P1581 FEEDING IMMUNITY’S CLOCK. THE REGULATION OF CIRCADIAN IMMUNE RESPONSES BY NUTRITIONAL CUES.

Topic: 30. Infections in hematology (incl. supportive care/therapy)

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Background: Disruption of circadian rhythm is associated with inflammatory diseases, metabolic syndrome and cancer. In mice, the time of day strongly influences lethality in response to LPS, with survival greatest at the beginning compared to the end of the light cycle (Halberg et al. 1960; Marpegan et al. 2009; Nguyen et al. 2013). Myeloid-cell intrinsic circadian clock components control inflammatory cytokine production (Gibbs et al. 2012; Curtis et al. 2015; Bellet et al. 2013), and metabolic inputs influence lethality in response to LPS (Wang et al. 2016; Weis et al. 2017; Traba et al. 2017), but the relative contributions of these inputs to daily changes in sepsis susceptibility are not known.

Aims: In this study we aim at better understanding the relative contributions of the light- and feeding cycle to daily changes in sepsis susceptibility and the metabolic requirements of hematopoietic stem cells as the origin of immune cells.

Methods: Using time restricted feeding, we have dissociated light from feeding cues to investigate sepsis survival in mice. Using animals deficient for BMAL1 in myeloid cells or hepatocytes we have further characterized a critical role for a functional clock in the liver to convey time-of-day dependent sepsis susceptibility. Further, we have generated several RNAseq datasets to better understand the molecular mechanisms in the liver upon time restricted feeding, but also the metabolic changes that occur in hematopoietic stem cells upon inflammatory stimulation. In addition we are complementing this transcriptional profiling with functional metabolic assays.

Results: Our work shows that feeding, rather than light, controls time-of-day dependent LPS sensitivity. Mortality following LPS administration after 12 hours of food deprivation was associated with hypoglycemia, rather than inflammatory cytokine production, and this was independent of the clock regulator BMAL1 expressed in myeloid cells. In contrast, deletion of BMAL1 in hepatocytes globally disrupted the transcriptional response to the feeding cycle in the liver and resulted in constitutively high LPS sensitivity. Using RNAseq and functional validation studies we identified hepatic farnesoid X receptor (FXR) signaling as a BMAL1 and feeding-dependent regulator of LPS susceptibility. These results show that hepatocyte-intrinsic BMAL1 and FXR signaling integrate nutritional cues to regulate survival in response to innate immune stimuli.

As the origin of all immune cells, hematopoietic stem cells (HSCs) undoubtedly play a critical role in the inflammatory response. We are therefore currently extending our research to investigate the effects of nutritional cues on HSCs, and the metabolic changes that are critical to mount appropriate stress responses. To this end, we have generated time resolution bulk and single cell RNA sequencing data of in vivo stimulated HSCs and are complementing this transcriptional information with functional assays to better profile metabolic cues.

Summary/Conclusion: Targeting specific pathways will allow us to assess their relevance in the context of inflammation and shed light on
previously published contradictory findings. At the same time, understanding the molecular programs operational in response to these cues has the potential to identify novel pathways for targeting to enhance endotoxemia resistance.