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In This Issue

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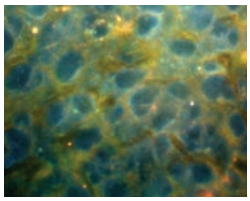
In this issue

RAGE against an immune response The receptor for advanced glycation end products (RAGE) is involved in the immune system's response pathways, but its specific role in the innate and adaptive immune response pathways remains unknown. Generation of mice devoid of RAGE and mice with tissue-specific expression of RAGE enabled Peter Nawroth and colleagues to study the function of this cell-surface receptor in these different immune response pathways (pages 1641–1650). Experimental autoimmune encephalomyelitis (EAE) was used to monitor the adaptive immune response. Although RAGE–/– mice responses were similar to those in wild type, RAGE overexpressing mice displayed an amplified reaction, indicating that RAGE is not required for the initiation of the adaptive immune response but is involved in the perpetuation of inflammation. Using the delayed-type hypersensitivity (DTH) model to monitor the responses to inflammation, the researchers found that RAGE–/– mice did not display reduced DTH inflammatory responses. This result is surprising given that previous studies have shown that the application of sRAGE, a soluble truncated form of the receptor that competes for RAGE ligands, did reduce inflammation. RAGE–/– mice were, however, protected from lethal septic shock during multibacterial peritonitis induction by […]

Thyrotropin receptor can be so insensitive

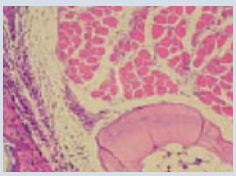
In Graves autoimmune disease, thyrotropin receptor (TSHR) antibodies bind to and stimulate TSHR, causing hyperthyroidism. Takao Ando and colleagues used a hamster antibody (MS-1) with TSHR-stimulating activity to characterize TSHR antibody pathogenesis mechanisms (pages 1589–1595). In an acute study using MS-1 injection in mice, they found a dose-dependent relationship between serum thyroxine and MS-1 antibody levels. In a chronic study, nude mice were injected with MS-1–secreting hybridoma cells, and although serum MS-1 levels were higher than in the acute study, serum thyroid hormone levels were similar to those in pretreatment controls. The authors confirmed that there was no loss of MS-1 bioactivity; thus, chronic stimulation of TSHR seemed to cause desensitization of the receptor. This conclusion was further supported by in vitro studies on TSHR-expressing Chinese hamster ovary cells. A dose-dependent loss of TSHR responsiveness in the presence of high concentrations of MS-1 was due to TSHR downregulation and loss of receptor function. This study provides one explanation for the poor correlation between serum TSHR-antibody concentration and thyroid function seen in Graves disease patients.

Silence of the *IL-12Rβ2*



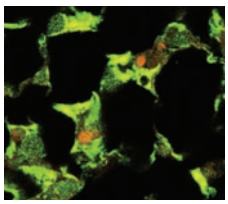
Human primary B cell tumors and transformed human B cell lines lack *IL-12Rβ2* transcript expression, but maintain *IL-12Rβ1* expression. Normal, naive, germinal center B cells and normal memory B cells constitutively express both *IL-12R* genes. Irma Airoldi and colleagues reasoned, therefore, that *IL-12Rβ2* gene silencing contributes to neoplastic B cell expansion (pages 1651–1659). They researched the role of methylation in silencing this gene and found that gene methylation occurred in transformed B cell lines. Treatment with 5-Aza-2′-deoxycytidine, a selective DNA methylase inhibitor, resulted in de novo expression of the *IL-12Rβ2* transcript in primary neoplastic B cells. Furthermore, these drug-treated cells underwent apoptosis in response to IL-12 treatment. Similarly, apoptosis was induced when *IL-12Rβ2* was transfected into transformed B cell lines and cells were treated with human recombinant IL-12 (hrIL-12). SCID-NOD mice injected with tumorigenic B cells expressing *IL-12Rβ2* and treated with hrIL-12 had tumors that were significantly smaller and less malignant than those in mice treated with PBS. *IL-12Rβ2* indeed acts as a tumor suppressor and aids IL-12 action as an antitumor agent.

RAGE against an immune response



The receptor for advanced glycation end products (RAGE) is involved in the immune system's response pathways, but its specific role in the innate and adaptive immune response pathways remains unknown. Generation of mice devoid of RAGE and mice with tissue-specific expression of RAGE enabled Peter Nawroth and colleagues to study the function of this cell-surface receptor in these different immune response pathways (pages 1641–1650). Experimental autoimmune encephalomyelitis (EAE) was used to monitor the adaptive immune response. Although *RAGE*$^{-/-}$ mice responses were similar to those in wild type, RAGE overexpressing mice displayed an amplified reaction, indicating that RAGE is not required for the initiation of the adaptive immune response but is involved in the perpetuation of inflammation. Using the delayed-type hypersensitivity (DTH) model to monitor the responses to inflammation, the researchers found that *RAGE*$^{-/-}$ mice did not display reduced DTH inflammatory responses. This result is surprising given that previous studies have shown that the application of sRAGE, a soluble truncated form of the receptor that competes for RAGE ligands, did reduce inflammation. *RAGE*$^{-/-}$ mice were, however, protected from lethal septic shock during multibacterial peritonitis induction by cecal ligation and puncture. This protection was lost in *RAGE*$^{-/-}$ mice crossed with overexpressing RAGE mice, emphasizing the critical role of RAGE in perpetuating the innate immune response.

Benefits of a PKCβ blockade



Ischemia/reperfusion (I/R) lung injury induces a slew of cellular pathways that lead to organ dysfunction and damage. Rapid activation of PKCβII occurs upon injury and affects several downstream targets. Shi-Fang Yan and colleagues explore the impact of PKCβII in I/R by subjecting *PKCβ*$^{-/-}$ mice and wild-type mice fed a PKCβ inhibitor to single-lung ischemia followed by reperfusion (pages 1615–1623). PKCβ inactivation by both gene deletion and pharmacological blockade protected mice from severe lung injury. Downstream effects of PKCβII activation that occur after I/R, such as ERK1/2 phosphorylation and *Egr-1* expression, were reversed in PKCβ-blocked mice. Proinflammatory/prothrombotic genes normally upregulated in I/R also showed decreased expression levels in the PKCβ-blocked mice. Activation of the AP-1 and NF-κB transcriptional pathways were also diminished. These results mark PKCβII as a central mediator of I/R pathobiology and a promising therapeutic target for I/R injury.