IN BRIEF

COVID-19

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 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.

ORIGINAL ARTICLE Zhang, Y. et al. The ORF8 protein of SARS-CoV-2 mediates immune evasion through potently downregulating MHC-I. Preprint at *bioRxiv* https://doi.org/10.1101/2020.05.24.111823 (2020)

COVID-19

Many paths to COVID-19 lymphocyte dysfunction

Longitudinal tracking of immune responses against SARS-CoV-2 can provide insight into mechanisms of immune dysfunction in COVID-19. Mathew et al. carried out deep profiling of the T cell and B cell compartments in peripheral blood of patients with COVID-19, convalescent donors and healthy controls, using high-dimensional cytometry and multiplexed cytokine analyses. By overlaying immune and clinical features, the study identifies temporal patterns in populations of activated plasmablasts, effector memory T cells and $CD4^+$ follicular T cells. Unsupervised cluster projection identifies three 'immunotypes' with distinct COVID-19 severity outcomes. Notably, one subgroup has $CD4^+$ T cell and plasmablast activation associated with severe COVID-19; another subgroup has minimal or no lymphocyte response. This study underscores the various immune trajectories in COVID-19 and may explain differences in the response to immunosuppression.

ORIGINAL ARTICLE Mathew, D. et al. Deep immune profiling of COVID-19 patients reveals patient heterogeneity and distinct immunotypes with implications for therapeutic interventions. Preprint at *bioRxiv* https://doi.org/10.1101/2020.05.20.106401 (2020)

COVID-19

SARS-CoV-2 cross-reactivity in healthy donors

In this preprint by Ng et al., binding IgG antibodies to conserved epitopes from SARS-CoV-2 S and N proteins were detected by flow cytometry and ELISA in approximately 10% of healthy individuals with a recent history of infection by human endemic coronaviruses (HCoVs). Of note, sera from the same donors were found to have SARS-CoV-2 neutralization activity comparable to that of samples from seropositive patients with COVID-19, which suggests that cross-neutralizing antibodies developed in response to previous HCoV exposure might interfere with SARS-CoV-2 entry into target cells. Further studies are needed to assess the potentially protective role of pre-existing cross-reactive antibodies in healthy individuals in the context of COVID-19 immunopathogenesis.

ORIGINAL ARTICLE Ng, K. et al. Pre-existing and de novo humoral immunity to SARS-CoV-2 in humans. Preprint at *bioRxiv* https://doi.org/10.1101/2020.05.14.095414 (2020)

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DENDRITIC CELLS

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.

To explore the cDC dichotomy in inflammatory settings, the authors studied the lungs of mice infected with pneumonia virus of mice (PVM). cDCs were separated from MCs by surface staining for CD26 and CD64, respectively, and XCR1 and CD172a were used to distinguish cDC1s from cDC2s, respectively. On infection, the proportion of MCs in the lungs increased, while cDC1s and cDC2s decreased. However, another DC population appeared in infected lungs that was positive for CD26, CD172a, CD64 and MAR-1; they named these cells inflammatory cDC2s (inf-cDC2s). Unlike MCs, inf-cDC2s accumulated in lung-draining lymph nodes in infected mice, thus demonstrating DC-like migratory capacity.

In vitro assays of DC function showed that inf-cDC2s were better than cDC2s at inducing $CD4^+$ T cell proliferation. Although not as efficiently as cDC1s, inf-cDC2s could also induce $CD8^+$ T cell proliferation and

ALLERGY

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,

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