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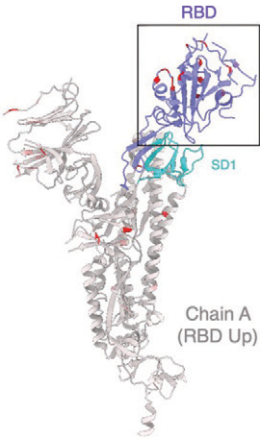
Optimized RBD-Based Protein Vaccine against COVID-19

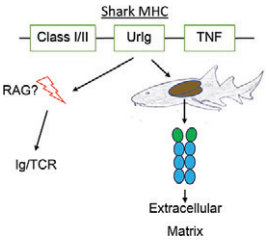


In this Top Read, Yu et al. (p. 981) produced and characterized a novel SARS-CoV-2 receptor binding domain (RBD)-based vaccine that protects susceptible mice from infection. Several RBD constructs were expressed, purified, and combined with one of two adjuvants (aluminum hydroxide [Alum] or dimethyldioctadecylammonium bromide [DDA] and D-(+)-trehalose 6,6′-dibehenate [TDB]). DDA/TDB yielded the highest neutralizing Ab titers and CD4 T cell responses compared with Alum and any RBD protein tested. An HEK293F-produced RBD construct that included the SD1 subdomain (RBDSD1) induced the highest Ag-specific neutralizing IgG titers, as well as cytokine-producing (IFN-γ and TNF-α) CD4 T cell responses, relative to RBD alone or RBD constructs produced in other cell types. Fusion of a monomeric fragment crystallizable tag to RBDSD1, yielding RBDSD1mFc, enhanced this response. Immunization with an RBDSD1mFc construct containing the Beta version of SARS-CoV-2 strain B1.351 sequence resulted in Abs that blocked binding of multiple SARS-CoV-2 variant spikes to angiotensin-converting enzyme 2 (ACE2). Immunization of human ACE2 knock-in mice with this RBD construct in DDA/TDB yielded complete protection from intranasal challenge with SARS-CoV-2. In summary, the authors have produced a novel RBD-based protein vaccine formulation that elicits broad humoral and cellular immunity against SARS-CoV-2, which could be used in human clinical trials against COVID-19.

LXRα Inhibits Antiviral Response

In this Top Read, Song et al. (p. 1006) show how grass carp liver X receptor α (gcLXRα) inhibits antiviral responses to make fish more susceptible to grass carp reovirus (GCRV) infection. Grass carp liver cells that overexpressed gcLXRα had significantly higher viral titers of GCRV than the gcLXRα knockdown cells. However, gcLXRα did not interact directly with the GCRV protein, but bound to other proteins integral in the antiviral response. Type I IFN production was reduced by gcLXRα binding to both IRF3 and CBP, which inhibited the formation of the IRF3–CBP complex, necessary for IFN transcription. Heterodimers of gcLXRα and retinoid X receptor disrupted the RIG-I–like receptor antiviral signaling pathway. Together, these data demonstrate that gcLXRα inhibits antiviral responses, resulting in increased susceptibility to viral infections.

Shark UrIg Is a Nonrearranging Ag Receptor–like Gene



Previous studies examining the MHC-linked genes of cartilaginous fish identified an Ag receptor–like gene in the MHC class III region of catshark. In this Top Read, Flajnik et al. (p. 1042) characterized this gene, which they name "UrIg," and reported preliminary features of the UrIg protein. UrIg gene orthologs were identified in several shark genomes and full-length transcriptomes that contain domain features characteristic of Ig/TCR V genes, but lacked transmembrane exons, alternative splicing sites, and encoded cysteines that could stabilize a heterodimer of H and L chains. Recombinantly produced UrIg confirmed that the VC1C2C3 mRNA encodes a four-domain, disulfide-linked H chain. Dimeric UrIg was detected in many tissues, including spleen, thymus, and liver, and monomeric UrIg was found in the brain, though UrIg mRNA was mostly restricted to the liver. Immunohistochemistry experiments showed that UrIg protein is found in the extracellular matrix, suggesting that UrIg is produced in the liver and transported to other tissues through the circulation. Finally, phylogenetic analyses show that, whereas the VJ and C1 domains resemble Ag receptors, C2 and C3 domains cluster weakly to C domains of any other known Ig/TCR domain, suggesting, altogether, that UrIg is a primordial Ig of unknown function.

4-OI and DMF Induce Annexin A1 Secretion

Annexin A1 is a calcium-dependent phospholipid-binding protein that plays a role in the anti-inflammatory effects of glucocorticoids. In this Top Read, Diskin et al. (p. 1032) demonstrate that Krebs cycle metabolic derivatives, 4-octyl-itaconate (4-OI) and dimethyl fumarate (DMF), induce annexin A1 secretion in activated macrophages. Treatment with either 4-OI or DMF increased the secretion of annexin A1 in LPS-treated bone marrow–derived macrophages. However, neither endogenously produced itaconate nor fumarate showed similar effects. The 4-OI- and DMF-induced secretion of annexin AI was dependent on the transcription factor, NRF2, and the ATP binding cassette transporter A1 (ABCA1). In vitro, annexin A1 was present in the cytosol of macrophages with reduced expression of either NRF2 or ABCA1, but not in the culture supernatant. Finally, pretreatment of septic mice with 4-OI or DMF led to an increased serum level of annexin AI. These data show that annexin A1 availability can be enhanced through induced secretion rather than expression or transcription.

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