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In This Issue

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Related Content

Proteolysis Breaks Tolerance toward Intact α345(IV) Collagen, Eliciting Novel Anti–Glomerular Basement Membrane Autoantibodies Specific for α345NC1 Hexamers

J Immunol (February,2013)

Alport Alloantibodies but Not Goodpasture Autoantibodies Induce Murine Glomerulonephritis: Protection by Quinary Crosslinks Locking Cryptic α3(IV) Collagen Autoepitopes In Vivo

J Immunol (September,2010)

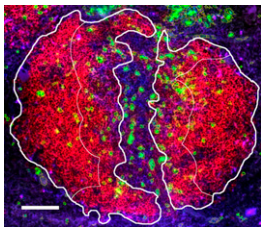
Murine Membranous Nephropathy: Immunization with α3(IV) Collagen Fragment Induces Subepithelial Immune Complexes and FcγR-Independent Nephrotic Syndrome

J Immunol (April,2012)

THE JOURNAL OF IMMUNOLOGY

In This Issue

TLR9 Tackles Tolerance



TLR9, an innate immune sensor of dsDNA, has been shown to both promote and regulate autoimmunity in several mouse models of systemic lupus erythematosus (SLE). Nickerson et al. (p. 1447) examined the role of TLR9 in establishing and breaking B cell tolerance. Using bone marrow chimeras of TLR9$^{-/-}$ SLE-prone mice and anti-DNA mAb transgenic mice, the authors demonstrated that TLR9 expression in B cells was essential for the production of anti-DNA autoantibodies in SLE-prone mice. TLR9 did not specifically promote autoreactivity, as the frequency of developing B cells expressing Vλ1, an L chain that promotes dsDNA binding, was unaffected by TLR9. However, TLR9 deficiency increased the proliferation of recirculating anergic mature B cells, but not immature B cells. TLR9 was required for the accumulation of anergic anti-DNA B cells and their maturation to Ab-producing cells within the splenic follicle and lymph nodes through the extrafollicular pathway. Although TLR9 enhances the generation of autoreactive Abs, a tolerogenic role for TLR9 was also observed as TLR9 did not alter the anergic state of autoreactive anti-DNA B cells in SLE mice, measured through BCR downregulation and Syk phosphorylation. Additionally, TLR9 contributed to the exclusion of anergic B cells in the follicle. Taken together, these results demonstrate important functions for TLR9 in both establishing and breaking B cell tolerance in a model of SLE.

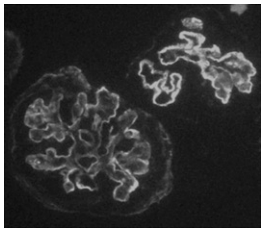
OmniRat to the Rescue!

Producing human monoclonal Abs (mAbs) for pharmaceutical use has become increasingly important as medicine turns to immunotherapy as a treatment or cure. However, previous methods, such as in vitro manipulation of human B cells or humanization of rodent mAbs, can be laborious and somewhat limited in scope. Hypothesizing that human Ab production could be more efficient in animals if the interaction between the human membrane IgH chain and host cell signaling machinery was improved, Osborn et al. (p. 1481) developed a humanized rat strain, OmniRat. The authors engineered OmniRat to carry a chimeric IgH locus that consisted of human IgH/Igκ/Igλ linked to the rat C_H region. These animals also carried a completely human IgL locus. To maximize the expression of human idiotypic Abs, the expression of endogenous Ig loci was blocked with specifically designed zinc-finger nucleases and the animals were bred to homozygosity. OmniRat animals had normal B cell numbers and produced high affinity serum IgG when immunized against several human Ags. The development of the OmniRat technology provides an exciting new source of high affinity human mAbs against a specific target Ag of choice, which may be useful for the creation of novel Ab-based therapies.

Certain Recombination

The vast diversity present in Ab repertoires is generated by V(D)J recombination, a process that includes the contraction and looping of *Ig* gene loci. Xiang et al. (p. 1819) discovered a novel *cis*-acting sequence that controls the contraction of the murine *Igκ* L chain locus. Named Cer, for contracting element for recombination, this 650 bp sequence within the *Igκ* V-J intervening region binds CCCTC-binding factor (CTCF), contains DNase I hypersensitive sites (HS1-2), and is responsible for locus contraction and Vκ gene use in pre-B cells. Targeting Cer for deletion resulted in preferential usage of proximal Vκ genes and less frequent usage of upstream Vκ genes compared with alleles in wild-type mice. In addition, more Igκ$^+$ B cells were found in the spleen and *Igκ* rearrangement was observed in T cells. Both wild-type and Cer-deleted mice had similar levels of Vκ germline transcription and H3K4me3 epigenetic marks. However, the Cer-deleted mice had much less locus contraction in their pre-B cells. Thus, the authors have identified Cer as a region necessary for controlling the looping and contraction of the *Igκ* locus, and potentially limiting rearrangement to the B cell lineage.

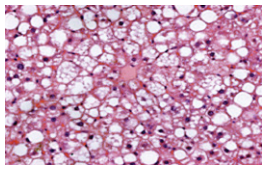
Noninflammatory Autoantibodies



Glomerulonephritis (GN), including that found in Goodpasture disease and Alport syndrome, is caused by an autoimmune response against kidney tissue, including the glomerular basement membrane (GBM). Goodpasture disease is characterized by rapidly progressive GN caused by autoantibodies to (noncollagenous domain) NC1 monomers of α3(IV) collagen. In this issue, Olaru et al. (p. 1424) have discovered a novel human anti-GBM IgG4 subclass-restricted autoantibody. This Ab was specific for α345NC1 hexamers, a proteolytic breakdown product of collagen α3NC1 monomers. What was unique about this Ab was that it bound GBM but elicited only a mild nonprogressive GN. Mice could be immunized with autologous murine GBM NC1 hexamers and also produce autoantibodies specific for α345NC1 hexamers that bound the GBM but did not cause disease. Further work with *Col4a3*$^{-/-}$ Alport and *COL4A3*-humanized mice led to the conclusion that tolerance developed for autologous intact α3α4α5(IV) collagen even in the presence of α345NC1 hexamer-specific autoreactive B cells. Alport syndrome GN is caused by mutations in the collagen *COL4A3*, *COLA4*, or *COLA5* genes, leading to a lack of tolerance to α3α4α5(IV) collagen and the production of inflammatory subclasses of

anti-α345NC1 IgG. By comparison, proteolysis in normal hosts reveals the autoimmunogenic epitopes of α3α4α5(IV) collagen hexamers eliciting an anti-α345NC1 response that is restricted to the noninflammatory, nonpathogenic IgG subclasses discovered by the authors.

The Galectin-9 Diet



Interactions between T cell Ig and mucin domain (Tim)-3 and its ligand, Galectin-9 (Gal-9), a β-galactoside–binding lectin, are crucial in immune regulation. Despite expression of TIM-3 on hepatic NKT cells which have a role in the pathogenesis of nonalcoholic fatty liver disease (NAFLD), the function of Tim-3/Gal-9 signaling has not been well established. In a mouse model of diet-induced NAFLD, Tang et al. (p. 1788) characterized Tim-3^+ NKT cells and showed that these cells had higher expression of CD25, elevated levels of IL-4 and IFN-γ, and higher in vitro proliferation rates compared with Tim-3^- NKT cells. Incubation of Tim-3^+ NKT cells with recombinant Gal-9 showed dose- and time-dependent apoptosis that could be blocked by anti–Tim-3 Ab or by a Gal-9 inhibitor. Mice fed a high fat (HF) diet, compared with a normal diet, showed an increase in Tim-3 expression on NKT cells that was associated with an increase in NKT apoptosis and the progression of steatosis. Interestingly, i.p. injections of Gal-9 significantly increased the frequency and proliferation of NKT cells in HF-fed mice. IL-15 has been shown to mediate the proliferative effects of Gal-9. The authors demonstrated an increase in IL-15 mRNA and protein levels in HF-fed mice that could be abolished by blocking IL-15. Gal-9 treatment in HF-fed mice limited steatosis and lowered body weight; this was NKT-dependent as the effects of Gal-9 were greatly diminished in a CD1 knockout mouse. In summary, the authors demonstrate a role for Tim-3/Gal-9 signaling in regulating hepatic NKT cell apoptosis and secondary proliferation, which contribute to the pathogenesis of NAFLD.

microRNA Masters Eosinophil Fate

Many microRNAs (miRs) are known to regulate the differentiation and lineage commitment of hematopoietic progenitor cells; however, the regulation of eosinophil progenitor cell differentiation by miRNAs has yet to be understood. Using ex vivo bone marrow eosinophil progenitor cell cultures, Lu et al. (p. 1576) observed an upregulation of miR-223 during eosinophil differentiation. Similar cultures from miR-$223^{-/-}$ mice showed an increase in eosinophilic progenitor cell proliferation. IGF1R, a receptor that promotes cell proliferation and inhibits apoptosis, is a known target of miR-223 and is significantly increased in miR-$223^{-/-}$ progenitor cell cultures. Inhibition of IGF1R completely reversed the increased eosinophil progenitor cell proliferation in miR-$223^{-/-}$ cultures. In addition, miR-$223^{-/-}$ progenitor cultures demonstrated a delayed upregulation of CCR3, a marker of mature eosinophils, suggesting that the increase in the progenitor cell population represented a delay in maturation. To confirm these observations, the authors compared microarray gene expression profiles of eosinophil progenitor cells expressing or lacking miR-223 on days 4, 8, and 12 of culture and saw that although early (day 4) progenitor cell growth was not dependent on miR-223, 33 genes were differentially expressed, including CCR3, on day 8. Taken together, these results demonstrate a role for miRs, specifically miR-223, in regulating the growth and differentiation of eosinophil progenitor cells.