ~50% of mast cells in the ear skin, mainly in a perivascular location. The RFP^+ mast cell population was on average 35% closer to the nearest blood vessel than the total mast cell population.

The authors therefore hypothesized that perivascular mast cells in the skin have direct access to the blood. In line with this, 15–20% of ear skin mast cells could acquire a circulating antibody–fluorophore conjugate (2B8–PE) specific for the mast cell marker KIT, even though this conjugate remains intravascular owing to its high molecular weight. Peritoneal mast cells could not acquire intravenous 2B8–PE, which is consistent with a lack of direct access to the blood.

Intravital high-resolution confocal microscopy showed that some mast cells in ear skin have relatively stable projections into the blood vessel interior. These projections could extend towards and engulf IgE-coated intravascular beads. The perivascular mast cells favoured localization near smooth muscle actin $(SMA)^-$ capillaries and venules rather than SMA^+ arterioles, presumably as penetrating a blood vessel is easier in the absence of SMA. Indeed, after infusion with RFP–Fcε, RFP^+ mast cells were more often associated with SMA^- blood vessels than with SMA^+ blood vessels.

Together, the results indicate that a subset of perivascular mast cells in the skin but not the peritoneum can actively acquire IgE directly from the blood. Further knowledge of the mechanism, regulation and tissue specificity of this sampling process could lead to new therapeutic targets in allergic disease.

Kirsty Minton

> "some mast cells in ear skin have relatively stable projections into the blood vessel interior"

ORIGINAL RESEARCH PAPER Cheng, L. E. *et al.* Perivascular mast cells dynamically probe cutaneous blood vessels to capture immunoglobulin E. *Immunity* 3 Jan 2013 (doi:10.1016/j.immuni.2012.09.022)