LIVER

Decoding hepatocyte ploidy

A new study finds that diploid hepatocytes proliferate faster than their polyploid counterparts, suggesting that polyploid status functions as a growth suppressor in the liver. The data inform research on liver oncogenesis and regeneration.

Polyploid hepatocytes represent >50% of the hepatocyte population in human livers, but the roles of diploid and polyploid cells in homeostasis and disease are not fully understood. Research has been hampered by a dearth in suitable animal models and the ability of hepatocytes to change their ploidy status during proliferation.

In a new paper, Wilkinson et al. used mice with liver-specific *E2F7* and *E2F8* double-knockout (LKO), which are functionally comparable to control animals. Measuring hepatocyte ploidy status, livers from LKO mice contained 20-fold more diploid and 3-fold fewer polyploid hepatocytes than those of control mice. In contrast to other settings, polyploidy in hepatocytes has been suggested to be protective against tumorigenesis. Indeed, using a diethylnitrosamine–phenobarbital liver tumour model, the researchers found profuse tumour formation in LKO mice but not in control mice livers. In a transplantation experiment, the team noticed that LKO hepatocytes repopulated livers faster than control hepatocytes. Further testing showed that control hepatocytes were outcompeted by faster-proliferating LKO hepatocytes.

To avoid confounding effects of the LKO, the team analysed proliferation of wild-type hepatocytes and found that diploid cells entered and progressed through the cell cycle faster than polyploid cells in vitro and in vivo. Finally, the team tested whether ploidy status altered sensitivity to growth factors, finding similar responses in both diploid and polyploid hepatocytes.

Clemens Thoma

ORIGINAL ARTICLE Wilkinson, P. D. et al. The polyploid state restricts hepatocyte proliferation and liver regeneration. *Hepatology* https://doi.org/10.1002/hep.30286 (2018)

INTESTINAL TRACT

Endocannabinoids counterbalance intestinal inflammation

Transepithelial migration of neutrophils is a key event in the induction of intestinal inflammation. Now, a pathway involving the intestinal secretion of endocannabinoids to counterbalance this process has been described, which could lead to new therapeutic strategies for IBD.

Understanding how intestinal epithelial cells control inflammation at mucosal surfaces is crucial for treating IBD. "We previously established that epithelial cells secrete the eicosanoid lipid hepoxilin A_3 (HxA_3) via the surface efflux pump MRP2, resulting in migration of neutrophils from the submucosa to the luminal surface where their unregulated actions can drive inflammatory events," explains lead author Beth McCormick. "This latest study describes our discovery of a novel pathway that counterbalances the HxA_3–MRP2 pro-inflammatory pathway."

The team investigated the role of another efflux transporter restricted to the luminal epithelial surface, P-glycoprotein (P-gp). They found that supernatants collected from the apical surface of homeostatic colonic epithelial cell monolayers suppressed HxA_3-stimulated neutrophil migration in vitro. This effect was lost in P-gp-deficient cells and in cells exposed to a P-gp inhibitor. Analyses of the P-gp-dependent lipidome secreted by the epithelial cells identified *N*-acylethanolamine (NAE)-type endocannabinoids as the molecules suppressing neutrophil migration. P-gp-deficient mice lacked NAE secretion, suggesting a role for P-gp in the secretion of the effector molecules. Finally, in mice deficient in the peripheral endocannabinoid

> "These new findings give insight into pathways crucial for maintaining epithelial homeostasis"

IMMUNOLOGY

Intestinal homeostasis is reliant on self-maintaining macrophages

A new study has identified a small population of self-maintaining gut-resident macrophages in adult mice — notably, these cells had unique transcriptional profiles depending on their anatomical niches.

Macrophages reside in every tissue in the body. As well as defending against pathogens, they have important roles in tissue development, tissue homeostasis and wound repair. Gut-resident macrophages (gMacs) are highly heterogeneous, with distinct phenotypic and functional features depending on their localization within the different layers of the intestine. For the past few years, gMacs in adult mice were thought to be continually replenished by bone-marrow-derived monocytes. As this hypothesis is at odds with the process in other tissues, in which embryonic progenitor cells also give rise to tissue-resident macrophages, Guy Boeckxstaens and colleagues sought to better define the origin of gMacs.

> "…gMacs in adult mice were thought to be continually replenished by bone-marrow-derived monocytes…"

Using fate-mapping approaches in mice, the authors identified a small self-maintaining population of gMacs, derived from embryonic progenitor cells, in the lamina propria and muscularis externa that was not replenished by circulating monocytes. Gene expression analysis revealed substantial differences between gMacs located in the muscularis externa and those located in the lamina propria, and between gMacs that self-maintained and those derived from monocytes. Self-maintained gMacs in the lamina propria were especially heterogeneous; importantly, single-cell gene expression analysis revealed distinct, specialized gMac subpopulations that corresponded to the niche these cells resided in, such as close association with Paneth cells, blood vessels or enteric neurons.

Bone marrow monocytes were able to repopulate these niches when self-maintaining gMacs were depleted;