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Top Reads

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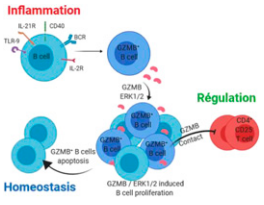
Generation of Regulatory B Cells Expressing Granzyme B



In this Top Read, Chesneau et al. (p. 2391) characterize suppressive B cells expressing granzyme B (GZMB). In healthy donors, GZMB$^+$ B cells are predominantly within the plasmablast subset of B cells. However, induction of plasmablasts in vitro from isolated B cells failed to increase GZMB expression. The addition of a stimulation mixture containing IL-21, anti-BCR, CpG oligodeoxynucleotides, and IL-2 was sufficient to induce GZMB expression in 90% of B cells by day 3 of culture. Because cleavage of procaspase-3 by GZMB initiates the caspase-dependent apoptotic pathway, GZMB$^+$ B cells were more sensitive to apoptosis, and their proportion within cultures was decreased by day 6 of culture. GZMB inhibitors decreased both ERK1/2 phosphorylation and B cell proliferation, suggesting that GZMB induces proliferation in an ERK1/2-dependent manner. Suppression of allogeneic and autologous T cell proliferation by in vitro–generated GZMB$^+$ B cells was cell contact dependent and partially GZMB dependent but did not require uptake of GZMB by T cells. These data highlight the biology of in vitro–generated, suppressive GZMB$^+$ B cells and suggest their potential in future cell-based therapy.

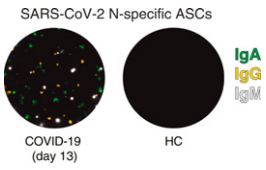
IgG Breaks Tolerance of Human Microglia

In this Top Read, van der Poel et al. (p. 2511) show that IgG-myelin immune complexes (IgG-ICs) in the brains of multiple sclerosis (MS) patients potentiate inflammation by microglia. Myelin bound to IgG in the brain tissue of 8 out of 11 MS postmortem donors. The presence of IgG-IC in the donor brains correlated with an increase in lesion load. In accordance with previous data, microglia isolated from these donors were unresponsive to IgG-IC, Poly I:C, or LPS when given individually. However, the combination of either Poly I:C or LPS with IgG-IC increased transcription of proinflammatory cytokines, suggesting that costimulation with IgG-IC breaks microglial tolerance to microbial ligands. FcγR is the main IgG receptor on human myeloid immune cells, and blocking of FcγRII and FcγRIIa completely inhibited proinflammatory cytokine gene expression. These data provide a mechanism by which cerebral microglia immune tolerance can be broken in patients with MS.

Mechanisms Driving Immune Responses to Biologics

A major drawback of using biological products (BP) clinically is the development of antidrug Abs (ADAs). Although it is hypothesized that BP aggregates act as danger signals recognized by dendritic cells (DCs) to facilitate the development of an anti-BP CD4 T cell–dependent response, little is known regarding the mechanisms driving the production of ADAs. In this Top Read, Nabhan et al. (p. 2351) demonstrated that aggregates of infliximab (IFX), an anti–TNF-α chimeric Ab, induced maturation of human monocyte-derived DC (moDC). Compared with untreated moDC, those treated with IFX aggregates enhanced T cell proliferation and production of IL-5, IL-9, and IL-13. Treatment of moDC with anti-FcγRIIa Abs inhibited DC activation and decreased cytokine and chemokine production in response to IFX aggregates. Consistent with these observations, inhibition of spleen tyrosine kinase (Syk), which is activated following Fcγ receptor binding, also decreased DC activation and cytokine and chemokine production in response to IFX aggregates. Furthermore, Syk inhibition of aggregate-stimulated moDC significantly decreased T cell proliferation and production of IL-5, IL-9, and IL-13. Thus, these results demonstrate that BP aggregates are capable of inducing DC and T cell activation via the FcγRIIa and Syk signaling pathway.

B Cell and Ab Responses in COVID-19 Patients



In this Top Read, Varnaitė et al. (p. 2437) provide a detailed description of clinical and immunological parameters in 20 patients hospitalized with COVID-19. Whereas no significant difference between the numbers of CD3$^+$CD4$^+$ T cells and CD19$^+$ B cells was observed between COVID-19 patients and healthy controls, the former had a significant decrease in the number of circulating CD45$^+$ lymphocytes. Unsurprisingly, T and B cells from COVID-19 patients were more activated than those from healthy controls. Compared with healthy controls, COVID-19 patients had a significant expansion of Ab–secreting cells (ASC). The expansion of ASCs in COVID-19 patients correlated with an increase in total SARS-CoV-2 Ag–specific ASC, suggesting total ASC expansion may reflect the magnitude of the SARS-CoV-2–specific response. Consistent with these observations, 16 of 20 COVID-19 patients developed SARS-CoV-2–neutralizing Abs, and the levels of SARS-CoV-2–specific IgA, IgG, and IgM positively correlated with neutralizing Ab titers, indicating that total Ab levels could be predictive of neutralizing Ab titer during acute infection. Finally, IL-6 and C-reactive protein levels, which were previously shown to be higher in patients with a longer

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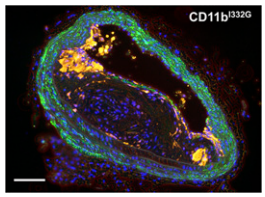
duration of hospitalization, negatively correlated to total Ag-specific IgG and neutralizing Ab titers in COVID-19 patients. Together, these data provide crucial information on B cell and Ab responses during SARS-CoV-2 infection.

A Mouse Model of Constitutively Active Integrin



Because CD11b/CD18 plays an integral role in processes such as leukocyte recruitment and resolution of inflammation, it is a promising therapeutic target for the treatment of inflammatory disease. To better understand molecular pathways of CD11b activation, in this Top Read, Martinez et al. (p. 2545) report the development of a knock-in (KI) mouse model in which a point mutation within the *Itgam* gene promoted an active, higher-affinity conformation of the ligand-binding I/A-domain (CD11b αA-domain). KI neutrophils displayed reduced adhesion and migration in vitro. In vivo, KI animals displayed reduced recruitment of neutrophils and macrophages in the setting of sterile peritonitis. Furthermore, mutation of CD11b protected mice against the development of atherosclerosis in the setting of hyperlipidemia via the reduction of macrophage recruitment into atherosclerotic lesions. Thus, this study reports a model that may be used to gain deeper insight into pathways that can be therapeutically targeted for the treatment of inflammatory diseases, such as atherosclerosis.