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EDITORIAL

In focus in HCB

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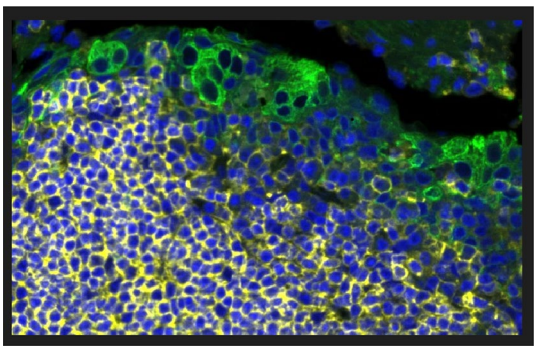

In this month's editorial, we highlight one original contribution describing studies aimed at characterizing the role of Su (var) 3–9, an enhancer of seste, trithorax (SET)-domain bifurcated histone lysine methyltransferase (SETDB1) during epithelial regeneration and remodeling using an ischemia/reperfusion injury mouse model. We also highlight a review article on tumor heterogeneity and the tumor microenvironment. We hope you enjoy these highlights and peruse the other manuscripts published in this issue as well.

Histone methylation and intestinal ischemia reperfusion injury

Intestinal ischemia reperfusion injury (IRI) is a life-threatening clinical condition (Acosta 2010). During the course of the ischemia and reperfusion, the intestinal mucosa undergoes distinctive degenerative and regenerative changes, which are accompanied by epigenetic modifications and transcriptional alterations (Eltzschig and Eckle 2011; Tang and Zhuang 2019). In their present work on mice, Ikenoue and coauthors (2024) have investigated the likely significance of histone methylation during epithelial regeneration after IRI. They focused on SETDB1, a histone H3K9-specific methyltransferase (Markouli et al. 2021), which is important for maintaining intestinal stem cell homeostasis (Južnić et al. 2021). Ischemia was induced in a segment of the distal ileum by occluding the peripheral branches of the superior mesenteric artery for 75 min (Gubernatorova et al. 2016) followed by reperfusion for 3, 24, and 48 h. By light microscopy, the epithelial repair was completed after 48 h of reperfusion. Quantitative immunohistochemistry for SETDB1 revealed an increase of positive cells after 24 h of reperfusion (twofold in crypts and fourfold in villi) and return to control levels after 48 h of reperfusion. Immunohistochemistry for histone H3K4, H3K9, H3K27, H3K36, and 79me3 showed a dramatic decrease in the trimethylation status at 24 h of reperfusion. Furthermore, crypt elongation, together with increased number of Ki-67-positive cells, indicated active cell proliferation. Additional immunohistochemistry demonstrated a reduction of stem cells in the crypts as well as a deficiency of Paneth and goblet cells and ectopic expression of Muc2 in the crypt bottom. These observations led the authors to conclude that SETDB1 plays a role during epithelial regeneration after IRI, which involves epigenetic transcriptional regulation. In another set of experiments, the effect of sinefungin, a SET-domain containing histone methyltransferase inhibitor, was studied. The inhibitor was administered intraperitoneally (10 mg/kg/day) for two consecutive days before the experiment and immediately following 75 min of ischemia. The inhibitor treatment improved the histone methylation status during IRI, generally prevented the appearance of the IRI-associated morphological changes, and maintained crypt cell proliferation. Together, this work in mice demonstrated a role of SETDB1 during the regenerative phase of IRI and that the methyltransferase inhibitor

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sinefungin may have therapeutic potential in ischemic bowel disease.

It is all about the (micro)environment

Much interest has been focused recently in the critical role played by the tumor microenvironment (TME) in tumor heterogeneity and targeted therapy (Junttila and de Sauvage 2013; Roma-Rodrigues et al. 2019). Indeed, with the rapid development of multiple "spatial omics" and highly multiplexed immunostaining techniques, the ability to morphologically map both the transcriptome and limited proteome to specific cells and regions within tumors and their surrounding TME has begun to reveal keen insights into these complex cellular and extracellular interactions (Barkley et al. 2022; Lewis et al. 2021; Phillips et al. 2021; Viratham Pulsawatdi et al. 2020; Wang et al. 2021). In the current issue of the journal, Imodoye et al. (2024) have provided a detailed and very well written review concerning the models proposed for the origins of tumor heterogeneity and the potential role of the TME in driving this heterogeneity, as well as implications for patient therapy. They begin with describing several tumor heterogeneity models, including the clonal evolution theory, the cancer stem cells theory, and the role of TME. Within the section on the TME, subsections discuss the contribution of the following specific components to overall tumor heterogeneity: (1) cancer-associated fibroblasts; (2) immune cells, including macrophages, T cells, natural killer cells (NK cells), and dendritic cells; (3) vasculature and angiogenesis; and (4) extracellular matrix (ECM; mainly composed of collagen, fibronectin, laminin, hyaluronic acid, and matrix metalloproteinases). These sections are followed by a discussion of the role of these ECM components, including importantly cancer-associated fibroblasts, on possible cancer therapeutic resistance. Next, the authors review recent evidence supporting the influence of tumor heterogeneity on the immune response (immune surveillance) of the host and then discuss techniques used to analyze tumor heterogeneity, including single-cell sequencing (especially single-cell RNA-seq), single-cell proteomics (flow cytometry and mass spectrometry), and spatial transcriptomics (see above). Finally, the review highlights descriptions of emerging immunotherapies for combating tumor heterogeneity. Sections illustrate published results using: (1) adoptive cell therapies (ACT), including tumor-infiltrating lymphocytes (TILs), transgenic T-cell receptor (tgTCR)-modified T cells (tgTCR-T cells), chimeric antigen receptor (CAR)-modified T cells (CAR-T cells), and unmodified or modified innate immune cells; (2) polyclonal T-cell therapy; and (3) patient-specific cancer (mainly neoantigen) vaccines. The review contains several detailed drawings nicely illustrating the concepts presented therein and concludes with a section featuring overall conclusions and future perspectives for investigating the role of the TME in overall tumor heterogeneity and the consideration for patient therapeutic options.

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