Top Reads

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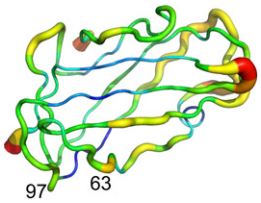
Introducing Top Reads

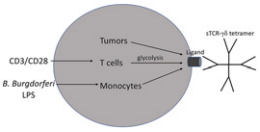
The Journal of Immunology is excited to announce that In This Issue is now Top Reads! This feature highlights a small number of manuscripts regarded by reviewers and editors as the top 10% in their field. If you are short on time, this section is a great way to preview some of the new and exciting articles in each issue!

From IgE Binding to Hypoallergenic Epitopes



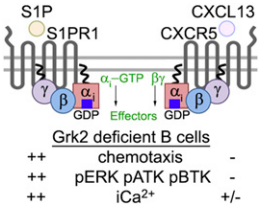
This Top Reads article features analysis of allergen epitope–Ab binding, in an effort to design hypoallergens with decreased IgE reactivity. Glesner et al. (p. 2545) investigate human Ab binding of the house dust mite allergen epitope Der p 2. Crystallography data of the Der p 2 in complex with an IgG single-chain variable fragment (mAb 7A1) revealed that epitope binding is mediated by H-bonds, hydrophobic interactions, and a cation-π interaction involving Lys^{96}. A conformational change upon Ab binding was observed using both crystallography and nuclear magnetic resonance (NMR). Based on this, the authors created two double mutants of Der p 2, Arg^{31}Ala-Lys^{33}Ala and Lys^{96}Glu-Ile^{97}Glu. Although these changes significantly decreased the ability of the mutants to bind mAb 7A1, the overall structures of the mutants were conserved relative to the wild type. Mutant epitopes also showed lower binding to plasma IgE from allergic patients, suggesting a similar reactivity profile between mAb 7A1 and human IgE. Therefore, this study provides a better understanding of allergen epitope binding and facilitates rational design of hypoallergens with reduced IgE activity, which may be used to mitigate adverse reactions in response to immunotherapy.

TCR-γδ: Are You My Ligand?



This Top Reads article demonstrates how γδ TCR (TCR-γδ) tetramers can be used in unbiased searches for TCR-γδ ligands. Although γδ T cells have been shown to play important roles in infection, autoimmunity, and cancer, their ligands remain elusive. To identify potential ligands, Collins et al. (p. 2369) cloned a soluble TCR-γδ (sTCR-γδ) from a synovial Vδ1 γδ T cell clone from a Lyme arthritis patient. The sTCR-γδ was tetramerized and validated via competitive and dose-dependent binding assays. Of the 24 tumor cell lines screened for sTCR-γδ tetramer binding, nine cell lines, all of epithelial and fibroblast origin, significantly bound sTCR-γδ tetramer. RNAseq was used to characterize the transcriptomes of the cell lines, and candidate genes were determined by comparing the data from tetramer-positive lines to tetramer-negative lines. Whereas immature monocytes and T cells displayed low sTCR-γδ tetramer binding, an increase in binding was observed upon maturation. sTCR-γδ was used to probe lysate from activated monocytes and identified 291 unique proteins. A comparison between the lysate proteins and the ligands identified from RNAseq revealed 16 common proteins, including Annexin A2 and heat shock protein 70, both previously proposed to be TCR-γδ ligands. Finally, the authors demonstrated that expression of TCR-γδ ligands was eliminated by trypsin, or by inhibition of transcription, translation, or endoplasmic reticulum–Golgi transport, suggesting proteins as likely TCR-γδ ligands. These data demonstrate an unbiased approach to identifying candidate ligands for human γδ T cells, allowing for a better understanding of their activation and function.

GRK2 Regulates B Cell Trafficking



Previous studies have implicated a role for G protein–coupled receptor kinase 2 (GRK2) as a central regulator of sphingosine-1-phosphate (S1P)R1 desensitization in B cells. In this Top Reads article, Hwang et al. (p. 2401) further examine the phenotype of mice specifically lacking GRK2 in B cells. These mice developed a severe immune phenotype characterized by a reduction of bone marrow-resident IgD^+ cells, splenomegaly with loss of white pulp and expanded red pulp, a deficit of Peyer patches, and small lymph nodes (LNs) containing reduced numbers of B cells. Excessive S1PR1 signaling and inadequate homeostatic chemokine receptor signaling was attributed to this phenotype, with CXCL13 being the most severely compromised. Administration of an S1PR1 antagonist to GRK2-deficient mice partially normalized the signaling defects and immune phenotype, as evidenced by B cell trafficking into LNs and splenic follicles. Together, these data reveal the dependence of $G\alpha_i$ signaling pathways in controlling B cell trafficking as well as immune organ architecture and function.

Innate Immunity in Allergies

Although allergic diseases are primarily mediated by type 2 allergen-specific responses, recent evidence suggests that innate immunity may also play a critical role in the pathogenesis of allergic diseases. In this Top Reads article, She et al. (p. 2520) sought to identify unknown innate immune stimulatory factors in environmental allergens.

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Among all allergens tested, only house dust mite (HDM) allergens, the most common aeroallergen, induced high levels of type III IFN transcripts. Further analysis demonstrated that HDM allergens containing a dsRNA species (HDM-dsRNA) activate a TLR3-mediated IFN response in vivo. TLR3 signaling was shown to counteract the development of exaggerated type 2 immune responses, as HDM-sensitized mice deficient in the dsRNA-sensing pathway displayed severe eosinophilia, elevated type 2 cytokines, mucus overproduction, and airway hyperreactivity when challenged with HDM. Conversely, administration of purified HDM-dsRNA at a low dose was sufficient to prevent the onset of severe type 2 lung inflammation. Collectively, these data report a previously unrecognized role for an allergen-associated dsRNA that modulates the severity of allergen-associated lung inflammation.