

The sea squirt, a marine invertebrate, houses a treasure trove of natural products made by its microbiome.

of the sea squirt revealed a bacterium that produces turbinmicin, a molecule that effectively kills drug-resistant fungi by blocking vesicle trafficking, a core cellular process.

Interrogation of a chemically diverse library of small molecules is fundamental to any effort designed to discover new, bioactive natural products. To achieve this goal, Zhang *et al.* leveraged liquid chromatography-mass spectrometry profiling of 1482 strains of actinobacteria from marine invertebrates (3). One strain was prioritized on the basis of its chemical diversity, as deduced with metabolomic analysis; its array of fermentation products was then fractionated by using a two-step chromatographic approach. Turbinmicin was identified and prioritized on the basis of its antifungal potency and structural characteristics. Purified turbinmicin demonstrated broad-spectrum activity against diverse clinical isolates of human fungal pathogens, including those resistant to each of the three established antifungal classes. Judging from this activity profile, turbinmicin likely kills fungi through a mechanism that is distinct from azoles (inhibition of the biosynthesis of the membrane sterol ergosterol), polyenes (ergosterol depletion), or echinocandins (inhibition of the biosynthesis of the cell wall 1,3- β -D-glucan). Turbinmicin reduced fungal burden in mouse models of drug-resistant fungal infection caused by *Candida auris* and *Aspergillus fumigatus* and was well tolerated in mice. The benefit of turbinmicin production to the *Micromonospora* sp. producer or to the ascidian host remains unknown because this marine environment is not an established reservoir for these human fungal pathogens.

With 20 years having elapsed since the last antifungal class was approved for treatment of invasive infections, scientists are encouraged by recent progress with the clinical development of multiple new drugs (7, 8). Improvements have been made for existing antifungal classes, as exemplified by rezafungin, a more stable next-generation echinocandin that enables intravenous administration once a week rather than every day. Ibrexafungerp exemplifies a different chemical class of compounds that engages with an established drug target by binding to an overlapping but distinct region of the echinocandin target. Compounds with new targets are also advancing rapidly in clinical development, as with olorofim, which inhibits the synthesis of DNA building blocks, and fosmanogepix, which inhibits localization of key cell wall-anchored proteins. Each of the established and emerging antifungal drugs targets essential proteins

or components of the fungal cell, as is likely the case with turbinmicin. A central challenge in the development of effective antifungals is ensuring sufficient fungal selectivity to avoid deleterious effects to the human host, which shares many conserved essential cellular processes.

Leveraging a genetically tractable yeast model system, Zhang *et al.* profiled a library of mutants with reduced dosages of individual essential genes and deletion of specific nonessential genes (9–11). A reduced dosage of the essential vesicle-mediated trafficking gene *SEC14* conferred profound hypersensitivity to turbinmicin, as did deletion of nonessential regulators of this process. Consistent with the hypothesis that turbinmicin blocks vesicle-mediated trafficking by inhibiting Sec14, the compound impaired localization of a cargo protein to the plasma membrane. Turbinmicin could be docked into a specific Sec14 binding pocket, which is also consistent with Sec14 being a proximal target of the natural product. Further analysis of the binding mode, biochemical consequences and fungal selectivity of target engagement, and pharmacological properties will enable future development efforts.

There is also great opportunity in developing drug combinations that enhance potency and evade resistance, as well as in exploring the therapeutic potential of compounds that inhibit microbial virulence (12). Exploring the complex chemical communication that transpires between kingdoms in diverse environments is poised to catalyze the discovery and development of resistance-evasive therapeutic strategies for life-threatening infectious diseases. ■

REFERENCES AND NOTES

1. M. C. Fisher *et al.*, *Science* **360**, 739 (2018).
2. G. D. Brown *et al.*, *Sci. Transl. Med.* **4**, 165rv13 (2012).
3. F. Zhang *et al.*, *Science* **370**, 974 (2020).
4. G. D. Wright, *Nat. Prod. Rep.* **34**, 694 (2017).
5. J. O'Brien, G. D. Wright, *Curr. Opin. Biotechnol.* **22**, 552 (2011).
6. J. Davies, *J. Antibiot. (Tokyo)* **66**, 361 (2013).
7. K. Kupferschmidt, *Science* 10.1126/science.aaz9475 (2019).
8. J. R. Perfect, *Nat. Rev. Drug Discov.* **16**, 603 (2017).
9. J. S. Piotrowski *et al.*, *Nat. Chem. Biol.* **13**, 982 (2017).
10. T. Roemer, C. Boone, *Nat. Chem. Biol.* **9**, 222 (2013).
11. A. Xue, N. Robbins, L. E. Cowen, *Ann. N. Y. Acad. Sci.* 10.1111/nyas.14484 (2020).
12. N. Robbins, G. D. Wright, L. E. Cowen, *Microbiol. Spectr.* 10.1128/microbiolspec.funk-0002-2016 (2016).

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IMMUNOLOGY

Transferring allergies in the womb

Maternal antibodies prime fetal mast cells in utero for subsequent postnatal allergy responses

By Marc E. Rothenberg

Allergic diseases, which affect 10 to 30% of the global population, have a high degree of heritability contributed by a combination of parental factors (1). In addition to genetics, such parental factors include the amount of maternal immunoglobulin E (IgE), the antibody type that binds to allergens, which directly correlates with the risk of allergy in offspring (2). On page 941 of this issue, Msallam *et al.* (3) delve into the relationship of maternal IgE and fetal mast cells in mice and humans, demonstrating that IgE crosses the placenta and binds to fetal mast cells, and relate this to the subsequent development of allergic responses in offspring.

Mast cells reside in various tissues near mucosal interfaces, blood vessels, and nerve fibers. They serve as cellular guards, sensing a variety of chemical, pathogenic, and biophysical triggers, and subsequently release pleiotropic molecules that contribute to diverse responses ranging from protective immunity to exacerbation of inflammation. Mast cells are traditionally considered the primary cells responsible for allergies because they express the high-affinity IgE receptor Fc ϵ R1. Upon cross-linking with IgE, Fc ϵ R1 induces cellular activation, including degranulation and release of preformed and de novo immune mediators such as histamine, leukotrienes, proteases, and cytokines. The formation of IgE and its specificity for distinct antigens (allergens) is an essential pathogenic process in diseases such as atopic eczema, food allergies, asthma, and hay fever.

During embryonic development, mouse mast cells and macrophages develop from the yolk sac at an earlier stage than other

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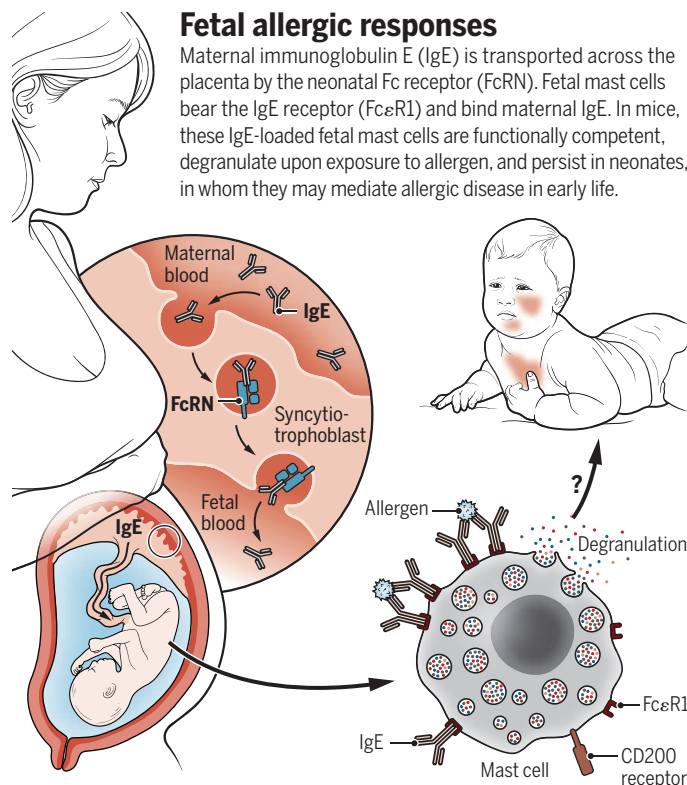
leukocytes (4). Why mast cells are present so early in development may be related to their role in organ development, but their functional competence has been unclear. Msallam *et al.* show that mouse fetal mast cells are functional and that mast cells, particularly those readily detectable and abundant in fetal skin, become loaded with surface-bound maternal IgE. These IgE⁺ mast cells could respond to and degranulate upon exposure to an experimental allergen recognized by the IgE intravenously given to the mother, and this occurred even before birth. Furthermore, pups born to allergic mothers developed allergic responses, including airway hyperreactivity, upon their first postnatal exposure to the experimental allergen originally given to the mother (see the figure).

Fetal IgE has not been deeply studied, and whether it is produced by the fetus or derived from the mother (similar to most IgG in the fetus) is not agreed upon. However, emerging studies have provided evidence that human IgE in umbilical cord blood is maternally derived (5). Thus, the findings by Msallam *et al.* fit well with these data. The authors also identify the neonatal Fc receptor (FcRN) as the key IgE transporter, expressed by fetal endothelial cells and syncytiotrophoblast cells in the placenta. Previously, FcRN was shown to transfer IgG across the placenta (6).

Although fetal mast cells are capable of mediating classical allergic responses, it is important to note that the models used by Msallam *et al.* rely on artificial experimental systems that involve unnaturally high doses of passive IgE administration and allergen sensitization schemes that are likely stronger than those that occur naturally in humans (7). Additionally, the presence of allergen-specific IgE and the ability of allergens to degranulate mast cells are not sufficient for the development of allergies, as many individuals elicit these responses in the absence of clinical symptoms. Indeed, the development of allergic diseases involves other key immunocytes, including basophils, eosinophils, innate lymphoid cells, T helper type 2 cells, and regulatory T cells. Even when focusing on mast cells, their activation status is influenced by a variety of inhibitory signals including expression of the inhibitory receptor CD200R (8), which was present on fetal mast cells (3). Furthermore, IgG can neu-

Fetal allergic responses

Maternal immunoglobulin E (IgE) is transported across the placenta by the neonatal Fc receptor (FcRN). Fetal mast cells bear the IgE receptor (FcεR1) and bind maternal IgE. In mice, these IgE-loaded fetal mast cells are functionally competent, degranulate upon exposure to allergen, and persist in neonates, in whom they may mediate allergic disease in early life.



tralize antigens and directly inhibit mast cells (9); the roles of CD200R and IgG were not assessed by Msallam *et al.* Additionally, the degree of allergic inflammation seen in newborn mice could be considered modest: Lung eosinophils increased by a factor of ~2, whereas a factor of >10 increase in eosinophils is typically seen in human asthma and experimental asthma models in adult mice.

Msallam *et al.* found that human fetal lung and skin mast cells were IgE⁺ and appeared to be functionally mature. Notably, by 14 weeks of gestation, human fetal mast cells were already present in the skin at numbers comparable to those of adults. IgE may not only equip these mast cells to respond to allergens, but also promote their functional maturation and activation potential, creating a skin environment with primed mast cells, perhaps contributing to the “sensitive” skin of newborns. Indeed, a variety of unexplained newborn rashes, including infant atopic eczema, may be influenced by in utero-conditioned mast cells. Conversely, it is interesting to speculate that IgE-loaded mast cells may equip newborns with early-life protection against threatening infections.

A substantial body of evidence supports the idea that the development of allergic disease involves an “allergic march,” which starts in the infant skin and subsequently develops into food allergy and then respiratory allergy (10). Msallam *et al.* demonstrated that loading of fetal mast cells with

maternal IgE is transient, gone by 6 weeks of age in mice; this time period is a critical window for long-term immune polarization, as exemplified by the recent recognition that early-life exposure to allergens is protective for the development of food hypersensitivity (11).

An immediate implication of the results is the occurrence of vertical transmission of anaphylaxis. However, this is not a phenomenon readily observed in humans because infants rarely have anaphylaxis and mothers seldom pass specific allergies (e.g., to penicillin or peanut) to their offspring (11, 12). Perhaps this is due to the short lifespan of the surface-bound IgE, estimated to be 70 days (13), meaning that maternal IgE would be gone by the time most infants begin to develop acute allergic reactions when solid foods are introduced. Instead, mothers pass on the tendency to develop allergies but not specific antigen sensitization. Although this has been attributed to the transfer of genetic variants in allergy susceptibility genes and commensal microbiota, the findings of Msallam *et al.* raise the possibility that in utero events, most notably the priming of mast cells with surface IgE, may contribute to a variety of subsequent immune responses, perhaps by promoting the continuation of the type 2 immune polarization that is characteristic of neonates (14). ■

REFERENCES AND NOTES

1. N. P. Azouz, M. E. Rothenberg, *J. Clin. Invest.* **129**, 1419 (2019).
2. C. A. Liu *et al.*, *J. Allergy Clin. Immunol.* **112**, 899 (2003).
3. R. Msallam *et al.*, *Science* **370**, 941 (2020).
4. R. Gentek *et al.*, *Immunity* **48**, 1160 (2018).
5. K. Bønnelykke, C. B. Pipper, H. Bisgaard, *J. Allergy Clin. Immunol.* **121**, 646 (2008).
6. D. D. Patel, J. B. Bussell, *J. Allergy Clin. Immunol.* **146**, 467 (2020).
7. F. D. Finkelman, M. Wills-Karp, *J. Allergy Clin. Immunol.* **121**, 603 (2008).
8. S. Zhang, H. Cherwinski, J. D. Sedgwick, J. H. Phillips, *J. Immunol.* **173**, 6786 (2004).
9. O. Malbec, M. Daëron, *Immunol. Rev.* **217**, 206 (2007).
10. H. Han, F. Roan, S. F. Ziegler, *Immunol. Rev.* **278**, 116 (2017).
11. G. Du Toit *et al.*, *N. Engl. J. Med.* **372**, 803 (2015).
12. G. Pouessel *et al.*, *Clin. Exp. Allergy* **50**, 74 (2020).
13. M. G. Lawrence *et al.*, *J. Allergy Clin. Immunol.* **139**, 422 (2017).
14. S. L. Prescott, *Curr. Opin. Allergy Clin. Immunol.* **3**, 125 (2003).

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