Immune evasion via SARS-CoV-2 ORF8 protein?

In this preprint, Zhang et al. elucidate a potential immune evasion strategy involving the SARS-CoV-2 ORF8 protein. They show that expression of ORF8, which directly binds to MHC class I molecules, downregulates their surface expression on HEK293T cells. ORF8 co-localizes with MHC class I molecules in lysosomes, thereby disrupting antigen presentation. When healthy human donor-derived cytotoxic T lymphocytes (CTLs) sensitized to the SARS-CoV-2 epitope Ssp-1 were exposed to autologous dendritic cells pre-pulsed with Ssp-1, there was a reduced killing of ORF8-expressing HEK293T cells compared with ORF8 non-expressing cells. These results were replicated using CTLs isolated from a patient recovering from COVID-19 that responded to a mixture of SARS-CoV-2 N and S proteins. This potential mechanism for SARS-CoV-2 evasion of host immune surveillance warrants further investigation.

Case of mistaken identity

Distinguishing dendritic cells (DCs) from macrophages has long been problematic, owing to overlapping features and functions between the various subsets. Now, Lambrecht, Guilliams and colleagues identify a new DC subset that arises in inflammatory conditions that assumes the characteristics of DCs, monocytes and macrophages and may explain why antigen-presenting functions have been wrongly attributed to monocyte-derived cells (MCs).

Conventional DCs are classified into phenotypically and functionally distinct subsets: type 1 cells (cDC1s) depend on the transcription factor interferon regulatory factor 8 (IRF8) for their capacity to present and cross-present antigen to CD8+ T cells, and type 2 cells (cDC2s) are driven by IRF4 to promote CD4+ T cell responses. But inflammation muddies the water. MCs are recruited to inflamed tissues and can be easily confused with cDC2s.

Does IgE sialylation hold the key to allergy?

Allergic reactions are induced when IgE, bound to mast cells and basophils via the high affinity receptor FcεRI, is crosslinked by an otherwise innocuous antigen, inducing the release of allergic mediators. However, many people have allergen-specific IgE yet do not experience allergic symptoms, and it is unclear why IgE induces allergy in some circumstances but not in others. Reporting in Nature, Shade et al. now demonstrate that sialylation of IgE is a key determinant of allergic pathogenicity.

The authors compared IgE from sera of individuals with peanut allergy with IgE from non-atopic individuals. When incubated with human mast cells and crosslinked with anti-IgE, they found that ‘allergic IgE’ induced significantly stronger degranulation than ‘non-atopic IgE’, despite comparable binding of IgE to the mast cells. Mass spectrometry revealed that IgE from the different cohorts differed with regard to post-translational modifications: allergic IgE had significantly increased terminal sialylation of specific glycan residues whereas non-atopic IgE was enriched in complex glycans terminating in galactose. Indeed,