Journal Pre-proof

This Month in AJP

PII: S0002-9440(24)00002-6
DOI: https://doi.org/10.1016/j.ajpath.2024.01.001
Reference: AJPA 4020

To appear in: The American Journal of Pathology

Received Date: 5 January 2024
Accepted Date: 5 January 2024

Please cite this article as: This Month in AJP, The American Journal of Pathology (2024), doi: https://doi.org/10.1016/j.ajpath.2024.01.001.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Copyright © 2024 Published by Elsevier Inc. on behalf of the American Society for Investigative Pathology.
This Month in AJP

Modeling Nonalcoholic Steatohepatitis
The lack of preclinical animal models limits development of interventions for nonalcoholic steatohepatitis (NASH). Using primary human hepatocytes and non-parenchymal liver cells from healthy or NASH donors, Tan et al (Am J Pathol, AJPA-D-23-00393) developed a three-dimensional bioprinted liver tissue model of NASH with diseased, healthy, and chimeric tissues. The bioprinted tissue from cells from patients inherently exhibited a NASH phenotype. Chimeric bioprinted tissue implicated hepatic stellate and liver sinusoidal endothelial cells in disease progression. This preclinical organoid model may help identify clinically active targets to design therapies to combat NASH.

Reducing Hepatic Inflammation
Activation of vitamin D receptor (VDR) in hepatocytes protects against cholestatic liver injury. Using cultured cells and a mouse model, Wen et al (Am J Pathol, AJPA-D-23-00644) studied the underlying mechanisms. VDR agonist, PAL, activated macrophage autophagy by inhibiting activation of the ROS-p38-MAP kinase pathway, which further suppressed inflammasome-generated cleaved, active forms of interleukin-1β, eventually resulting in reduced inflammation. VDR may be targeted to treat cholestatic liver disease.

Understanding Lung Inflammation
Treatment options are limited for patients suffering from chronic respiratory viral infection. mTORC1 inhibitor, Rapamycin can enhance inflammation resolution during active influenza viral replication; however, its use in post viral clearance is unclear. Using a mouse model of severe viral lung infection, Huckestein et al (Am J Pathol, AJPA-D-23-00550) studied its efficacy post viral clearance. Mice were treated with rapamycin on days 12 to 20 post viral infection, corresponding to virus clearance time. Rapamycin treatment decreased lung inflammation as well as the frequency of exudate macrophages, T cells, and B cells in the lung. Rapamycin administration may help manage post-viral chronic lung inflammation.

Reducing Trauma-Induced Heterotopic Ossification
mTOR has been implicated in chondrogenic and osteogenic processes of heterotopic ossification (HO); however, the underlying mechanisms remain unknown. Using mouse cell cultures and a mouse model of trauma-induced HO, Mao et al (Am J Pathol, AJPA-D-23-00403) studied the upstream pathways. Overactive insulin-like growth factor 1 (IGF-1) promoted HO progression in mice. IGF-1/IGF-1 receptor (IGF-1R) activated PI3K/Akt signaling, which promoted the phosphorylation of mTOR that resulted in the chondrogenic and osteogenic differentiation of
tendon-derived stem cells into chondrocytes and osteoblasts *in vitro* and *in vivo*. IGF-1R, PI3K, and mTOR inhibitors mitigated HO formation. Targeting IGF-1 signaling cascades may help manage HO.

**Preventing Corneal Scarring**

Corneal scarring can result in blindness. Using mouse models of corneal neovascularization and fibrosis, Cao et al (Am J Pathol, AJPA-D-23-00579) tested the potential of a small molecule inhibitor of galectin-3, GB1265, in preventing corneal scarring. Topical application of GB1265 decreased corneal angiogenesis, corneal fibrosis, immune cell infiltration, as well as the expression of proinflammatory cytokine, interleukin-1β, in injured corneas. GB1265 application reduced corneal opacity and helped identify associated fibrosis promoting genes and signaling pathways. Topical application of GB1265 may reduce corneal angiogenesis and corneal fibrosis.