Disease-causing IgE antibodies are regulated to avoid allergic responses

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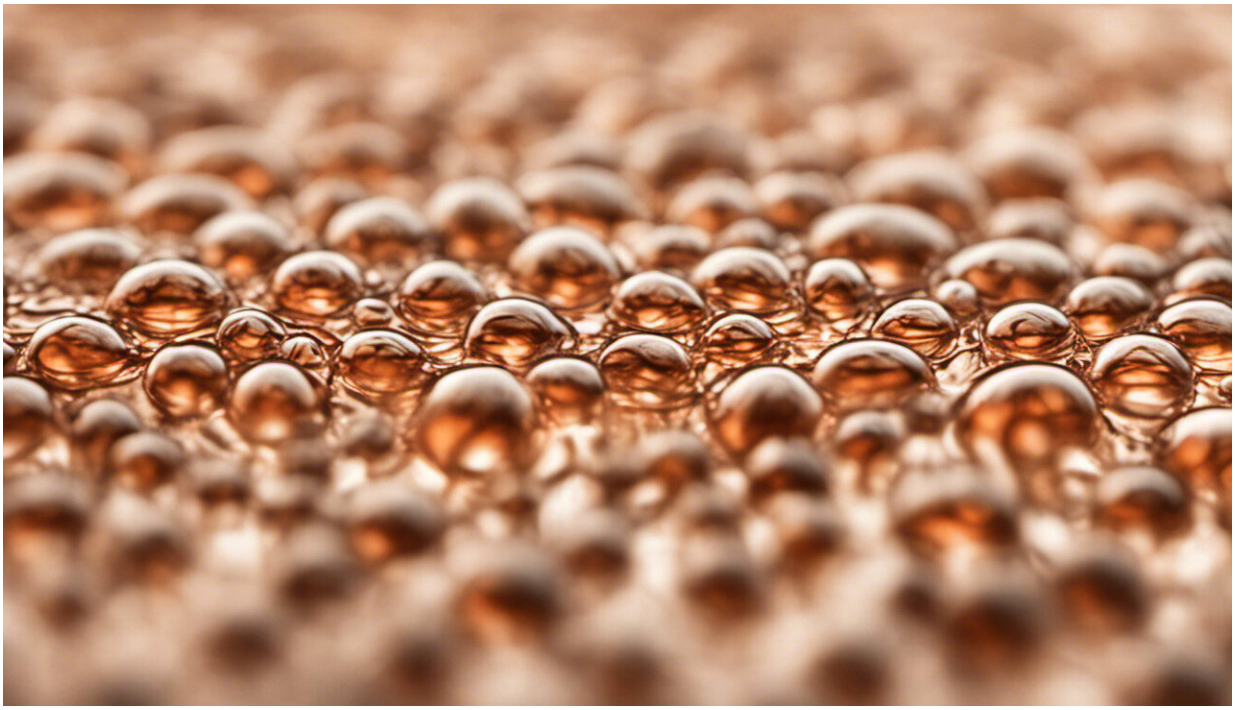

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The immunoglobulin E (IgE) antibody released by the immune system is a pivotal defense against gut parasites and toxins. However, the same antibody when misdirected can also cause allergic responses to food or substances in the environment. An international team led by researchers at the A*STAR Singapore Immunology Network has now discovered a

regulatory mechanism that keeps IgE levels in check.

A better understanding of the process of IgE production and how it can be subverted should enable scientists to develop the next generation of allergy treatments. "If we know the mechanism, potentially we could intervene therapeutically to prevent the development of severe allergic and anaphylactic reactions," says A*STAR immunologist Maria Curotto de Lafaille, who led the research.

A type of white blood cell known as a B cell can change the antibodies that it produces through a process known as immunoglobulin class switching. B cells that produce IgE can arise through one of two distinct switching mechanisms. Either the B cells go through a sequential process that involves another type of immunoglobulin, IgG, as an intermediary, or they take a direct route to IgE generation. The sequential process creates IgE with high affinity for antigens—the substances that can trigger an immune response and can cause severe allergic reactions. In contrast, the direct switching pathway produces IgE antibodies that bind their antigens weakly. These low-affinity antibodies can compete with the problematic IgE to prevent anaphylaxis.

The origin, functional properties and population dynamics of IgE-producing cells had been poorly understood. To track the dynamics of IgE production in a living system, Curotto de Lafaille and her colleagues created a new mouse strain that fluoresces whenever and wherever IgE antibodies are produced. Using the mouse model, the researchers showed that IgE-producing cells that undergo the direct switching pathway at germinal centers—sites in the lymphatic system where B cells differentiate and mutate to enhance their antigen binding—tend to get stuck in that developmental state and end up 'failing to thrive'. "These cells have a lot of defects and they end up dying," says Curotto de Lafaille.

The failure of the IgE cells to directly produce antibodies with strong binding ability imposes a strong constraint on IgE-based immune responses. "If you easily make so many high-affinity IgE cells, you'd be constantly in danger of life threatening reactions like anaphylaxis," Curotto de Lafaille explains. "That's why there's an evolutionary pressure to limit this process."

More information: He, J.-S., Meyer-Hermann, M., Xiangying, D., Zuan, L. Y., Jones, L. A. et al. "The distinctive germinal center phase of IgE+ B lymphocytes limits their contribution to the classical memory response." *Journal of Experimental Medicine* 210, 2755–2771 (2013). dx.doi.org/10.1084/jem.20131539

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