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AUTOCOMMENTARY

TRPV2 regulates BAT thermogenesis and differentiation

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Brown adipose tissue (BAT) is specialized for the efficient dissipation of chemical energy in the form of heat, and it is a major site for mammalian non-shivering thermogenesis.[1] Upon activation of brown adipocytes in BAT by either cold or β−adrenergic receptor stimulation, uncoupling protein 1 (UCP1) in mitochondria uncouples the respiratory chain, leading to heat generation. Since BAT has recently become recognized to be present even in adult humans,[2] BAT could be a target for the prevention and treatment of obesity. Thus, understanding the molecular mechanisms underlying BAT thermogenesis and differentiation is the subject of intense investigation.

Transient receptor potential vanilloid 2 (TRPV2), a non-selective calcium-permeable cation channel, was cloned as an analog of TRPV1 in 1999. TRPV2 is activated by noxious heat with an activation temperature threshold above 52°C and by a number of chemical ligands. Moreover, it was reported to be a mechanosensor that played important roles in many types of cells.[3] Several studies reported the involvement of TRP channels in the functions of adipose tissue. TRPV1 activation−mediated Ca^{2+} influx prevents adipogenesis, and it was proposed to play anti−adipogenic roles *in vivo*.[4] TRPM8 stimulation by menthol increased UCP1 expression in brown adipocytes and BAT through PKA phosphorylation[5] whereas knockdown of TRPV4 facilitated UCP1 expression in 3T3-F442A adipocytes.[6]

We recently reported that TRPV2 is more highly expressed in mouse brown adipocytes than TRPV1, TRPV3, TRPV4 and TRPM8. Moreover, the expression of TRPV2 was significantly increased in differentiated brown adipocytes compared with pre-adipocytes at mRNA, protein and functional levels.[7] Therefore, we hypothesized that TRPV2 plays significant roles in BAT thermogenesis and differentiation (Fig. 1).

The expression of thermogenic genes, *Ucp1* and peroxisome proliferator-activated receptor gamma coactivator 1α (*Pgc1α*) was significantly lower in brown adipocytes isolated from TRPV2 knockout (TRPV2KO) mice compared with wild-type mice. This difference was observed at both a basal level and upon induction by β-adrenergic receptor activation or adenylyl cyclase activator administration. Similar reductions in the expression of *Ucp1* and *Pgc1α* genes were observed when intracellular calcium was chelated by BAPTA-AM, suggesting that TRPV2 activation-induced calcium influx is involved in the thermogenic gene induction upon β-adrenergic receptor activation. Moreover, TRPV2KO mice exhibited an energy imbalance, with heavier adipose tissues and increased sizes of lipid droplets and adipocytes in BAT. BAT thermogenesis was impaired in TRPV2KO mice upon administration of a β3-adrenergic receptor agonist, and TRPV2KO mice failed to maintain their body temperature upon cold stimulation without changes in their activities. On the other hand, sympathetic nervous activity was not altered in TRPV2KO mice. These findings support the concept that TRPV2-mediated calcium influx regulates BAT thermogenesis

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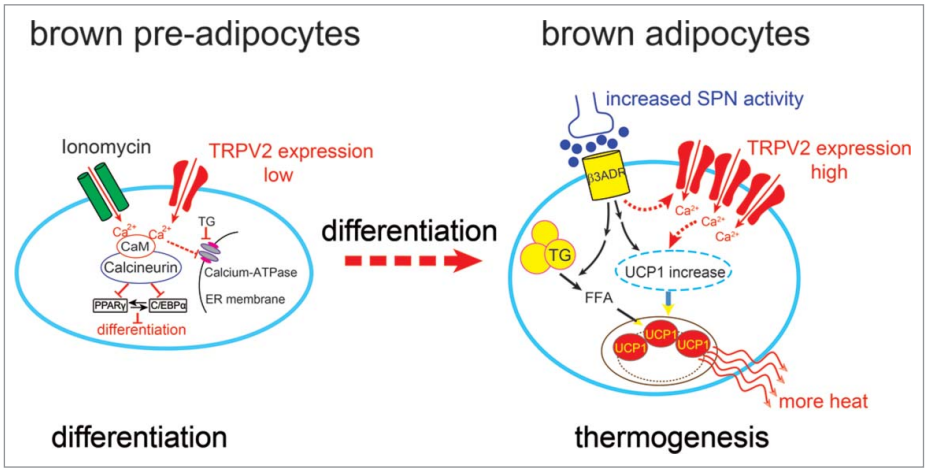

Figure 1. A schematic model of the involvement of TRPV2 in the differentiation (left) and thermogenesis (right) of BAT. Membrane stretch and/or other endogenous ligand-induced activation of TRPV2 increases $[Ca^{2+}]_i$, a process that could prevent the differentiation of mouse brown adipocyte via a calcineurin pathway (left). Upon cold exposure, norepinephrine is released from sympathetic nerves (SPN) and activates β3-adrengergic receptors in BAT. Subsequently, TRPV2 expression is upregulated and more calcium enters the cells via TRPV2, facilitating UCP1 expression and heat production.

(Fig. 1[8]). In addition, TRPV2KO mice were prone to obesity and showed insulin resistance after a high fat diet (HFD) treatment. These findings further support the notion of TRPV2 involvement in BAT thermogenesis. It has been reported that TRPV1-, TRPV4- and TRPM2-knockout mice are resistant to HFD−induced obesity, a phenotype opposite to the one observed in TRPV2KO mice. These results suggest that activation of TRPV2 could be an intriguing therapeutic approach for the treatment and prevention of human obesity. Of course, it would be necessary to develop specific TRPV2 agonists. Upregulation of TRPV2 in obese and diabetic (db/db) mice[8] also indicates the involvement of TRPV2 in BAT thermogenesis under pathological conditions. Our results suggest that TRPV2 makes important contributions to BAT thermogenesis and contributes to the obese phenotype in TRPV2KO mice fed with HFD.

In addition to the induction of thermogenic genes in differentiated mouse brown adipocytes described above, we have recently shown that TRPV2 is involved in the differentiation of mouse brown adipocytes (Fig. 1) (ref. 7). Calcium influx through TRPV2 activated by ligands or mechanical stimulation inhibited differentiation of mouse brown adipocytes in a dose-dependent or strength-dependent manner, respectively. Importantly, brown adipocyte differentiation was facilitated in cells from TRPV2KO mice. TRPV2-mediated inhibition of brown adipocyte differentiation was recovered by a calcineurin inhibitor, FK506 or cyclosporine A,[7] suggesting the involvement of a calcineurin-dependent pathway in the process. Interestingly, TRPV2-dependent inhibition of mouse brown adipocyte differentiation occurred only in the early stages of differentiation (differentiation day 0–3) and not in the late stages (differentiation day 4–6). Ionomycin shows a similar phenomenon, indicating that calcium influx in the early differentiation stage could inhibit the differentiation of adipocytes. The TRPV2-dependent inhibition of brown adipocyte differentiation apparently contradicts the TRPV2 involvement in thermogenesis described before because thermogenesis occurs only in the differentiated brown adipocytes. Stage-dependent allocation of TRPV2 functions might explain the apparently opposite TRPV2 contribution to mouse brown adipocytes to some extent.

Precisely how is TRPV2 activated for inhibiting differentiation and for induction of thermogenic genes in mouse brown adipocytes? Endogenous ligands for TRPV2 activation in brown adipocytes are still unknown. Candidate TRPV2-activating stimuli include mechanical stimulation (membrane stretch), lipid metabolites, LPC (lysophosphatidylcholine), LPI (lysophosphatidylinositol) and endocannabinoids.[3] Moreover, IGF-1 is known to enhance transient translocation of TRPV2 from intracellular compartments to the plasma membrane.[3] An increase in TRPV2 incorporation into the plasma membrane could be sufficient for TRPV2 activation due to membrane stretch. Activation mechanisms of TRPV2 could vary with the stage of differentiation, which might explain

the apparently different functions of TRPV2 in mouse brown adipocytes. Further investigation is needed.

In conclusion, our studies established novel roles for the mechano-sensitive TRPV2 channel in thermogenesis and differentiation of mouse brown adipocyte. In brown adipocytes, TRPV2 activation might be due to membrane stretch mediated through lipid droplet accumulation. TRPV2 activation might be necessary to prevent over-differentiation of brown adipocytes and to maintain BAT thermogenesis under pathologic/physiological conditions. With the recent reports that BAT is present in adult humans,[2] approaches modulating BAT function through TRPV2 could be intriguing ways to treat human obesity and related-metabolic disorders.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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