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## In This Issue

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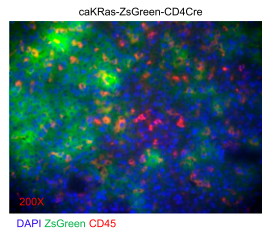
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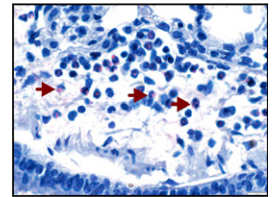
## When CD4Cre Strays off Target

The CD4Cre transgenic driver has been used widely to analyze T cell-specific gene function. In an effort to investigate how selective enhancement of KRas impacts T cell homeostasis and tolerance, Chen et al. (p. 1208) crossed the CD4Cre driver onto mice harboring a stop-floxed allele encoding constitutively active KRas (caKRas). Unexpectedly, the authors found expression of caKRas in alveolar macrophages (AMFs), alveolar epithelial cells (AECs), and bronchial epithelial cells (BECs) due to highly efficient Cre-mediated recombination in these cell populations. Subsequently, caKRas expression in these cells was associated with AMF accumulation in the lung, as well as AEC and BEC hyperplasia, culminating in multiple adenomas, loss of pulmonary function, and early lethality. Interestingly, AMFs, AECs, and BECs did not express detectable levels of the Cre protein, suggesting that the recombinase is either transiently expressed in these cells or is only expressed in their precursors. This study suggests that caution in data interpretation is warranted when using the CD4Cre transgenic driver for gene manipulation, as observed phenotypes may not be T cell-specific.



## Surfactant Protein Regulates Eosinophil Resolution in Asthma

Surfactant protein A (SP-A) is one of four related factors known to be important to airway inflammation. To better understand the contribution of SP-A and its allelic variants, Dy et al. (p. 1122) created a SP-A knockout (SP-A KO) mouse along with two strains that each express an allelic variant of SP-A (223Q and 223K). Using these mouse strains and an OVA-sensitization challenge protocol, they were able to show that SP-A is a chemoattractant. This was also confirmed with *in vitro* migration assays using physiological concentrations of SP-A. The chemoattractant ability of SP-A was also independent of allelic variation. The authors also found that SP-A from human donors who were homozygous for the Q allele could induce apoptosis in eosinophils and could rescue SP-A KO mice following aerosol challenge. Together, these data show the importance of SP-A in resolving eosinophilia and also provide insights into the impact of genetic variation on this process.



## Cytotoxic CD4<sup>+</sup> T Cells in Acute Viral Responses

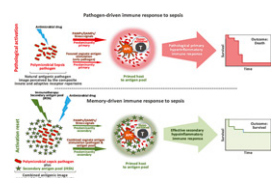
Cytotoxic CD4<sup>+</sup> T cells (CD4-CTLs) have been reported in chronic viral infections and have been thought to require chronic Ag exposure and progressive differentiation for acquisition of their unusual effector function. In this issue, Meckiff et al. (p. 1276) show that CD4-CTLs are generated during acute EBV infection, also known as infectious mononucleosis (IM). They found that peptide-MHC class II tetramer<sup>+</sup> CD4<sup>+</sup> T cells expressing perforin (Perf) and granzyme B (GzmB) were transcriptionally distinct from classical CD4-CTLs. Additionally, Perf/GzmB expression strongly correlated with CD38 expression in total CD4<sup>+</sup> T cells, as well as in the EBV-specific CD4<sup>+</sup> subset. The percentage of EBV Ag-specific CD4<sup>+</sup> T cells expressing Perf/GzmB was highest in the acute phase of infection. Although the percentage of Perf/GzmB<sup>+</sup> CD4<sup>+</sup> T cells decreased throughout the infection, EBV-specific T cells maintained function longer than the total CD4<sup>+</sup> T cell population. These data show that CD4-CTLs are induced early in chronic infection, but are not always maintained in long-term memory.

## Templated Mutagenesis in Murine and Human B Cells

Somatic hypermutation drives affinity maturation of Ag-specific Abs. Whereas chickens, sheep, and rabbits use gene conversion to diversify expressed Ig loci, mice and humans were thought to rely solely on untemplated somatic point mutations. In this issue, Dale et al. (p. 1252) demonstrate that somatic hypermutation in murine and human B cells use a gene conversion-like mechanism, referred to as templated mutagenesis, to generate somatic variants. This mechanism was shared among human IgM<sup>+</sup>/IgG<sup>+</sup>/IgA<sup>+</sup> CD138<sup>+</sup> plasmablasts. The authors observed linkage disequilibrium between mutations, which inversely relates to the genetic distance between those mutations. Templated mutagenesis also uses donors from variable segments 5' to the rearranged VDJ in both mice and humans, as well as from segments on the other allele. Finally, non-Ig sequences placed at the IgH locus mutate such that they share microhomology with tracts from the IgHV repertoire. Together, these studies indicate a role for templated mutagenesis during somatic hypermutation of murine and human B cells.

## Shifting the Balance in Sepsis Treatment

Sepsis is usually treated with combination of broad-spectrum, high-dose antimicrobials. However, these regimens are not always successful. In this issue, Nowill et al. (p. 1298) induce a shift in adaptive immunity that, in



addition to antimicrobial treatment, provides significant protection during sepsis. Therapeutic inoculation with Immune Response Shifter (IRSh), a combination of nine well-defined Ags against which most humans have preformed immune memory, was given to mice on days 0 and 4 following sepsis induction. Additionally, some IRSh-treated mice were given a course of the antibiotic imipenem. IRSh plus imipenem-treated mice showed a significant increase in survival compared with either treatment alone. T cell expansion was observed in the spleens of mice receiving imipenem alone, but a majority of these T cells, particularly the CD8<sup>+</sup> subset, was also CD69<sup>+</sup>, suggesting hyperactivation and

a proinflammatory response. Mice treated with both imipenem and IRSh showed a dramatic drop in the CD69<sup>+</sup> CD8<sup>+</sup> central memory T cells. Additionally, combination therapy reduced activation of naive T cell subsets. Proteomic analysis showed that proinflammatory mediators, molecules involved in cytokine storm, regulatory feedback proteins, and proapoptotic factors were differentially downregulated in surviving animals that received the combination treatment, compared with controls. Together, these data suggest a potentially improved sepsis treatment, in which patients could undergo systemic and repeated reactivation of established memory to reset unfavorable immune responses.