Macrophages Modulate Myocardial Healing

Macrophages may promote fibrosis by interacting with fibroblasts. Using the established angiotensin II (AngII) mouse model, Falkenham et al (Am J Pathol 2015, 185:927-942) studied the role of infiltrating macrophages in the development of myocardial fibrosis. Depletion of monocytes via administration of clodronate liposomes during AngII infusion significantly reduced macrophage infiltration and fibrosis in the heart independent of blood pressure. However, inhibiting nonclassical M2 macrophage migration in AngII/Cx3cr1<sup>−/−</sup> mice resulted in increased macrophage infiltration and fibrosis, as well as an M1 phenotype shift. The M1 shift up-regulated pro-inflammatory cytokines, such as tumor necrosis factor α and IL-1β, and decreased anti-inflammatory mediators, such as transforming growth factor β. Macrophages, such as M2, may offer protection and prevent excessive tissue injury.

miR-155 Enhances Fas-Induced Liver Injury

Both miR-155 and Fas-induced apoptosis have been implicated in liver diseases. Chen et al (Am J Pathol 2015, 185:1033-1044) further probed the role of miR-155 in Fas-induced liver injury by giving mice Jo2 anti-Fas antibody to induce hepatocyte injury. Mir155 knockout (KO) mice showed extended survival and decreased liver tissue damage, apoptotic hepatocyte numbers, and Fas-induced caspase activation in liver tissue compared to wild-type mice. Cultured hepatocytes from Mir155 KO mice resisted Fas-induced apoptosis. Mcl1 was identified as a direct target of miR-155 in hepatocytes, and hepatocytes with Mir155 deletion expressed more myeloid cell leukemia-1 protein. Pretreatment with Mcl1-specific siRNA reversed the protection against Fas-induced hepatic injury in Mir155 KO mice whereas restoration of Mir155 expression in Mir155 KO mice enhanced Fas-induced apoptosis in hepatocytes. Inhibiting miR-155 may aid in the management of Fas-induced hepatic injuries and liver diseases.

FOXO1 Deletion Contributes to Periodontitis

The host response in periodontitis represents both protective and destructive forces. Using dendritic cell (DC) lineage-specific FOXO1-deleted mice, Xiao et al (Am J Pathol 2015, 185:1085-1093) investigated the role of transcription factor FOXO1 in the activating adaptive immune response in oral pathogen-induced periodontal disease. DC FOXO1-deleted mice displayed reduced recruitment of DCs to oral mucosal epithelium, DC expression of IL-12 in mucosal surfaces, and ability of DCs to stimulate an adaptive immune response. Reduced DC function enhanced vulnerability to periodontitis via a mechanism mediated by a compensatory increase in the osteoclastogenic factors, IL-1β, IL-17, and RANKL. FOXO1 expressed in DCs may be necessary for a protective humoral immune response.

MED15 May Predict Recurrence of Head and Neck Cancers

SMAD-dependent transforming growth factor (TGF)-β signaling is frequently altered in head and neck squamous cell carcinoma (HNSCC) with active SMAD signaling correlating with poor survival. Shaikhbrahim et al (Am J Pathol 2015, 185:1114-1122) explored the involvement of mediator subunit MED15, which is critical for TGF-β signaling and has been implicated in other cancers. SMAD-dependent TGF-β activity correlated with MED15 expression in patient tissue samples. MED15 was over-expressed in primary tumors, lymph node metastases, and recurrences compared to no or low expression in all benign tissues. MED15 overexpression in recurrences correlated with high mortality rate, with the greatest frequency occurring in oral cavity and oropharyngeal tumors. MED15 expression also correlated between primary tumors and corresponding lymph node metastases. In cultured HNSCC cell lines, MED15 knockdown reduced proliferation and migration. MED15 may serve as a prognostic marker and therapeutic target for recurrences in HNSCC patients.

Myeloid ADAM10 Shifts Plaque Phenotype

Expression of the metalloprotease ADAM10 is associated with atherosclerotic plaque progression. Van der Vorst et al (Am J Pathol 2015, 185:1145-1155) examined the causal role of ADAM10 in atherosclerosis by transplanting bone marrow from conditional knockout mice lacking Adam10 in the myeloid lineage into lethally irradiated atherogenic mice. Although total plaque size was not affected, myeloid Adam10 deficiency enhanced plaque stability by increasing fibrosis and reducing relative macrophage content in the plaque. In vitro, Adam10 deficiency promoted an anti-inflammatory phenotype in macrophages, dampened pro-inflammatory responses of macrophages, and decreased the matrix-degrading and migration capacities of the macrophages. Myeloid ADAM10 may diminish atherosclerotic plaque stability by shifting the balance from fibrosis toward inflammation.