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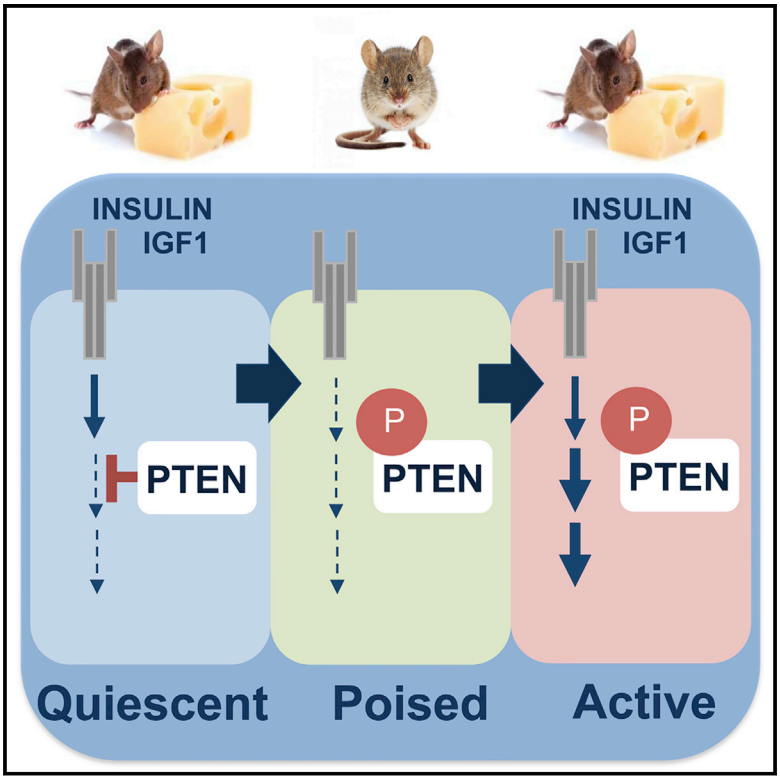
Dormant Intestinal Stem Cells Are Regulated by PTEN and Nutritional Status

Graphical Abstract



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In Brief

Richmond et al. show that PTEN is required for dormant intestinal stem cell (d-ISC) maintenance and regeneration after intestinal injury. Changes in nutrient status (fasting) lead to transient PTEN inhibition, rendering d-ISCs functionally poised to contribute to regeneration upon re-feeding via cell-autonomous activation of the insulin/growth factor→PI3K→AKT→mTORC1 pathway.

Highlights

- Dormant stem cells (d-ISCs) contribute to intestinal regeneration after fasting
- Decreased nutrients lead to transient PTEN inhibition and increased d-ISC numbers
- Cell-autonomous activation of PI3K→AKT→mTORC1 signaling mediates d-ISC response
- PTEN is essential for d-ISC maintenance and intestinal regeneration

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Dormant Intestinal Stem Cells Are Regulated by PTEN and Nutritional Status

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SUMMARY

The cellular and molecular mechanisms underlying adaptive changes to physiological stress within the intestinal epithelium remain poorly understood. Here, we show that PTEN, a negative regulator of the PI3K→AKT→mTORC1-signaling pathway, is an important regulator of dormant intestinal stem cells (d-ISCs). Acute nutrient deprivation leads to transient PTEN phosphorylation within d-ISCs and a corresponding increase in their number. This release of PTEN inhibition renders d-ISCs functionally poised to contribute to the regenerative response during re-feeding via cell-autonomous activation of the PI3K→AKT→mTORC1 pathway. Consistent with its role in mediating cell survival, PTEN is required for d-ISC maintenance at baseline, and intestines lacking PTEN have diminished regenerative capacity after irradiation. Our results highlight a PTEN-dependent mechanism for d-ISC maintenance and further demonstrate the role of d-ISCs in the intestinal response to stress.

INTRODUCTION

The physiological response to fasting has had enormous selective pressure throughout evolution and has been linked to disease prevention and improved clinical outcomes for many conditions (Longo and Mattson, 2014). Additionally, clinicians have increasingly recognized the value of providing even small-volume enteral feeds to maintain and augment the recovery of the critically ill patient by preserving bowel mucosal integrity, thereby helping to prevent enteral-systemic bacterial translocation. Despite its relevance to human health, surprisingly little is known regarding how fasting affects metabolically dynamic and expensive tissues such as the gut. Some insight comes from animals that feed sporadically, such as snakes and hibernating mammals, which exhibit an astonishing capacity to modulate the intestinal mucosa in response to the presence or absence of enteral nutrition (Dunel-Erb et al., 2001; Secor et al., 1994). Similarly, humans and rodents that undergo periods of fasting or receive all their nutrition intravenously experience marked intestinal atrophy (Chappell et al., 2003). These findings underscore the requirement of luminal nutrition for intestinal maintenance and highlight an important energy-conserving mechanism. Under fed conditions, energy consumed by the intestinal mucosa represents ~15% of the total basal metabolic rate (Aiello and Wheeler, 1995), and after an extended fast, up to 25% of newly available calories are committed to restoring the intestinal mucosa (Secor et al., 1994), emphasizing the critical importance of intestinal homeostasis to the body. The cellular and molecular mechanisms underlying intestinal adaptation to fasting and re-feeding, however, remain poorly characterized. We propose that this process is regulated in part at the level of intestinal stem cells (ISCs).

Intestinal adaptation to fasting involves dramatic alterations in cell number, cycling frequency, and cell turnover, suggesting fundamental changes in stem/progenitor cell function (Dunel-Erb et al., 2001). In mice, a diverse array of ISC markers has been described and used to characterize this functionally heterogeneous population (Carlone and Breault, 2012; Goodell et al., 2015; Ritsma et al., 2014; Takeda et al., 2011; Tao et al., 2015; Yan et al., 2012). The spectrum of ISCs includes rapidly cycling crypt base columnar ISCs (CBC ISCs) marked by *Lgr5* expression and slowly cycling, relatively dormant ISCs (d-ISCs) marked by *mTert* (telomerase), *Bmi1*, *Lrig1*, *HopX*, and *Dclk1* (Barker et al., 2007; Montgomery et al., 2011; Powell et al., 2012; Sangiorgi and Capecchi, 2008; Takeda et al., 2011; Westphalen et al., 2014). CBC ISCs play a dominant role during daily intestinal maintenance and are sensitive to intestinal stress and injury (Barker et al., 2007; Carlone and Breault, 2012; Metcalfe et al., 2014; Ritsma et al., 2014). In contrast, d-ISCs, located in the "+4" supra-Paneth position, are resistant to stress and are activated upon injury to restore homeostasis (Metcalfe et al., 2014; Montgomery et al., 2011; Powell et al., 2012; Ritsma et al., 2014; Sangiorgi and Capecchi, 2008; Takeda et al., 2011; Tian et al., 2011). Adding additional complexity, recent data suggest a level of cellular plasticity within the ISC population, thereby allowing for inter-conversion between compartments (Goodell et al., 2015; Muñoz et al., 2012; Ritsma et al.,