NONO couples the circadian clock to the cell cycle.

Abstract:
Mammalian circadian clocks restrict cell proliferation to defined time windows, but the mechanism and consequences of this interrelationship are not fully understood. Previously we identified the multifunctional nuclear protein NONO as a partner of circadian PERIOD (PER) proteins. Here we show that it also conveys circadian gating to the cell cycle, a connection surprisingly important for wound healing in mice. Specifically, although fibroblasts from NONO-deficient mice showed approximately normal circadian cycles, they displayed elevated cell doubling and lower cellular senescence. At a molecular level, NONO bound to the p16-Ink4A cell cycle checkpoint gene and potentiated its circadian activation in a PER protein-dependent fashion. Loss of either NONO or PER abolished this activation and circadian expression of p16-Ink4A and eliminated circadian cell cycle gating. In vivo, lack of NONO resulted in defective wound repair. Because wound healing defects were also seen in multiple circadian clock-deficient mouse lines, our results therefore suggest that coupling of the cell cycle to the circadian clock via NONO may be useful to segregate in temporal fashion cell proliferation from tissue organization.