

There is a clock protecting your gut: a lesson from the fly

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On a daily basis, animals are in constant contact with harmful pathogens and/or xenobiotic substances during each meal. Most eukaryotes have evolved highly specialized gut epithelial cells, which defend the organism from damages caused by the ingested hazards. In response to these damages, a population of stem cells regenerates the gut epithelium. These intestinal stem cells (ISCs) proliferate and replace the dying cells (Biteau *et al.*, 2011). The regenerative biology of the gut is essential for survival across the entire animal kingdom. The disclosed mechanisms that drive the regenerative proliferation of ISCs are conserved from flies to humans (Casali and Batlle, 2009). Recent studies of

signaling networks that regenerate the intestinal epithelium have benefitted from the tractable genetics and ease of *in vivo* studies of *Drosophila melanogaster*. As such, a wealth of insight into the mechanisms that evolved to protect the gut barrier from environmental stresses in mammals has been drawn from the humble fruit fly. Although many pathways that regulate ISC proliferation and healing have been identified, it is still unclear how healing pathways are synchronized with cellular pathways that regulate normal cellular behavior under non-stressful conditions. In their recent paper published in the journal "Cell reports" issue 3, 996-1004, April 25th 2013, Karpowicz P. *et al.* reported that ISC regenerative proliferation under stress conditions is regulated by the ancient conserved circadian pathway in the gut of *Drosophila* (Karpowicz *et al.*, 2013). Most organisms have evolved a circadian clock in order to anticipate daily environmental changes in light and temperature. Furthermore, it is established that most cells harbor their own circadian machinery. The circadian pathway

plays a pivotal role in synchronizing and integrating physiological and biochemical processes (Allada and Chung, 2010). The work presented by Karpovicz P. *et al.* opens a new field of investigation about the function of the circadian pathway in regenerative biology. Karpovicz P. *et al.* performed a transgenic RNAi screen for transcription factors required in *Drosophila* ISCs for regeneration following damage by dextran-sodium sulfate (DSS), a chemical that models inflammatory bowel disease in flies and mice (Amcheslavsky *et al.*, 2009). The groups involved in this study identified the circadian transcription factor *period* as essential for promoting ISC proliferation in response to the DSS-induced damage. The work also demonstrated that not only *period*, but every component of the canonical core clock are essential to trigger regenerative proliferation of ISCs following damage to the gut. Using very elegant *in vivo* genetic analysis techniques, Karpovica P. *et al.* established that the clock acts in the gut cells to regulate the cell cycle transition in ISCs upon stress. Their work fueled the emerging novel idea

that circadian programming could coordinate the stem cell stage and proliferation according to signaling from internal and external milieu. This research, carried on in the simple model organism, drew a starting point for new investigation, which could lead to a better understanding about the difference between normal stem cells and neoplastic stem cells not only in the fly but also in mammals. A better understanding of the mechanisms that associate the clock to regenerative proliferation of stem cells will also help to shed light on the mechanisms that trigger tumorigenesis.

References

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