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Short Commentary Open Access

Thermo-sensitive Transient Receptor Potential Channels Regulate Thermogenesis and Differentiation in BAT

Kunitoshi Uchida[1] and Makoto Tominaga[2,3,4]*

[1]Department of Physiological Science and Molecular Biology, Fukuoka Dental College, Fukuoka, Japan
[2]Thermal Biology Group, Exploratory Research Center on Life and Living Systems, Okazaki, Japan
[3]Division of Cell Signaling, National Institute for Physiological Sciences, Okazaki, Japan
[4]Department of Physiological Sciences, SOKENDAI (The Graduate University for Advanced Studies), Okazaki, Japan

Abstract

Brown and beige adipocytes are major sites for non-shivering thermogenesis and its modulation could be an important application for body weight control and obesity prevention. Recently, some of thermo-sensitive Transient Receptor Potential (thermo-TRP) channels are found to be expressed in brown and beige adipocytes. Especially, TRPV2 expressed in brown adipocytes positively regulates non-shivering thermogenesis and negatively regulates differentiation. On the other hand, TRPV4 expressed in white adipose tissue may impair the "browning" of white adipocytes. Further analysis of thermo-TRP channel functions in adipocytes could provide new clinical approaches to treat human obesity and related metabolic diseases.

Keyword: Brown adipocytes; Calcium; Differentiation; Non-shivering thermogenesis; Thermosensitive TRP channel

Brown Adipose Tissue (BAT) which is composed of brown adipocytes is a major site of mammalian non-shivering thermogenesis and energy dissipation. Recruitable brownish adipocytes, termed "beige adipocytes" (also known as "brite adipocytes"), were discovered in White Adipose Tissue (WAT). Beige adipocytes are induced by sympathetic nerve activation after cold exposure or treatment with β3-adrenergic receptor agonists. Although the gene expression profile in beige adipocytes is different from that in brown adipocytes to some extent, both brown and beige adipocytes express the thermogenic genes such as mitochondrial uncoupling protein 1 (UCP1) and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (Pgc1α), and have high thermogenic ability [1]. The modulation of thermogenesis in brown and beige adipocytes could be an important application for body weight control and obesity prevention. Non-shivering thermogenesis in brown adipocytes occurs through the sympathetic nerve action after activation of sensory or vagus nerve upon cold exposure or intake of pungent foods. The release of norepinephrine from sympathetic nerve terminals is an initial step, followed by UCP1 activation and increase in H^+ conductance in mitochondria. Possible mechanisms for UCP1 activation downstream of β3-adrenergic receptor activation have been proposed in several studies. However, mechanisms and extent of increase in intracellular Ca^{2+} concentrations ($[Ca^{2+}]_i$) in brown adipocytes are not understood well while some reports suggest the involvement of certain intracellular Ca^{2+} signaling.

Transient Receptor Potential (TRP) ion channels constitute a major class of calcium-permeable cation channels, most of which are non-selective. Several TRP channels exhibiting thermosensitive ability have been identified in mammals with 11 thermo-sensitive TRP (thermo-TRP) channels reported in mammals to date. Thermo-TRP channels are expressed in many tissues and involved in a wide variety of physiological functions, including detection of various physical and chemical stimuli in vision, taste, olfaction, hearing, touch, and thermo sensation. Thermo-TRP channels expressed in vagus nerve can control thermogenesis [2]. On the other hand, recent analyses have reported the expression of thermo-TRP channels in BAT and the regulation of thermogenesis by those thermo-TRP channel functions in brown and beige adipocytes. We demonstrated that activation of TRPV2 could enhance thermogenesis and impair differentiation of brown adipocytes [3,4]. TRPV2-deficient primary brown adipocytes showed decreased mRNA levels of multiple genes involved in mitochondrial oxidative metabolism such as UCP1 and Pgc1α, and impairment of increases in the expression of thermogenic genes responding to isoproterenol, a β-adrenergic receptor agonist. Similar results were observed when intracellular calcium was chelated with BAPTA-AM in primary brown adipocytes, suggesting that calcium influx is involved in thermogenic gene induction upon β-adrenergic receptor activation. Indeed, when we measured body temperature and locomotion activity of freely behaving mice by thermo probes implanted in the peritoneal cavity, core body temperature was significantly decreased upon cold exposure in TRPV2-deficient mice without changes in locomotion activity. Moreover, TRPV2-deficient mice exhibited impairment of increases in UCP1 expression upon cold stimulation (4°C). On the other hand, sympathetic nerve activities were not different between wild-type and TRPV2-deficient mice, suggesting that sensing of cold temperature was intact in TRPV2-deficient mice. It was concluded that $[Ca^{2+}]_i$ increases through TRPV2 activation enhance non-shivering thermogenesis as shown in Figure 1.

Although expression of TRPV2 was increased during the differentiation of primary brown adipocytes, TRPV2 is also expressed in pre-adipocytes and its activation by agonists (2-aminoethoxydiphenyl borate and lysophosphatidylcholine) or mechanical stimulation prevented the differentiation of primary brown adipocytes through a calcineurin pathway. TRPV2 could prevent over-development of brown adipocytes.

The role of TRPV4 in adipocytes was reported to be different in that TRPV4 in WAT may negatively regulate the "browning" of white adipocytes or differentiation of beige adipocytes [5]. Knockdown of TRPV4 enhanced the basal and norepinephrine-induced induction of the thermogenic genes. In WAT, inhibition of TRPV4 significantly enhanced thermogenic gene expression and led to the development of

***Corresponding author:** Tominaga M, Division of Cell Signaling, National Institute for Physiological Sciences, Okazaki, Japan, Tel: +81-564-59-5286; E-mail: tominaga@nips.ac.jp

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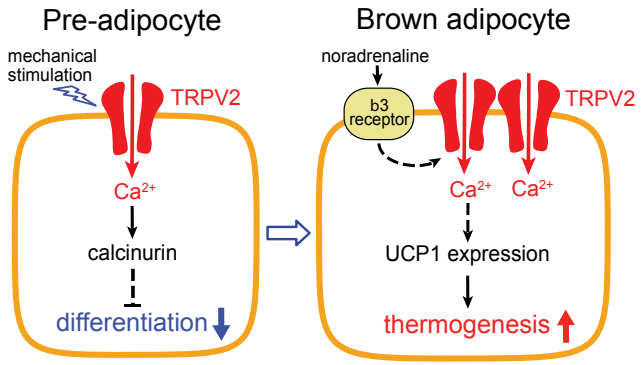

Figure 1: The roles of TRPV2 in BAT differentiation and thermogenesis. TRPV2 negatively regulates the differentiation of pre-adipocytes by modulating the expression of the genes related to differentiation through a calcineurin pathway. Mechanical stimulation by membrane stretch could activate TRPV2. In differentiated brown adipocyte, activation of β3-adrenergic receptor *via* sympathetic nerve activity enhances the expression of the genes related to thermogenesis such as uncoupling protein 1 (UCP1).

metabolically active brown fat-like features. These reports suggest that TRP channels in adipocytes are intriguing targets to regulate energy metabolism for preventing and combating human obesity. However, there are still several questions remain to be addressed. How are these TRP channels activated endogenously, and how $[Ca^{2+}]_i$ increases modulate non-shivering thermogenesis? Further animal and human studies are needed to address these questions, and clarification of the clinical significance of thermo-TRP channels could provide new clinical approaches to treat human obesity and related metabolic diseases.

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