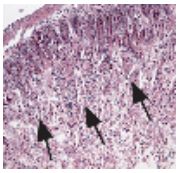
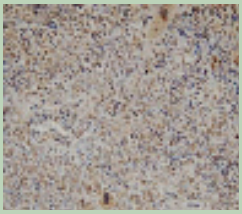
CO gives sepsis the heave-HO(-1)



The inflammatory phase of sepsis, characterized by a systemic response to infection, has life-threatening effects if left unchecked. However, therapies aimed at limiting inflammation have had little success and have the potential to hamper the antimicrobial immune response. In this issue (pages 239–247), Chung and colleagues have identified CO, generated by heme oxygenase-1 (HO-1), as a natural mediator of mouse host defense against sepsis-causing infections that does not modify the inflammatory response, making it a potential therapeutic for the treatment of individuals with sepsis. HO-1–deficient mice were more susceptible to the lethal effects of polymicrobial sepsis induced by cecal ligation and puncture (CLP) than were WT mice. In contrast, mice overexpressing human HO-1 (hHO-1) in vascular SMCs and intestinal myofibroblasts showed increased survival following CLP compared with WT mice. More specific analysis indicated that overexpression of hHO-1 did not alter the inflammatory response, but it did increase neutrophil phagocytosis of *Enterococcus faecalis* bacteria. Further studies demonstrated that HO-1–deficient mice administered a CO-releasing molecule did not show increased susceptibility to the lethal effects of CLP-induced sepsis and, more clinically relevant, WT mice administered the CO-releasing molecule after the onset of CLP-induced sepsis showed improved survival.

GPC1 facilitates tumor metastasis

The prognosis for individuals diagnosed with pancreatic ductal adenocarcinoma (PDAC) is poor, largely because diagnosis often comes after metastases have occurred. Establishing a role for the heparan sulfate proteoglycan glypican-1 (GPC1), which acts as a coreceptor for heparin-binding growth factors that drive the growth, metastasis, and angiogenesis of many types of human tumor, in facilitating the full mitogenic, metastatic, and angiogenic potential of human pancreatic cancer cell lines has led Aikawa and colleagues to suggest that targeting GPC1 might provide a new approach to treating individuals with PDAC (pages 89–99). In vitro analysis of a human pancreatic cancer cell line in which expression of GPC1 was downregulated using an antisense approach indicated a role for GPC1 in cell proliferation and anchorage-independent growth. Consistent with these observations, these cells showed reduced tumor growth, metastasis, and angiogenesis when transplanted into immunocompromised mice. A role for host GPC1 was also established, as pancreatic cancer cell lines expressing normal levels of GPC1 showed decreased tumor growth, metastasis, and angiogenesis when transplanted into immunocompromised mice lacking GPC1. In addition, fewer metastases were detected following the transplantation of a mouse melanoma cell line into immunocompromised mice lacking GPC1, indicating that the importance of GPC1 to tumor metastasis is not restricted to PDAC.



OutRAGEd by atherosclerosis

Perturbation of EC function is a crucial event in the initiation of atherosclerosis. Harja and colleagues have now revealed a role for RAGE (receptor for advanced glycation endproduct) in this triggering event as well as in the subsequent pathogenesis of atherosclerosis in a mouse model of the disease (pages 183–194). Both *apoE*$^{-/-}$ mice also lacking RAGE and *apoE*$^{-/-}$ mice engineered to express a dominant-negative form of RAGE (DN-RAGE) in ECs developed less severe atherosclerosis than *apoE*$^{-/-}$ mice. Decreased atherosclerotic disease was associated with a less dramatic loss of EC function and decreased vascular inflammation. Further analysis determined that JNK signaling downstream of RAGE activation by its ligands was important for RAGE to facilitate vascular inflammation. The relevance of these observations to human disease was highlighted by the demonstration that both ectopic expression of DN-RAGE and knockdown of RAGE expression in human aortic ECs prevented RAGE ligands from inducing EC dysfunction and JNK-mediated upregulation of VCAM-1, a crucial early event in the development of atherosclerosis.

Anticancer drugs boost fetal hemoglobin levels

Sickle-cell disease (SCD) is an inherited blood disorder caused by a point mutation in the β-globin chain of hemoglobin (Hb). Although hydroxyurea, a new SCD therapeutic that increases fetal Hb (HbF) expression, benefits some adults with moderate and severe SCD, it does not work for all individuals. In this issue (pages 248–258), Moutouh–de Parseval and colleagues have identified lenalidomide and pomalidomide, immunomodulatory anticancer drugs, as potent inducers of HbF in erythrocytes derived in vitro from CD34$^+$ cells isolated from both healthy individuals and patients with SCD. Detailed analysis identified the mechanism underlying these effects of pomalidomide — it increased transcription of the gene encoding the γ-globulin chain of Hb. At the cellular level, both drugs were more effective than hydroxyurea at inducing HbF expression by erythrocytes derived from CD34$^+$ cells from healthy individuals, and the effects of pomalidomide and hydroxyurea on HbF expression were synergistic. As pomalidomide was able to induce HbF expression in CD34$^+$ cells from patients with SCD, the authors suggested that it might provide a new therapy for SCD, either alone or in combination with hydroxyurea. Future studies are likely to evaluate the potential of pomalidomide as a therapy for other β-hemoglobinopathies, such as β thalassemia (a hereditary anemia caused by decreased β-globin production).