

Insights: Publications

Ketone Body Signaling Mediates Intestinal Stem Cell Homeostasis and Adaptation to Diet

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Little is known about how metabolites couple tissue-specific stem cell function with physiology. Here we show that, in the mammalian small intestine, the expression of *Hmgcs2* (3-hydroxy-3-methylglutaryl-CoA synthetase 2), the gene encoding the rate-limiting enzyme in the production of ketone bodies, including beta-hydroxybutyrate (β OHB), distinguishes self-renewing *Lgr5*⁺ stem cells (ISCs) from differentiated cell types. *Hmgcs2* loss depletes β OHB levels in *Lgr5*⁺ ISCs and skews their differentiation toward secretory cell fates, which can be rescued by exogenous β OHB and class I histone deacetylase (HDAC) inhibitor treatment. Mechanistically, β OHB acts by inhibiting HDACs to reinforce Notch signaling, instructing ISC self-renewal and lineage decisions. Notably, although a high-fat ketogenic diet elevates ISC function and post-injury regeneration through β OHB-mediated Notch signaling, a glucose-supplemented diet has the opposite effects. These findings reveal how control of β OHB-activated signaling in ISCs by diet helps to fine-tune stem cell adaptation in homeostasis and injury.

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