The American Journal of Pathology, Vol. 181, No. 1, July 2012

http://dx.doi.org/10.1016/j.ajpath.2012.05.004

This Month in *AJP*

HMGB1 Promotes NSAID-Induced Intestinal Damage

Damaged cells release high-mobility group box 1 (HMGB1), activating inflammatory pathways via Toll-like receptors (TLRs) 2 and 4 and advanced glycation end products (RAGE). Nadatani et al (**Am J Pathol 2012, 181:98–110**) examined the role of HMGB1 in small intestinal damage induced by nonsteroidal anti-inflammatory drugs (NSAIDs), such as indomethacin. In wild-type mice, recombinant human HMGB1 aggravated indomethacin-induced small intestinal damage and enhanced mRNA expression of inflammatory cytokines and intracellular signaling molecules. Blocking HMGB1 with neutralizing antibodies prevented these effects. TLR2- and RAGE-knockout mice were highly sensitive to indomethacin, whereas TLR4-knockout mice exhibited less severe intestinal damage, reduced TNF-α mRNA expression, and no added effect from exogenous HMGB1. Thus, HMGB1 appears to promote NSAID-induced small intestinal damage via TLR4-dependent signaling.

Linking Osteoporosis and Bone Marrow Failure after Pneumocystis *Infection*

Aside from susceptibility to opportunistic infections such as *Pneumocystis*, unexplained complications in HIV$^+$ and AIDS patients include osteoporosis and bone marrow failure, respectively. Wilkison et al (**Am J Pathol 2012, 181: 151–162**) evaluated the potential connection between these bone pathologies following *Pneumocystis* lung infection in mice lacking both lymphocytes and type-I IFN receptor (IFrag$^{-/-}$). *Pneumocystis* infection accelerated osteoclastogenesis as bone marrow failure progressed in these mice, consistent with induction of RANKL, TRAIL, and osteoprotegerin in the bone marrow of infected IFrag$^{-/-}$ mice. Biphosphonate treatment of IFrag$^{-/-}$ mice prevented bone loss and loss of hematopoietic precursor cells, which maintained activity *in vitro*; however, it did not prevent loss of mature neutrophils. Thus, deregulation of the RANKL/OPG/TRAIL axis—which is also deregulated in HIV$^+$ individuals—connects the bone loss and bone marrow phenotypes in this model.

VLPs Protect Against MRSA

Priming the lung environment in anticipation of future lung infections could provide an important novel therapy for emerging infectious diseases. To test this, Rynda-Apple et al (**Am J Pathol 2012, 181:196–210**) administered virus-like particles (VLPs) to mice before, or immediately after, lethal challenge with methicillin-resistant *Staphylococcus aureus* (MRSA). This protocol provided complete recovery from lung infection and near absolute clearance of bacteria within 12 hours, reduced host response-induced lung tissue damage, promoted recruitment and efficient bacterial clearance, and protected macrophages from MRSA-induced necrosis. Complete recovery occurred in VLP-dosed SCID mice but not in wild-type mice depleted of either Ly6G$^+$ or CD11c$^+$ cells. Early IL-13 production was also essential for protection. These results provide important insights into host anti-MRSA response mechanisms and suggest that VLPs could be a viable means of enhancing these mechanisms.

Novel Axis Joins Stromal Cav-1 and mTOR Signaling

To examine the effects of aging on mammary tumor growth, Mercier et al (**Am J Pathol 2012, 181:278–293**) used Cav-1 knockout (KO) mice as a model of accelerated host aging. Mammary tumor cells were orthotopically implanted into age-matched young female Cav-1$^{+/+}$ and Cav-1$^{-/-}$ mice. Tumors grown in Cav-1 KO mammary fat pads were significantly larger and showed increased stromal content, including a proliferative stroma with hyperactivated mTOR signaling. Systemic rapamycin treatment of mammary tumors grown in a Cav-1 KO microenvironment significantly inhibited tumor growth, decreased stromal content, and reduced the levels of both vimentin (oxidative stress marker) and phospho-S6 (aging marker) in Cav-1 KO cancer-associated fibroblasts. These results using Cav-1–deficient mice as a pre-clinical model may have important translational significance for the diagnosis and the therapeutic stratification of breast cancer patients.

Stem Cells Contribute to Vessel Graft Restenosis

Neointimal lesions commonly occur in artificial vessel grafts used to treat occluded blood vessels. To clarify the cell types involved, Tsai et al (**Am J Pathol 2012, 181:362–373**) established a novel mouse model of restenosis by grafting a decellularized vessel to the carotid artery. Grafts developed neointimal lesions that contained endothelial (ECs) and smooth muscle cells (SMCs), monocytes, and stem/progenitor cells. In stem cell medium, explanted cultures of neointimal tissues displayed heterogeneous outgrowth, expressed c-kit, Sca-1, and CD34, and showed clonogenic and multilineage differentiation capacities. Sca-1$^+$ cells could differentiate *in vitro* into ECs and SMCs in response to VEGF or PDGF-BB. *In vivo* local application of VEGF to decellularized vessels directed EC differentiation. Consequently, reduced SMC accumulation was observed, and the rate of neointimal formation was markedly reduced. Improved understanding of the cell types involved, together with the novel model system, may yield effective tools in the prevention or delay of restenosis.