Burning fat to keep your stem cells? The role of fatty acid oxidation in various tissue stem cells

Marlen Knobloch and Christian Widmann

Somatic stem cells have the ability to self-renew and differentiate, ensuring proper function and maintenance of various tissues throughout life. Cellular metabolism is emerging as a key player for somatic stem cell behavior, determining whether a stem cell remains quiescent or starts to proliferate [1–3]. Several recent studies have now identified the breakdown of lipids via fatty acid oxidation (FAO) as a major regulator of quiescence in different somatic stem cells. The quiescent populations of hematopoietic stem cells in the bone marrow [4] and neural stem cells in the brain [5▪] both rely on FAO for proper function. Pharmacological and genetic ablation of FAO via peroxisome proliferator-activated receptors (PPARs) and/or via the FAO rate-limiting enzyme carnitine palmitoyl transferase 1a (Cpt1a) *in vitro* and *in vivo* results in stem cell dysfunction and exhaustion. Furthermore, in skeletal muscle, the quiescent stem cells also rely on FAO and switch from FAO to glycolysis when proliferation is required [6], suggesting a common mechanism of stem cell regulation via FAO in very different tissues. Now another stem cell population, the intestinal stem cells (ISCs), has been added to the picture. In contrast to the above-mentioned quiescent stem cell populations, ISCs are highly proliferative, renewing the intestinal epithelial layer every 4–5 days, thus a similar role of FAO in regulating ISCs might surprise at a first glance. Mihaylova *et al.* [8▪], however, show that, despite being dispensable for acute ISC function, FAO does indeed play a role for long-term ISC maintenance, similar to the findings in other stem cell populations. Although a previous publication from the same group already showed the importance of dietary fatty acids for ISC function [7], they now link FAO changes in ISCs with effects occurring during fasting and aging [8▪]. Short-term fasting (24 h) induced an upregulation of PPARs and Cpt1a in ISCs and enhanced their function, measured via the capacity to form miniature intestinal tissues, termed organoids. Although an upregulation of PPARs upon fasting likely changes several pathways, the authors show that this effect was specific to an upregulation of FAO, as pharmacological and genetic ablation of Cpt1a blocked the enhanced organoid-forming capacity upon fasting, whereas it had minimal impact on baseline ISC function. Conversely, prolonged FAO inhibition decreased ISC number and function, suggesting that ISCs depend on FAO for their long-term maintenance. Interestingly, the authors show that the reduced number and function of ISCs in aged mice correlates with a reduced basal FAO metabolism in these cells and that fasting or PPAR activation boosts the function of ISCs from aged mice. Finally, evidence is provided that one of the FAO substrates, palmitic acid, is reduced upon fasting in aged mice and that providing palmitic acid exogenously enhances ISC function *in vitro*.

While all these publications suggest that enhancing FAO could have beneficial effects on several somatic stem cell compartments, another recent publication should be kept in mind: not only the 'good' stem cells, but also the 'bad' stem cells, those that may give rise to and/or maintain cancers, seem to be regulated by FAO. Wang *et al.* [9▪] show that breast cancer stem cells (BCSCs) highly express CPT1B, which is required for BCSC self-renewal and that CPT1B expression is controlled via a Leptin-LEPR-JAK-STAT3 mediated pathway. Remarkably, FAO seems to be specifically relevant in chemoresistant and recurring breast tumors, as shown by expression profiles of breast tumor tissue from patients and with several in-vitro experiments, indicating that FAO rather acts on the maintenance of BCSCs than enhancing proliferation *per se*.

The findings discussed in this editorial comment are in line with the emerging role of FAO as a conserved metabolic pathway for stem cell maintenance and quiescence, providing the basis for potential therapeutic interventions targeting key signaling molecules controlling FAO in the context of aging and cancer.

Department of Physiology, University of Lausanne, Lausanne, Switzerland

Correspondence to Christian Widmann, PhD, Department of Physiology, University of Lausanne, Rue du Bugnon 7, 1005 Lausanne, Switzerland. Tel: +41 21 692 5123; fax: +41 21 692 5505; e-mail: Christian.Widmann@unil.ch

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

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A recent article that demonstrates the importance of FAO for quiescent adult neural stem cells. This work also shows that manipulating FAO levels is sufficient to trigger quiescence exit.

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This works extends the notion that FAO controls the maintenance of stem cells, in this case in the intestinal tissue, and provides evidence that FAO signaling is compromised during aging.

9. ■ Wang T, Fahrmann JF, Lee H, *et al.* JAK/STAT3-regulated fatty acid b-oxidation is critical for breast cancer stem cell self-renewal and chemoresistance. Cell Metab 2018; 27:136–150.

A recent article on the role of fatty acid oxidation (FAO) in cancer stem cell maintenance. The novelty of this study resides in the characterization of the signaling route – the Leptin-LEPR-JAK-STAT3 pathway – that controls FAO in breast cancer cells.