interferon-γ (IFNγ) production, likely owing to the upregulation of IL-12 expression by inf-cDC2s. When carefully separated from inf-cDC2s, MCs did not induce $CD4^+$ or $CD8^+$ T cell proliferation. The superior antigen-presenting function of inf-cDC2s was consistent with their expression of activating Fc receptors, which were shown to mediate uptake of antibody–antigen complexes for enhanced antigen presentation to $CD4^+$ T cells.

RNA microarray analysis and single-cell RNA sequencing confirmed the hybrid phenotype of inf-cDC2s, showing shared gene expression with MCs and both cDC subsets, including upregulation of IRF4 as well as IRF8 to levels similar to those in cDC1s. However, inf-cDC2s were distinguished by upregulation of genes related to a type I interferon signature, pro-inflammatory cytokines and $CD4^+$ T cell differentiation. Interestingly, IRF8 was not required for inf-cDC2 development but was responsible for regulating a set of 88 genes involved in T cell activation and differentiation.

Further analysis revealed that Toll-like receptor-driven activation of type I interferons causes cell-intrinsic type I interferon receptor signalling and IRF8 activation, leading to the acquisition of inf-cDC2 features and functions. Finally, the authors confirmed that this inflammatory subset is induced in several other mouse models, including infection with influenza virus, house dust mite-induced asthma and parasitic or mycobacterial infection of the skin.

The authors suspect that the mistaken identity of contaminating inf-cDC2s in antigen-presenting cell populations may explain why MCs have been credited with antigen-presenting functions and migratory capacity in inflammatory settings.

Lucy Bird

ORIGINAL ARTICLE Bosteels, C. et al. Inflammatory type 2 cDCs acquire features of cDC1s and macrophages to orchestrate immunity to respiratory virus infection. *Immunity* https://doi.org/10.1016/j.immuni.2020.04.005 (2020)

the galactose and sialic acid contents of IgE were found to be strong predictors of allergic disease.

Using neuraminidase (NEU) digestion, the authors generated sialylated and asialylated mouse IgE (mIgE) of identical allergen specificity. These were tested in mouse models of passive cutaneous anaphylaxis and passive systemic anaphylaxis (PSA). In both models, sialylated mIgE induced much stronger reactions than its asialylated counterpart. However, the potency of asialylated mIgE was restored when these antibodies were re-sialylated — indicating that sialylation indeed regulates IgE activity. This also held true for human IgE as desialylation reduced its capacity to induce degranulation in a human mast cell line and in primary human basophils.

Interestingly, sialylation does not affect IgE interactions with FcεRI or with its specific antigen but instead appears to affect signalling downstream of FcεRI. Crosslinking of sialylated human IgE, compared with asialylated human IgE, induced stronger phosphorylation of the tyrosine kinase SYK and a higher Ca^{2+} flux in human mast cells. Further experiments showed that treatment with asialylated IgE, or even with asialylated fetuin, an unrelated glycoprotein, attenuates mast cell degranulation and inhibits pathology in the PSA mouse model. This suggests that the removal of sialic acid exposes a glycan with an inhibitory function on FcεRI signalling.

To investigate whether IgE sialylation can be therapeutically targeted, a fusion protein consisting of NEU and the IgE Fc domain (NEU^{Fc}) was generated. This protein binds to FcεRI, thereby targeting the desialylation activity of NEU specifically to IgE-bearing cells. Treatment with NEU^{Fc} in the PSA model potently attenuated allergen-induced pathology.

This study demonstrates that sialylation regulates IgE biology and suggests that allergic reactions may be tamed by removing sialic acid from IgE or by administering asialylated glycoproteins.

Alexandra Flemming

ORIGINAL ARTICLE Shade, K.-T. C. et al. Sialylation of immunoglobulin E is a determinant of allergic pathogenicity. *Nature* https://doi.org/10.1038/s41586-020-2311-z (2020)

Journal Club

FINDING THE VULNERABLE CHECKPOINT

It is now accepted that pivotal regulatory checkpoints of the immune response confer clinical therapeutic opportunities. Reductionist approaches to the identification of such nodes have conventionally relied upon murine disease models. Moreover, recent novel molecular and cellular approaches have facilitated the evaluation of human tissues from individuals with immune-mediated inflammatory diseases (IMIDs). Further progress will also be made using ex vivo cellular systems in which specific pathways can be modulated, as well as artificial intelligence and mathematical approaches.

However, to define the crucial function of a given moiety in the context of human IMIDs, there is no substitute for a clinical trial with a specific immune-targeted intervention. The seminal paper in this field, published in 1994, described the clinical benefits of a monoclonal antibody to tumour necrosis factor (TNF) in individuals with rheumatoid arthritis (RA). The preclinical rationale for this study was proposed by Ravinder Maini and Marc Feldmann on the basis of the identification of TNF and its properties in synovial tissues from patients with RA and successful targeting of TNF in mice. The implications of this trial were remarkable and supported the notion that functional cytokine hierarchies could be harnessed for clinical benefit. The convention of broad functional redundancy amongst cytokines was discarded, which had profound implications for future drug development.

In retrospect, several other cytokines, particularly IL-1, had similar levels of preclinical evidence to support their potential role as therapeutic targets in RA. However, IL-1 blockade did not have sufficient efficacy in the treatment of RA, which further highlights the crucial informative value of the TNF inhibition trial. Intriguingly, IL-1 blockade was subsequently found to have significant benefit in inflammatory monogenic disorders, other juvenile inflammatory syndromes and gout. Therefore, it seems that there are rarely 'ineffective drugs' but rather that cytokine inhibitors are effective only in the correct pathological context.

Deriving the preclinical rationale for progression to clinical trials remains a challenge even in 2020. Nevertheless, this first TNF inhibition study provided sufficient confidence in preclinical studies to drive a remarkable expansion of the field, resulting in biological therapeutics against several cytokines and their receptors, which variously confer clinical benefit across a range of IMIDs. Moreover, on the basis of such success, we can now seek a molecular taxonomy for IMIDs, based on clinical studies using specific cytokine inhibitors to define dominant immune pathways for each disease.

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ORIGINAL ARTICLE Elliott, M. J. et al. Randomised double-blind comparison of chimeric monoclonal antibody to tumour necrosis factor α (cA2) versus placebo in rheumatoid arthritis. *Lancet* **344**, 1105–1110 (1994).