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Stem Cells Matter in Response to Fasting

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The molecular processes underlying intestinal adaptation to fasting and re-feeding remain largely uncharacterized. In this issue of *Cell Reports*, Richmond et al. report that dormant intestinal stem cells are regulated by PTEN and nutritional status.

Fasting has been practiced since ancient times by different ethnic or religious groups throughout the world. It is known that fasting can be a powerful trigger that causes robust metabolic responses, including reduced insulin secretion and glycogenesis, thus promoting survival. Fasting is also known to promote longevity, in part by reducing risks of cancer, diabetes, heart diseases, and neurodegeneration (Longo and Mattson, 2014). However, the underlying mechanisms regarding whether and how fasting affects tissue homeostasis and regeneration remain largely unclear.

Previously, Yilmaz et al. (2012) reported that calorie restriction promotes self-renewal of intestinal stem cells (ISCs) indirectly through the inhibition of the mammalian target of rapamycin complex 1 (mTORC1) pathway in Paneth cells. Paneth cells in turn act as a regulatory niche to augment stem-cell function in response to calorie restriction by reducing mTORC1 signaling. However, how adult stem cells directly respond to the change in nutritional states remains unresolved. In this issue of *Cell Reports*, Richmond et al. (2015) reveal the differential responses of rapidly cycling ISCs (r-ISCs) and dormant ISCs (d-ISCs) to fasting.

The role of Paneth cells in supporting ISCs in response to calorie restriction was previously shown in a study where Paneth cells isolated from calorie-restricted mice were found to promote expansion of $Lgr5^+$ ISCs in organoid culture more effectively than cells from well-fed mice (Yilmaz et al., 2012). Richmond et al. (2015) directly assessed changes to $Lgr5^+$ r-ISCs in response to fasting and revealed reduced $Lgr5^+$ cell numbers and declined Lgr5-induced lineages (Figure 1). The authors also investigated the role of the mTOR pathway, which is normally not active in d-ISCs due to the suppression by its upstream factor PTEN. PTEN and its inactive isoform, phosphor (p)-PTEN, are known to be present in quiescent +4 ISCs, and function respectively to control quiescent and active states of +4 ISCs by regulating the PI3K-Akt pathway (He et al., 2004, 2007). Given that PTEN can also function as a gatekeeper of the fasting-fed transition (Pal et al., 2012), the authors reasoned that PTEN may regulate d-ISCs. Indeed, they found that fasting led to PTEN inhibition, as revealed by conversion into the p-PTEN state and activation of mTOR in d-ISCs, rendering d-ISCs into a functionally poised or primed state (Figure 1). Upon subsequent re-feeding, these primed d-ISCs increased in number and robustly contributed to lineage regeneration, as evidenced by an increased mTert-induced lineage tracing. Afterward, however, the d-ISCs initiated programmed cell death to get rid of excessive ISCs produced during the fasting-refeeding process and eventually returned to their dormant state and original number (Figure 1). Richmond et al. (2015) confirmed the function of PTEN as a negative regulator of the PI3K→AKT signaling pathway in d-ISCs and further showed its role in maintaining d-ISCs via inhibition of the mTORC1 activity. This conclusion is further supported by the fact that lacking PTEN attenuated post-injury regenerative capacity, which depends primarily on d-ISCs, but not r-ISCs, because the latter are sensitive to irradiation. Richmond et al. (2015) thus shed new light on the PTEN-dependent mechanism for d-ISC maintenance and further demonstrate the role of d-ISCs functioning as reserve ISCs in response to fasting.

This original finding regarding the fasting response by r-ISCs and d-ISCs is largely consistent with previously proposed functions of active and quiescent stem cells coexisting in the intestinal crypt (Li and Clevers, 2010). Reserve ISCs are defined by function and d-ISCs by state. The sensitivity of active ISCs and resistance of quiescent ISCs to chemo- and/or radio-therapy have been well documented (Asfaha et al., 2015; Takeda et al., 2011). However, the differential response to fasting by r-ISCs and d-ISCs is a novel observation (Figure 1). The primed or poised state described in this report is different from the active-cycling state, reflecting more appropriately a transitional state from dormancy into cycling.

Fasting may have an unrecognized role in cancer prevention and treatment. Recent studies suggest that the combination of fasting with chemotherapy is highly effective in treatment of cancer (Longo and Mattson, 2014). This can be explained in two aspects. Fasting may prime chemo-resistant cancer cells to increase sensitivity to treatment. Short-term fasting before and immediately after chemotherapy may minimize side effects, such as nausea and other adverse gastrointestinal reactions (Scrable, 2012). The work by Richmond et al. (2015) indicates that fasting-refeeding leads to more rapid restoration of the integrity and function of the intestine, thus suggesting that fasting-refeeding might reduce chemotherapy-associated side effects.

Here, we would like to point out that there are overlaps as well as distinctions

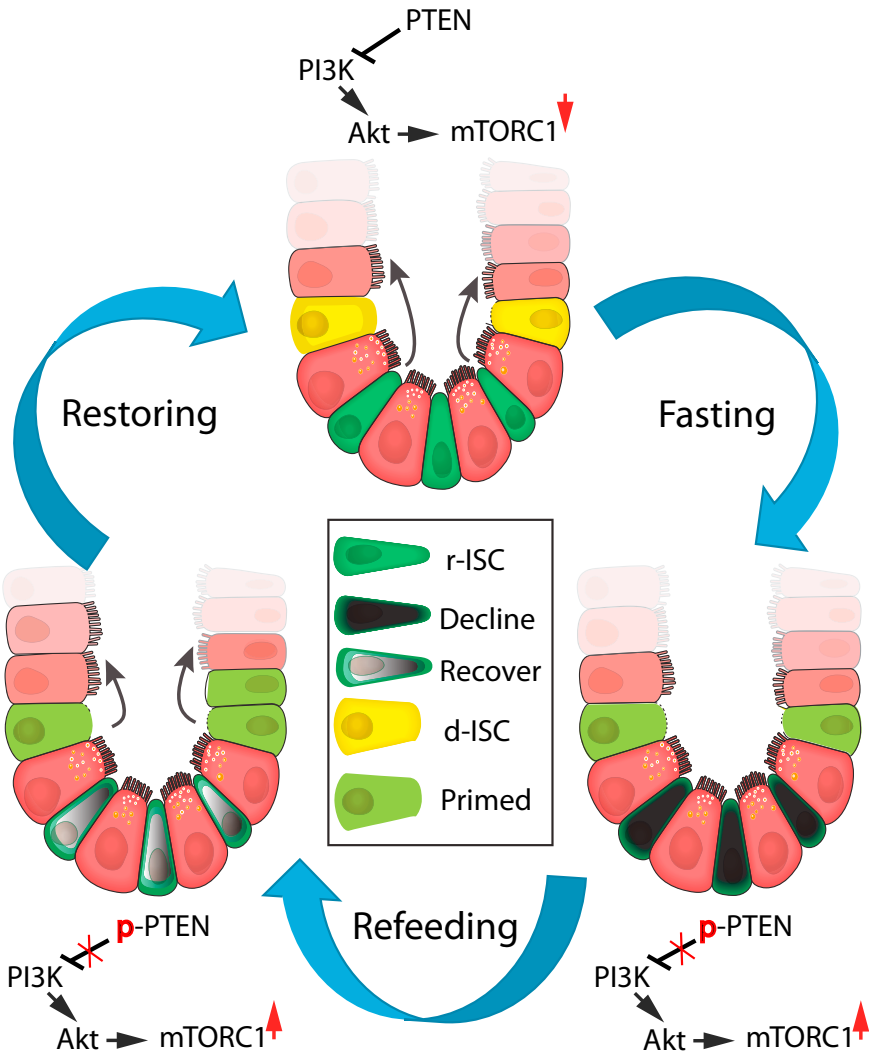

Figure 1. Differential Responses of Stem Cells to Fasting
Differential responses of r-ISCs and d-ISCs to fasting. Whereas r-ISCs (Lgr5^{+}) reduced in number and declined in Lgr5:Cre-induced lineages in response to fasting, d-ISCs (PTEN^{+} or mTert^{+}) became primed and increased in mTert:Cre-induced lineages upon refeeding.

between caloric restriction and fasting, with the former reducing daily caloric intake by 20%–40%, but maintaining meal frequency (Longo and Mattson, 2014), whereas the latter withdraws nutrients completely. Fasting may provide effective strategies to delay aging, reduce weight, and optimize health. The potent effects of different terms of fasting, including alternate day fasting or fasting for 2 days a week, should be studied, given that circadian rhythms are of high importance to metabolism control.

The PI3K→AKT→mTORC1 signaling pathway as highlighted in this study is essential for growth and survival (Richmond et al., 2015), the downstream of which still needs a better understanding such as cellular metabolism and regeneration. mTOR signaling is a critical target for therapeutic approaches and has driven the development of a number of mTOR inhibitors including rapamycin. Synergistic strategies with other means should be considered in an effort to enhance therapeutic efficacy, given that mTOR inhibitors remain a promising therapeutic option for cancer treatment.

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