Guava® and Amnis®
Flow Cytometers
are Now Part of Luminex.

Luminex
complexity simplified.

In This Issue

J Immunol 2012; 189:2067-2068; ;
doi: 10.4049/jimmunol.1290046
http://www.jimmunol.org/content/189/5/2067

This information is current as of February 21, 2019.

Supplementary Material **http://www.jimmunol.org/content/suppl/2012/08/20/189.5.2067.DC1**

Why *The JI*? Submit online.

- **Rapid Reviews! 30 days*** from submission to initial decision
- **No Triage!** Every submission reviewed by practicing scientists
- **Fast Publication!** 4 weeks from acceptance to publication

**average*

Subscription Information about subscribing to *The Journal of Immunology* is online at: http://jimmunol.org/subscription

Permissions Submit copyright permission requests at: http://www.aai.org/About/Publications/JI/copyright.html

Email Alerts Receive free email-alerts when new articles cite this article. Sign up at: http://jimmunol.org/alerts

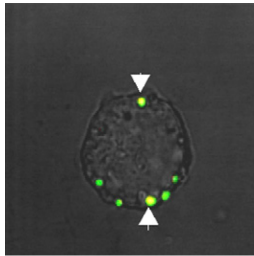
The Journal of Immunology is published twice each month by
The American Association of Immunologists, Inc.,
1451 Rockville Pike, Suite 650, Rockville, MD 20852
Copyright © 2012 by The American Association of
Immunologists, Inc. All rights reserved.
Print ISSN: 0022-1767 Online ISSN: 1550-6606.

Downloaded from http://www.jimmunol.org/ by guest on February 21, 2019

In This Issue

THE JOURNAL OF IMMUNOLOGY

Peptidoglycan Partners



The peptidoglycan (PGN) cell wall component of Gram-positive bacteria has been shown to bind to an unknown receptor and undergo phagocytosis and lysosomal degradation.This process generates NOD ligands that induce proinflammatory cytokine production. Sun et al. (p. 2423) now show that anti-PGN Abs are critical to inducing this cytokine response through a mechanism involving FcγRs. PGN was only able to bind to human neutrophils and monocytes in the presence of human plasma. They found that IgG from plasma was necessary and sufficient for PGN binding. Human plasma from healthy individuals had low but detectable levels of anti-PGN IgG. Treatment of neutrophils or monocytes with PGN combined with human plasma or IgG induced proinflammatory cytokine production, and this cytokine response required the presence of IgG. In contrast, F(ab′)2 fragments did not enable PGN binding or proinflammatory cytokine production, suggesting a role for the Fc region and FcγRs. Indeed, PGN internalization correlated with decreased expression of FcγRIII on neutrophils and FcγRII on monocytes. In addition, HEK293 cells transfected with FcγRIIa could bind and internalize PGN in the presence of human plasma. Together, these data provide evidence that PGN induces proinflammatory cytokine responses through a mechanism initiated by interactions with anti-PGN IgG and FcγRs.

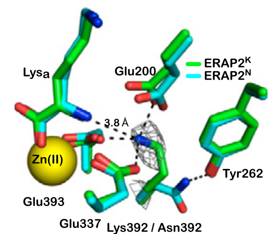
Neutrophils Nudge Sensitive Skin

Contact hypersensitivity (CHS) is a $CD8^+$ T cell-mediated response primed by skin sensitization with haptens. Recruitment of $CD8^+$ T cells to the skin site of hapten rechallenge requires prior neutrophil infiltration in response to increased CXCL1 and CXCL2 expression. Kish et al. (p. 2191) examine if expression of Fas ligand (FasL) and perforin by neutrophils is required for $CD8^+$ T cell recruitment during CHS. The FasL and perforin double-deficient *gld*/perforin$^{-/-}$ mouse strain did not develop CHS in response to sensitization and rechallenge with the hapten 2,4-dinitrofluorobenzene (DNFB), and practically no T cells were detected in the site of rechallenge relative to wild-type mice. In contrast, DNFB-primed $CD8^+$ T cells from *gld*/perforin$^{-/-}$ mice transferred into wild-type mice induced CHS upon DNFB challenge. DNFB rechallenge induced FasL and perforin expression in neutrophils but not DNFB-primed $CD8^+$ T cells in wild-type mice, suggesting a neutrophil-specific role for these proteins during $CD8^+$ T cell recruitment. Indeed, transfer of neutrophils from DNFB-sensitized and rechallenged wild-mice into *gld*/perforin$^{-/-}$ mice induced expression of the T cell chemoattractants CCL1, CCL2, and CCL5 at the site of DNFB rechallenge, and promoted $CD8^+$ T cell recruitment and CHS. These results better define the mechanism by which neutrophils influence T cell chemotaxis during CHS.

Multiplying in the Marrow

NK cells are an innate lymphocyte population critical to protection against viruses, but the mechanisms by which NK cells migrate and proliferate during respiratory virus infection are not well understood. Van Helden et al. (p. 2333) identified the bone marrow (BM) as the main site of NK cell proliferation using different respiratory virus infection models in mice. Intranasal influenza infection induced an influx of immature and mature NK cells into the airways of infected mice, but these NK cell subsets did not appear to proliferate. Instead, influenza infection was associated with a large increase in proliferation of both immature and mature NK cells in the BM. Mature NK cells transferred into naive congenic recipients underwent homeostatic proliferation in the BM and also proliferated in response to subsequent influenza or respiratory syncytial virus infection. Together, these observations reveal the BM as an important site of NK cell proliferation during respiratory virus infection.

Peptide Trimmer Troubles



Peptides presented by MHC class I (MHC I) molecules are generated from intracellular or endocytosed proteins through a series of proteolytic degradation steps involving the proteasome and vesicular or endoplasmic reticulum (ER)-localized aminopeptidases. ER aminopeptidase (ERAP) 1 and ERAP2 are involved in peptide trimming for Ag presentation. Population genetics studies have identified single nucleotide polymorphisms (SNPs) in ERAP1 and ERAP2 that are associated with an increased predisposition to some human diseases. Evnouchidou et al. (p. 2383) used biochemical and structural analyses to examine the effect of the common ERAP2 SNP rs2549782 on peptide trimming. This SNP codes for an N392K amino acid variation near the enzyme's active site. Biochemical analysis showed that the 392N allele excised N-terminal hydrophobic residues on peptide precursors at a significantly faster rate than the 392K allele. The faster excision rate was attributed to a difference in the catalytic turnover rate rather than substrate affinity. In addition, the 392N allele, but not the 392K allele, was able to complement ERAP1-mediated cleavage of N-terminal hydrophobic residues. Structural studies attributed the decreased catalytic efficiency of 392K to reduced stabilization of the

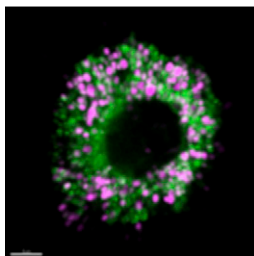
Copyright © 2012 by The American Association of Immunologists, Inc. 0022-1767/12/$16.00

www.jimmunol.org/cgi/doi/10.4049/jimmunol.1290046

Downloaded from http://www.jimmunol.org/ by guest on February 21, 2019

N-terminus of the peptide due to a disruption of interactions between amino acids that facilitate this enzymatic activity. Overall, these findings suggest that this ERAP2 polymorphism may contribute to human disease through its effect on Ag processing.

Exocytosis Exploration

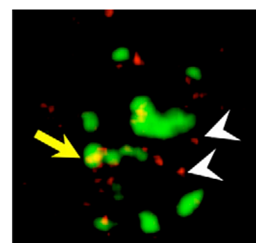


Two articles in this issue analyze the involvement of different GTPases in exocytosis.

The first article examines how mast cells release inflammatory mediators from secretory lysosomes through a tightly regulated exocytosis mechanism. The processes governing formation of lysosomes containing secretory granules and their subsequent exocytosis are not completely understood. Azouz et al. (p. 2169) assessed the contribution of Rab GTPases to exocytosis using a gain-of-function screen with constitutively active Rab GTPases coupled with a fluorescent exocytosis reporter in a mast cell line. Exocytosis was triggered by treatment with either FcεRI or a Ca^{2+} ionophore combined with a phorbol ester. Thirty Rab GTPases were identified as modulators of mast cell exocytosis, of which 26 had not been previously associated with this process. Rab GTPases that modulated exocytosis segregated into three different functional groups: Rab GTPases involved in secretory granule biogenesis, Rab GTPases that regulate transport through the endosomal recycling compartment, and Rab GTPases that coordinate the terminal events of exocytosis. Additional analysis showed that effects of some Rab GTPases of stimulus-dependent exocytosis required an intact actin cytoskeleton. Overall, these findings uncover a role for numerous Rab GTPases during mast cell exocytosis, which may provide insight into therapeutic targeting of mast cell responses.

The effect of cytoskeletal remodeling in mediating cytokine exocytosis by activated T cells is examined in the second article exploring exocytosis. Cytoskeletal remodeling occurs at the immunological synapse (IS) formed between T cells and APCs. Chemin et al. (p. 2159) used short-hairpin RNA (shRNA)-mediated silencing of the Rho GTPase Cdc42, a cytoskeleton rearrangement regulator, to assess its contribution to cytokine exocytosis in $CD4^+$ T cells. shRNA knockdown of Cdc42 significantly reduced secretion of IFN-γ upon T cell activation relative to control T cells expressing Cdc42. Although microtubule polymerization was required for cytokine secretion in T cells, microtubule organizing center (MTOC) polarity at the IS did not require Cdc42 and was not needed for IFN-γ secretion. shRNA silencing of Cdc42 did disrupt actin remodeling, which prevented formation of an actin ring at the IS and subsequent recruitment and exocytosis of IFN-γ–containing vesicles at this site. These results support a role for the GTPase Cdc42 in controlling actin-dependent cytokine exocytosis. Together, these studies highlight GTPase-dependent exocytosis as a mechanism used by multiple cells of the immune system to secrete key molecules.

Breaking through the Cell Cycle



B cell maturation involves generation of Ab diversity through class switch recombination (CSR) and somatic hypermutation, which require the activity of activation-induced cytidine deaminase (AID). AID causes double strand breaks (DSBs) in switch regions of the *Igh* locus to induce CSR during the G1 phase of the cell cycle, but recent evidence indicates that AID may also be causing DSBs on non-*Igh* (off-target) sites as well. Hasham et al. (p. 2374) examined the cell cycle dependency of AID-mediated off-target DSBs relative to AID-mediated DSBs in *Igh*. DSBs in off-target sites were generated during G1 and were still detected during S phase, during which they underwent DSB repair. Interestingly, off-target DSBs did not trigger the G1/S DNA damage checkpoint. *Igh* DSBs were also detected during S phase and underwent CSR. Taken together, these observations reveal a unique association between the cell cycle and DSB repair in response to AID activity on both *Igh* and non-*Igh* targets that suggest a mechanism that promotes CSR and protects against harmful chromosomal rearrangements.

Summaries written by Christiana N. Fogg, Ph.D.

Downloaded from http://www.jimmunol.org/ by guest on February 21, 2019