Using Components of the Circadian Clock to Regulate Stem Cell Fate Decisions

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Almost all organisms from bacteria to humans have molecular clocks that monitor the Earth's circadian rotation cycles and assure biological rhythms keep pace. The central 'master' clock resides in the superchiasmatic nucleus in the brain where it integrates light signals from the retina to coordinate a variety of vital physiological processes throughout the body. This is exemplified by the fact that perturbations to the clock not only impact sleep/wake cycles but also increase the risk for a number of diseases ranging from diabetes to cancer. Interestingly, peripheral cells also contain clocks that use the same molecular machinery and can be entrained by the master clock to oscillate in sync. While it is clear that master clock entrainment of peripheral cells is critical to systemic homeostasis, targeted uncoupling of peripheral oscillations from the central clock is required to meet the context-specific needs of different tissues. Yet, how this occurs is largely unknown. Metabolic processes exemplify the uncoupling phenomenon, as the content of the diet as well as feeding times appear to override centrally paced entrainment cues. As adipose tissue is integral to both the mediation of and response to systemic metabolism, we examined the role of circadian clock components in the regulation of adipocyte stem cell fate decision to elucidate the mechanism of this regulation. Adipogenesis is a multi-step process resulting in the conversion of undifferentiated progenitor cells into mature adipocytes. We have previously found that the circadian clock component Period3 (Per3) is a negative regulator of adipogenesis in bone marrow-derived stromal through a mechanism that involves interaction between Per3 and PPAR □, a transcription facto necessary and sufficient for commitment to the fat fate. Recent advances in stem cell biology enable the prospective identification and isolation of primary adipocyte stem cells from mouse adipose tissue. We are using this technology to elucidate the mechanisms by which the circadian clock in general, and Per3 in particular, regulates adipocyte fate decisions from these tissue resident adipocyte progenitors. Using a combination of knockout and tissue specific overexpression of Per3 in mouse models, we find that Per3 can toggle adipocyte differentiation signals in tissue resident adipocyte stem cells. Our studies have revealed multiple regulatory pathways downstream of Per3 that likely coordinate the adipogenesis signal. We anticipate that our findings will help elucidate the connection between the circadian clock and stem cell fate decisions.