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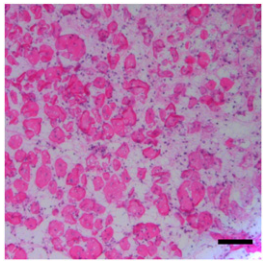
Nox2 Limits Monocyte Generation during Tissue Ischemia

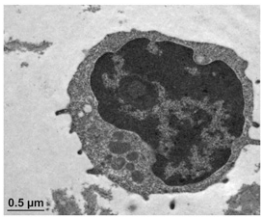


Repair of ischemic tissue damage is driven by activation of hematopoietic stem and progenitor cells (HSPCs) in the bone marrow (BM), resulting in the generation of myeloid cells. Reactive oxygen species (ROS) in the BM can regulate HSPC function, but a role for these labile molecules in monocyte generation following ischemic tissue damage is unclear. In this issue, Fang et al. (p. 2414) demonstrated that mice deficient in the NADPH oxidase 2 (Nox2 knockout [Nox2-KO]) had elevated proliferation and total numbers of lineage$^-$Sca-1$^+$c-Kit$^+$ (LSK) HSPC in the BM prior to and 3 d after induction of hindlimb ischemia. This was accompanied by a concomitant increase in the numbers of monocytes in the BM and tissues, and a reduction in tissue regeneration. Additional experiments revealed that hindlimb ischemia significantly increased reactive oxidants, such as hydrogen peroxide and 1-palmitoyl-2-arachidonoyl-*sn*-gylcero-3-phosphorylcholine, in the BM and plasma, which resulted in the activation of Lyn kinase in a Nox2-depedent manner. Interestingly, Nox2-sufficient neutrophils adoptively transferred into Nox2-KO mice reduced monopoiesis in the BM and blood during hindlimb ischemia and improved regeneration of ischemic muscles, suggesting an important role for the Nox2-ROS–Lyn kinase axis in neutrophils during tissue ischemia. Consistent with this, homing of neutrophils to the BM was increased 2 and 5 d after induction of tissue injury, and neutrophils homing to the BM exhibited significantly higher ROS levels than resident neutrophils, indicating that neutrophils returning to the BM likely contribute to ROS production. Together, these data suggest that Nox2 activity in the BM limits monocyte generation by HSPC to promote regeneration of damaged tissue and suggests a critical role for neutrophils in this process.

Activation of Dendritic Cells during Beryllium Exposure

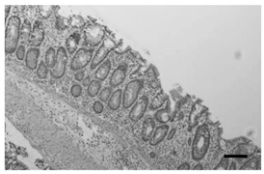
Chronic beryllium disease is a life-threatening metal-induced hypersensitivity. However, the innate immune mechanisms driving beryllium sensitization remain unclear. In this issue, Wade et al. (p. 2232) sought to determine the role of innate immune receptors TLR9 and IL-1R in mediating dendritic cell (DC) responses to beryllium. Ex vivo, alveolar macrophages exposed to $BeSO_4$ and $Be(OH)_2$ died, releasing DNA and IL-1α. In vivo, exposure of mice to $BeSO_4$ or $Be(OH)_2$ increased levels of DNA and IL-1α in bronchoalveolar lavage fluid (BALF) and the percentage of migratory DCs in lung-draining lymph nodes (LDLNs), compared with PBS controls. Cell-free soluble BALF from $Be(OH)_2$-exposed mice upregulated CD80 on wild-type (WT) bone marrow–derived DCs (BMDCs). DNA released from beryllium-exposed alveolar macrophages promoted TLR9-dependent upregulation of CD80 on BMDCs. In TLR9 knock out (TLR9KO) mice, the accumulation of DCs in the LDLNs following $Be(OH)_2$ exposure was partially reduced, but it was reduced to background levels in TLR9KO mice treated with anti–IL-1α Ab. Moreover, $Be(OH)_2$-induced upregulation of CD80 was reduced in TLR9KO mice treated with anti–IL-1α Ab compared with WT mice. Therefore, IL-1α and DNA play a redundant role in upregulation of CD80 on DCs following beryllium exposure. Together, these data demonstrate that $BeSO_4$ and $Be(OH)_2$ induce release of IL-1α and DNA from alveolar macrophages, which subsequently promotes migration of DCs to the LDLN via TLR9 and IL-1R activation, thus enhancing beryllium sensitization.

Hepatitis B Virus Inhibits TLR9



Previous work demonstrated that hepatitis B virus (HBV) inhibits TLR9 in plasmacytoid dendritic cells, but the impact of HBV on TLR9 signaling in B cells is unknown. In this issue, Tout et al. (p. 2331) showed that primary human B cells treated with HBV experienced a loss of TLR9 expression. Naive and CD27$^+$ memory B cells, as well as plasma cells, exposed to HBV experienced a loss of TLR9 expression and this effect was reversed using blocking anti-hepatitis B surface (HBs) Ab. Furthermore, HBV-mediated loss of TLR9 expression reduced proliferation and cytokine secretion, but increased Ig production in human B cells. Mechanistically, deletion of the cAMP responsive element (CRE) within the TLR9 promoter in a B cell line eliminated the inhibitory effect exerted by HBV. Specifically, HBV inhibited CREB phosphorylation to prevent its binding on the CRE site on the TLR9 promoter. The data were corroborated using HBV viral components (HBsAg and HBeAg) and primary B cells: HBsAg and HBeAg decreased TLR9 promoter activity comparably to HBV, whereas Dane particles (HBV virions) had a minor effect on TLR9 levels. TLR9-mediated B cell proliferation also was reduced in chronic hepatitis B patients, compared with the control group. Finally, mRNA expression of BCL-2, which is a downstream target of the CRE/CREB pathway, was reduced in patients, confirming the involvement of the CRE/CREB pathway in TLR9 downregulation. Taken together, these data demonstrate that HBV inhibits TLR9 function in human B cells.

Cross-Talk between Neutrophils and Intestinal Epithelial Cells



Previous work demonstrated that amphiregulin (AREG) plays a role in intestinal immune homeostasis. However, we know little about the mechanisms regulating AREG production by intestinal epithelial cells (IEC). In particular, it is not known whether neutrophils contribute to intestinal homeostasis by regulating IEC AREG expression. Thus, Chen et al. (p. 2492) examined the impact of neutrophil-derived factors on AREG production by IEC. Culture of intestinal epithelial enteroids, a three-dimensional primary culture system, in the presence or absence of neutrophil conditioned medium differentially regulated expression of genes implicated in IEC proliferation, differentiation, and junction formation, and upregulated AREG transcription. Administration of exogenous recombinant AREG conferred epithelial protection in a dextran sodium sulfate (DSS)-induced colitis model. However, neutrophil-depleted mice receiving AREG treatment experienced less severe systemic disease, compared with control neutrophil-depleted mice. Consistent with previous reports, treatment of mouse small intestinal epithelium (MSIE) cells with TGF-β increased AREG expression. When TGF-β was depleted in neutrophil conditioned medium prior to application to MSIE cell cultures, AREG production by MSIE cells was reduced. Therefore, neutrophil-derived TGF-β contributes to AREG production by IECs. In the presence of MEK selective inhibitors or small interfering RNA–mediated MEK1/2 silencing in IECs, AREG expression induced by TGF-β was decreased, indicating that MEK1/2 is required for this process. These data reveal a role for neutrophils in regulation of intestinal inflammation through induction of AREG by IECs, which, in turn, is dependent on TGF-β production by neutrophils.

Enhancing Anti–PD-L1 Responses with Chemotherapy

Clinical researchers are currently testing whether the addition of chemotherapeutic agents to treatment protocols will increase the efficacy of checkpoint inhibitors, such as anti–PD-L1. In this issue, Cubas et al. (p. 2273) explored the impact of different chemotherapies on immune responses generated by anti–PD-L1 in a murine syngeneic tumor model. Treatment of tumor-bearing mice with anti–PD-L1 increased the number of activated effector $CD8^+$ T cells in both the tumor and the draining lymph nodes (dLN) with a concomitant reduction in tumor size. When given as a single agent or in combination with anti–PD-L1, analogs of platinum and taxane class chemotherapeutics reduced both $CD4^+$ and $CD8^+$ T cell numbers, as well as $CD8^+$ T cell activation in peripheral tissues. In contrast, addition of chemotherapeutics either had no impact or increased the numbers of activated intratumoral $CD8^+$ T cells, demonstrating that the combination effect is dependent on preservation of the tumor-infiltrating lymphocyte (TIL) phenotype. Consistent with this, blockade of T cell egress from dLN during treatment had minimal impact on the activity of single agent or combination therapy, confirming that tumor responses to anti–PD-L1 are dependent on TILs at the time of treatment initiation. Combination of anti–PD-L1 and chemotherapies with known immune modulatory effects, such as cyclophosphamide and gemcitabine, greatly enhanced the antitumor activity of anti–PD-L1, but showed different effects on TILs. Addition of cyclophosphamide increased both numbers and activation of intratumoral $CD8^+$ T cells, whereas gemcitabine decreased $CD8^+$ T cell numbers and activation. Further analysis demonstrated that gemcitabine decreased suppressive macrophages, which likely outweighed the decrease in CTLs by reducing their response threshold, allowing fewer CTLs to control tumor growth. In summary, this study suggests that combining immunotherapeutic agents with chemotherapy is agent-specific and dependent on the tumor microenvironment at the time of treatment initiation.