Too much too soon – Tissue-specific inactivation of deiodinase type 3 prematurely exposes brown fat to thyroid hormone

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Declaration of Interest

The authors have nothing to declare.

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Invited Commentary

Correct levels of thyroid hormones are crucial for proper tissue development. This is most impressively demonstrated in congenital hypothyroidism leading to irreversible brain damage. Likewise, elevated thyroid hormone levels during pregnancy can have long-lasting negative impact on tissue development, e.g. by altering epigenetic programs for instance in heart or brain (1,2).

Deiodinases During Tissue Development

The exposure of developing tissues to thyroid hormone is tightly regulated by deiodinases (DIO’s). These enzymes can locally produce the active hormone 3,3’,5-triiodothyronine (T3) from its precursor T4 (primarily Dio2), but can also protect tissues from the hormone by degrading T3 and T4 (primarily Dio3). The regulation of deiodinase activity in developing tissues is therefore a major gatekeeper in timing the exposure to the hormone, which can then exert its powerful actions in shaping tissue function.

One of the first demonstrations of this important role was published in 2015, showing that a selective inactivation of Dio2 in the liver of mice causes increased susceptibility to hepatic metabolic disorders. These findings are puzzling at first, as Dio2 is not usually expressed in the adult liver. However, the enzyme is expressed during a short and seemingly crucial period during liver development. Here, its inactivation caused a delayed exposure of the developing liver to T3, leading to a mistimed neonatal expression of key genes in lipid metabolism and a permanently altered epigenetic landscape in this organ (3).

Deiodinase Type 3 in Brown Fat Development

Now, a second publication from the same group in this journal has further expanded our horizon regarding the unique role of deiodinases during development (4). Again, they have targeted a deiodinase that is not usually expressed at high levels in the adult tissue – this time Dio3 in brown adipose tissue (BAT). BAT is a specialized organ responsible for thermogenesis and has a critical role
in the regulation of body temperature in small mammals and newborns (5). Cold exposure leads to its activation whereupon the uncoupling protein 1 (UCP1) short-circuits the electron transport chain, allowing mitochondrial membrane potential to be transduced to heat. During mouse development, BAT emerges at embryonal day 14.5 and expands gradually until the end of pregnancy to prepare the embryo for the cold shock that comes with birth. Given its unique properties, BAT constitutes a promising target for the treatment of metabolic disorders, and thus mechanisms governing its activation are of great interest nowadays.

BAT is a well-known target of thyroid hormone action in adult animals, both through direct actions affecting its thermogenic capacity as well as indirect central actions through the sympathetic nervous system (6). Its main deiodinase is Dio2, which upon sympathetic stimulation cranks up local T3 production and in turn thermogenic capacity and heat production. Dio2 expression in BAT is first detectable at embryonic day 17.5 and knockout of this deiodinase leads to a decreased expression of genes defining BAT identity and an impaired differentiation of brown adipocytes. However, like in the liver, one of the sister enzymes, namely Dio3, also plays a key role during BAT development, although it is not expressed at high levels in the adult tissue. In contrast to Dio2, Dio3 expression is already highest at embryonic day 16.5 and progressively declines until postnatal day 1, suggesting that the switch in the expression of the two deiodinases marks the point of BAT activation by exposure to thyroid hormone. Fonseca et al. now show that selective inactivation of Dio3 with Ucp1-Cre mice in BAT (BAT-D3KO) indeed results in premature exposure of brown adipocytes to T3 signaling during embryogenesis, as indicated by early expression of important BAT genes (4). Most interestingly, this leads to changes in gene expression patterns of important metabolic/thermogenic BAT genes that persist into adulthood. While there was a slight reduction in body weight, no changes in energy homeostasis were observed at room temperature or cold. Most remarkably, when exposed to lower temperatures, BAT-D3KO mice showed a less pronounced drop in body temperature, suggesting that they may be more resistant to cold exposure. However, whether this effect is indeed mediated by enhanced BAT thermogenesis remains unclear to date, as Ucp1 levels...
were not different in adult BAT D3KO mice. Therefore, further functional studies, e.g. using infrared thermography, will be required to reveal the underlying mechanism. Moreover, a possible contribution of white adipose tissue to the phenotype needs to be tested, as this tissue can also express Ucp1 upon cold exposure or other events, thus likely causing Cre activation and subsequent Dio3 inactivation in these cells at later stages.

Conclusions for Thyroid Research

The adult phenotype of many classical knockout animals is a mixture of acute and developmental defects. Dissecting these differences is a major task in current thyroid hormone research, which requires clever and well controlled experimental designs. Therefore, recent studies usually rely on animal models that allow differentiating between these two effects, for instance by using a reactivatable mutation in a thyroid hormone receptor (2), conditional knockouts (7) or alternative techniques such as virus mediated gene expression in the adult animal (8). With the new insights from the aforementioned publications (3,4) - namely that genes responsible for the local control of thyroid hormone action may act developmentally in tissues that do not classically express these genes in the adult state - we need to be aware that this possibly unrecognized developmental action of our gene of interest may confound the interpretations of an adult knockout animal. In fact, a significant number of findings in thyroid research may be skewed by such an incomplete analysis – therefore reassessing older publications in the light of a previously unknown developmental action will be required. Controlling for this effect in all tissues at all times during development is a task of Sisyphean proportions; hence, the good old days of simply analyzing a straight knockout mouse as adult animal may be over for thyroid research.
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