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Opportunities to target mast cells in inflammatory diseases expand

Drugs that target mast cells could provide novel options to treat disorders involving chronic allergic inflammation.

Mark Zipkin

Mast cells are a crucial part of our immune defenses against bacteria, some parasites and venoms, but they are also key players in allergic reactions, in which inflammatory mediators, such as histamine, are released by mast cells in response to harmless substances. This negative side of mast cell activity can lead to chronic inflammation.

However, the extent of the importance of mast cells in many inflammatory diseases has been unclear. Now, the development of candidate drugs that target mast cells in a range of ways is illuminating their pathogenic roles and leading to treatment options for disorders in which mast cells are known to be pivotal, such as urticaria, as well as for other inflammatory disorders in which they are implicated, such as asthma and atopic dermatitis.

Mast cells as therapeutic targets

The earliest successful clinical interventions targeting the effects of mast-cell activity were antihistamines—small molecules that inhibit the effects of histamine by binding to the histamine H_1 receptor. Decades after their introduction, these remain part of the standard for care for disorders such as urticaria.

Several other mast cell products beyond histamine have been targeted in allergic and inflammatory disease, with mixed results. Inhibitors of leukotrienes, lipids produced by mast cells, are approved to treat asthma, rhinitis and urticaria, though safety concerns have limited their utility. Small-molecule antagonists of another lipid mediator, prostaglandin D2, or its binding partner on innate lymphoid cells, CRTH2, have been tested for asthma, rhinitis and other inflammatory diseases, but showed lackluster efficacy in recent clinical trials.

Monoclonal antibodies targeting inflammatory cytokines released by mast cells (as well as other immune cells) or their receptors, such as interleukin-5 (IL-5), the IL-5 receptor (IL-5R) or IL-4R, have been more successful, gaining approval for diseases such as eosinophilic asthma. Tetrameric β-tryptase—a protease secreted by mast cells in parallel with histamine—can also be inhibited by monoclonal antibodies such as MTPS9579A, which is currently in phase 2 testing for patients with asthma not controlled by corticosteroids (Table 1).

Multiple monoclonal antibodies are also in clinical development to disrupt upstream mast cell biology, following on from the success of omalizumab. This monoclonal antibody inhibits mast cell activation by targeting immunoglobulin E (IgE), to which allergens bind during allergic reactions, leading to IgE cross-linking and aggregation of FcεRI receptors. Omalizumab was approved for asthma in 2003 and for chronic spontaneous urticaria in 2014, and ligelizumab, a next-generation IgE-targeting monoclonal antibody, is in phase 3 testing for chronic spontaneous urticaria. IgE cross-linking can also be disrupted after it has bound to Fc receptors on mast cells with small-molecule BTK inhibitors, and remibrutinib is in clinical trials for chronic spontaneous urticaria.

Companies are also exploring other approaches to disrupting upstream pathways. Monoclonal antibodies can bind inhibitory receptors such as SIGLEC8, silencing both mast cells and pro-inflammatory eosinophils. Lirentelimab is in phase 3 testing for eosinophilic gastritis and duodenitis, an inflammatory disease driven by both cell types. Alternatively, by targeting the stem cell growth factor receptor tyrosine kinase KIT, the total number of mast cells can be depleted. Small-molecule inhibitors of KIT have been approved for mastocytosis, and CDX-0159, an anti-KIT monoclonal antibody, is in phase 1 testing for chronic urticaria.

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Table 1 | Selected investigational drugs targeting mast cell pathways for allergic/inflammatory diseases

Molecule	Company	Target	Type	Stage	Indication
Ligelizumab	Novartis	IgE	mAb	Phase 3	Chronic spontaneous urticaria
Lirentelimab	Allakos	SIGLEC8	mAb	Phase 3	Eosinophilic gastritis and duodenitis
MTPS9579A	Genentech	Tetrameric β-tryptase	mAb	Phase 2	Asthma
Remibrutinib	Novartis	BTK	Small molecule	Phase 2	Chronic spontaneous urticaria
CDX-0159	Celldex	KIT	mAb	Phase 1	Chronic spontaneous urticaria and chronic inducible urticaria

mAB, monoclonal antibody; IgE, immunoglobulin E