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Involvement of TRPV3 and TRPM8 ion channel proteins in induction of mammalian cold-inducible proteins

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ABSTRACT

Cold-inducible RNA-binding protein (CIRP), RNA-binding motif protein 3 (RBM3) and serine and arginine rich splicing factor 5 (SRSF5) are RNA-binding proteins that are transcriptionally upregulated in response to moderately low temperatures and a variety of cellular stresses in mammalian cells. Induction of these cold-inducible proteins (CIPs) is dependent on transient receptor potential (TRP) V4 channel protein, but seems independent of its ion channel activity. We herein report that in addition to TRPV4, TRPV3 and TRPM8 are necessary for the induction of CIPs. We established cell lines from the lung of TRPV4-knockout (KO) mouse, and observed induction of CIPs in them by western blot analysis. A TRPV4 antagonist RN1734 suppressed the induction in wild-type mouse cells, but not in TRPV4-KO cells. A TRPV3 channel blocker S408271 and a TRPM8 channel blocker AMTB as well as siRNAs against TRPV3 and TRPM8 suppressed the CIP induction in mouse TRPV4-KO cells and human U-2 OS cells. A TRPV3 channel agonist 2-APB induced CIP expression, but camphor did not. Neither did a TRPM8 channel agonist WS-12. These results suggest that TRPV4, TRPV3 and TRPM8 proteins, but not their ion channel activities are necessary for the induction of CIPs at 32 °C. Identification of proteins that differentially interact with these TRP channels at 37 °C and 32 °C would help elucidate the underlying mechanisms of CIP induction by hypothermia.

1. Introduction

Most transient receptor potential (TRP) channels are non-selective cation channels that open in response to changes in temperature, ligand binding and other alterations of the channel protein [1–3]. Mammalian TRP channels comprise 28 members and are divided into six subfamilies: TRPC (canonical), TRPM (melastatin), TRPV (vanilloid), TRPA (ankyrin), TRPP (polycystin) and TRPML (mucolipin) [1,4,5]. Several of them have thermosensitive abilities, and 11 thermosensitive TRP (thermo-TRP) channels have been reported in mammals, namely, TRPV1-4, TRPM2-5, 8, TRPC5, and TRPA1 [1,6,7]. They usually function as "multi-modal receptors" that respond to various chemical and physical stimuli. All thermo-TRP channels can be activated within specific temperature ranges and transduce inputs into chemical and electrical signals. TRPV1 and 2 are heat sensitive, TRPV3, 4 and TRPM2-5 are warm sensitive, while TRPM8, TRPA1 and TRPC5 are cold sensitive ion channels [1].

Cold-inducible RNA-binding protein (CIRP, also called CIRBP or A18 hnRNP) and RNA-binding motif protein 3 (RBM3) are the first proteins found to be induced by mild hypothermia in mammalian cells [8,9]. These proteins are highly similar to each other and constitutively expressed in the testis the temperature of which is physiologically lower than the body cavity temperature [10,11]. In addition to mild hypothermia, CIRP is inducible by other stimuli such as UV and hypoxia, and involved in spermatogenesis, UV-resistance, anti-apoptosis, cell cycle progression, tumorigenesis, circadian rhythms, and inflammatory responses [12]. RBM3 is also

Abbreviations: [Ca^{2+}]i, intracellular Ca^{2+} concentration; CIP, cold-inducible protein; CIRP, Cold-inducible RNA-binding protein; KO, knockout; RBM3, RNA-binding motif protein 3; RT-qPCR, reverse transcription-quantitative polymerase chain reaction; SRSF5, serine and arginine rich splicing factor 5; TRP, transient receptor potential.

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inducible by hypoxia, enhances global protein translation, and is believed to be a pleiotropic regulator of miRNA and mRNAs [12]. Previously, we found that serine and arginine rich splicing factor 5 (SRSF5, also called SRp40) which is distantly related to CIRP and RBM3 is a novel cold-inducible protein (CIP) that responds to mild hypothermia, hypoxia, doxorubicin, hypotonicity, and UV [13]. SRSF5 is constitutively expressed in male germ cells, and the level was decreased in human testicular germ cell tumors. Furthermore, we provided evidence that TRPV4 is necessary for the induction of CIPs.

In the present study, we established cell lines derived from TRPV4-knockout (KO) mice, and found that CIPs could be induced by mild hypothermia in the absence of TRPV4. Further analyses demonstrated that TRPV3 and TRPM8 are involved in addition to TRPV4 in the hypothermia-induced expression of CIPs, and suggested that their CIP-inducing activities are independent of the ion channel activities.

2. Materials and methods

2.1. Mice

TRPV4-deficient mice [14] were kindly provided by Dr. Makoto Suzuki, Department of Pharmacology, Jichi Medical School. The mutant mice were backcrossed to C57BL/6J wild-type mice before being used in the experiments. Experimental procedures involving animals and their care were conducted in conformity with institutional guidelines that complied with the Fundamental Guidelines for Proper Conduct of Animal Experiment and Related Activities in Academic Research Institutions under the jurisdiction of the Ministry of Education, Culture, Sports, Science and Technology, Japan.

2.2. Cells and cell culture

Human U-2 OS cell line was grown in Dulbecco's Modified Eagle Medium supplemented with 10% heat-inactivated fetal bovine serum. Mouse lung fibroblast cell lines were established by mincing the lung tissues from wild-type and TRPV4-KO mice in Dulbecco's Modified Eagle Medium supplemented with antibiotics and fetal bovine serum. These cells were cultured at 37 °C and 5% CO_2, and passaged twice weekly for more than 30 times before use. For hypothermia experiments, a humidified CO_2 incubator was used at 32 °C. Cell numbers were assessed by using a counting chamber under a microscope.

Transfection of cells was performed with Lipofectamine-3000 (Invitrogen) and DharmaFECT2 reagent (Dharmacon) for plasmids and siRNAs, respectively.

2.3. Western blot analysis

Protein extraction and western blot analyses were performed as described previously [13]. Briefly, about 3–10 μg of proteins were resolved on 12% sodium dodecyl sulfate/polyacrylamide gel electrophoresis, and electrotransferred to 0.45 μm PVDF membranes. They were first incubated overnight with primary antibodies at 4 °C and then with 1 μg/ml horseradish peroxidase-conjugated secondary antibody for 1 h at 25 °C. After washing, bands were revealed with a chemiluminescence reagent (Chemi-Lumi-One or Chemi-Lumi-One Super, Nacalai Tesque, Kyoto, Japan). Images were acquired with the ChemiDoc imaging system and quantification of protein bands was done with Image Lab v4.0 software (Bio-Rad Laboratories).

2.4. Reverse transcription (RT)-quantitative polymerase chain reaction (qPCR) and genomic PCR

Extraction of RNA and RT were performed as described [13]. The qPCR reaction was performed using THUNDERBIRD SYBR qPCR Mix (TOYOBO Co., Osaka) with the StepOnePlus Real-Time PCR System (Applied Biosystems). After heating at 95 °C for 1 min, amplification of the cDNA was performed for 40 cycles: denaturation, 95 °C for 10 s; annealing, 60 °C for 30 s. Data were analyzed using the delta-delta Ct method. All experiments were performed in triplicate with three independent experiments.

Genotypes of established cell lines were verified by PCR. DNAs were extracted from cultured cells, and the TRPV4-KO and wild-type alleles were detected by PCR amplification using the program temperature control system PC-701 (Astec, Fukuoka, Japan) and a set of 3 primers, TRPV4exon4F, TRPV4exon4R and TRPV4neoF. The PCR reaction included an initial 5-min denaturation at 94 °C. Amplification of the DNA was performed for 35 cycles: denaturation, 98 °C for 10 s; annealing, 64 °C for 30 s; and extension, 68 °C for 1 min. Wild-type DNA gives a band of about 0.8 kilobase pairs. Because of the Neo insertion between the two primer sites when the gene has been disrupted, TRPV4-KO DNA gives a band of about 1.2 kilobase pairs.

2.5. Primers, siRNAs and plasmids

The primer sets for RT-qPCR were as follows: for human CIRP, 5′-CTATAGCAGCCGGAGTCAGAG-3′ and 5′- AAGTCTAGTAACGAGGCCATCC-3'; for human RBM3, 5′- GGTTATGACCGCTACTCAGG-3′ and 5′- TTCAGCTACCTTGGCAGGTC-3'; for human SRSF5, 5′-GCGCAGT TGATTCGAGGAAG-3′ and 5′-TGGCCGCTGGATTTAGTCTC-3'; for human 18S rRNA, 5′-CTCAACACGGGAAACCTCAC-3′, and 5′-CGCTCC ACCAACTAAGAACG-3'. For genotyping of cells derived from TRPV4-KO mice, TRPV4exon4F: TGTTCGGGGTGGTTTGGCCAGGATAT, TRP V4exon4R: GCTGAACCAAAGGACACTTGCATAG, and TRPV4neoF: GCTGCATACGCTTGATCCGGCTAC were used.

For suppression of TRPV3 or TRPM8 expression in human cells, siGENOME Human TRPV3 (162514) or TRPM8 (79054) siRNA.SMARTpool (Dharmacon), respectively, was used according to the manufacturer's instructions. siGENOME Non-Targeting siRNA Control Pool #1 (Dharmacon) served as negative control siRNAs. Plasmids expressing shRNA against human TRPV4 were described previously [13]. To express TRPV4 mRNA resistant to the shRNA against human TRPV4, rat TRPV4 cDNA (NM_023970.1) in pIRES/puro2/EF1alpha promoter vector was used.

2.6. Reagents and antibodies

The sources of reagents were as follows: RN1734 (Tocris Bioscience, Bristol, UK), S408271 (Sigma-Aldrich), AMTB hydrochloride (Tocris Bioscience), 2-APB (Santa Cruz Biotechnology), camphor (Tokyo Chemical Industry, Tokyo, Japan), WS-12 (Tocris Bioscience), and Fura-2-AM (Molecular Probes). All other chemicals were purchased from Nacalai Tesque.

Rabbit polyclonal antibodies recognizing the C terminus of mouse CIRP and mouse RBM3 were prepared as described [13]. The sources of commercial antibodies were as follows: anti-ACTIN (mouse monoclonal, clone C4, Millipore), anti-SRSF5/SRp40 (rabbit polyclonal, MBL, Nagoya, Japan), anti-mouse immunoglobulins/HRP (goat polyclonal, DakoCytomation), and anti-rabbit immunoglobulins/HRP (goat polyclonal, DakoCytomation).

2.7. Ca^{2+} imaging

Ca^{2+} imaging was performed as described previously [13].

Briefly, cells were incubated with 2 μM Fura2-AM in a standard bath solution at 37 °C or 32 °C in the presence or absence of TRP antagonists. The Fura2 ratiometric fluorescence (340:380 nm) measurements were recorded, and the Ca^{2+} concentration (nM) was calculated.

2.8. Statistical analysis

Data are presented as the mean ± SEM. Statistical analyses were performed using unpaired Student's *t* test. All statistical analyses were carried out using Prism v6.0 software (GraphPad Software) or JMP10 software (SAS Institute, Cary, NC). A *P*-value of <0.05 was considered significant.

3. Results

3.1. TRPV4 is necessary for induction of CIP transcripts by hypothermia

By using western blot analysis, we previously showed that RN1734, an antagonist of TRPV4 channel activity, and shRNAs against TRPV4 could suppress induction of CIPs by mild hypothermia [13]. When we co-expressed rat TRPV4 which is resistant to the shRNAs against human TRPV4 in U-2 OS cells, the suppressive effects of shRNAs were reversed (Fig. 1A). RN1734 suppressed induction of CIPs at the transcript as well as protein levels (Fig. 1B and C).

3.2. Other thermo-TRPs may compensate for the absence of TRPV4

To analyze the effects of TRPV4-KO on induction of CIPs, we established lung fibroblast cell lines from wild-type and TRPV4-KO mice (Fig. 2A). Unexpectedly, CIPs were induced by hypothermia in the TRPV4-deficient cells (Fig. 2B). The induction of CIPs was suppressed by RN1734 in the wild-type cells (Fig. 2C), but not in the TRPV4-KO cells (Fig. 2D), indicating that TRPV4 does not contribute to the CIP induction in the latter cells. Suspecting compensation for TRPV4 by other thermo-TRP channels, we utilized several antagonists, and found that a TRPV3 channel blocker S408271 and a TRPM8 channel blocker AMTB could suppress induction of CIPs by hypothermia in the mouse TRPV4-KO cells (Fig. 2E and F).

3.3. Involvement of TRPV3 and TRPM8 in induction of CIPs

Both S408271 and AMTB significantly suppressed the induction of CIPs by hypothermia in human U-2 OS cells as well (Fig. 3A and B). Although S408271 and AMTB display selectivity for TRPV3 and TRPM8, respectively, over other TRP channels, they may have additional effects on other molecule(s) essential for the induction of CIPs. To exclude this possibility, we knocked down endogenous TRPV3 or TRPM8 mRNA by expressing specific siRNAs. siRNAs against TRPV3 suppressed the hypothermia-induced expression of CIPs (Fig. 3C). siRNAs against TRPM8 also showed suppressive effects on induction of CIPs (Fig. 3D).

3.4. TRP ion channel activities and induction of CIPs

We next examined whether activation of the TRPV3 or TRPM8 ion channel induces expression of CIPs or not. A TRPV3 ion channel agonist 2-APB that also activates TRPV1, TRPV2 and TRPV6 [15] induced CIPs at 25 μM (Fig. 4A). However, camphor which activates TRPV3 and TRPV1 channels [15] did not (Fig. 4B). WS-12 which activates TRPM8 channel [16] did not induce expression of CIPs (Fig. 4C).

As reported previously [13], intracellular Ca^{2+} concentration ($[Ca^{2+}]i$) was higher in U-2 OS cells cultured at 37 °C than those at 32 °C (Fig. 4D). In the presence of S408271, $[Ca^{2+}]i$ was significantly decreased at 37 °C, but not at 32 °C, suggesting that TRPV3 ion channel is open and contributes to calcium influx at 37 °C. In the presence of AMTB, $[Ca^{2+}]i$ was significantly decreased at 32 °C, but not at 37 °C, suggesting that TRPM8 ion channel contributes to calcium influx at 32 °C. Of note, $[Ca^{2+}]i$ was significantly higher at 37 °C than 32 °C in the presence of these antagonists.

4. Discussion

Transcript and protein levels of CIRP, RBM3 and SRSF5 are known to be increased by mild hypothermia [8,9,13]. Although involvement of the transcription factor Sp1 and the promoters in the CIRP gene, and enhancement of splicing efficiency in the induction of CIRP have been reported [17–19], precise mechanisms, especially the temperature sensors and the signaling pathways, by which hypothermia induces the expression of CIPs are poorly understood. By using antagonists and shRNA against TRPV4, we previously showed that TRPV4 is necessary for the induction of CIPs [13]. Here, we confirmed this by rescuing the gene function with

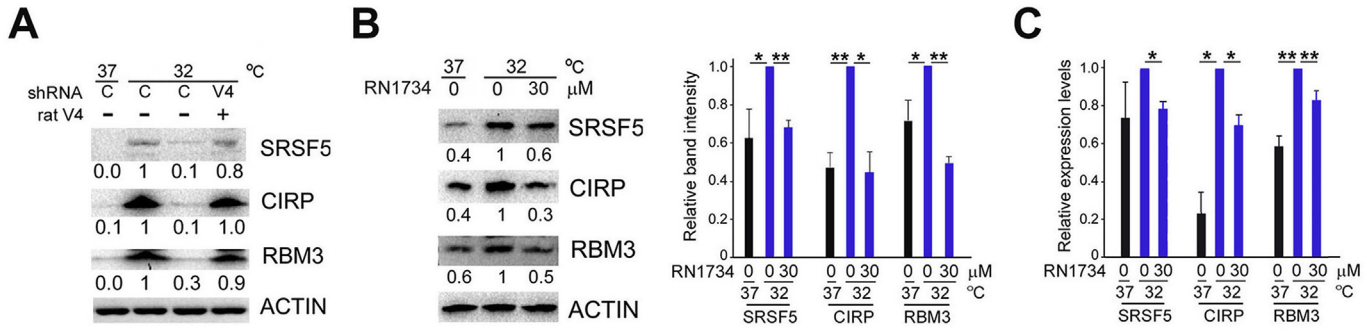

Fig. 1. TRPV4 is necessary for induction of CIP transcripts by hypothermia. (A) U-2 OS cells were transfected with plasmids expressing shRNAs against TRPV4 (V4) or vector alone (C) with (+) or without (-) plasmids expressing rat TRPV4. Transfected cells were cultured at 37 °C for 40 h, then transferred to the indicated temperatures, and protein levels were determined by western blot after further 8-h incubation. Relative band intensities after normalization to ACTIN expression are shown below the panels (representative of 2 independent experiments). (B) U-2 OS cells were cultured at 37 °C or 32 °C in the presence of RN1734 for 10 h, and analyzed by western blot. Band intensities relative to those at 32 °C were determined after normalization to ACTIN (left, representative results. Right, data indicate mean ± SEM; n = 3). *, $P < 0.05$. **, $P < 0.01$. (C) U-2 OS cells were cultured at 37 °C or 32 °C in the presence of RN1734 for 6 h, and analyzed by RT-qPCR and expressed as relative to those at 32 °C after normalization to 18S rRNA (data indicate mean ± SEM; n = 3 per group).

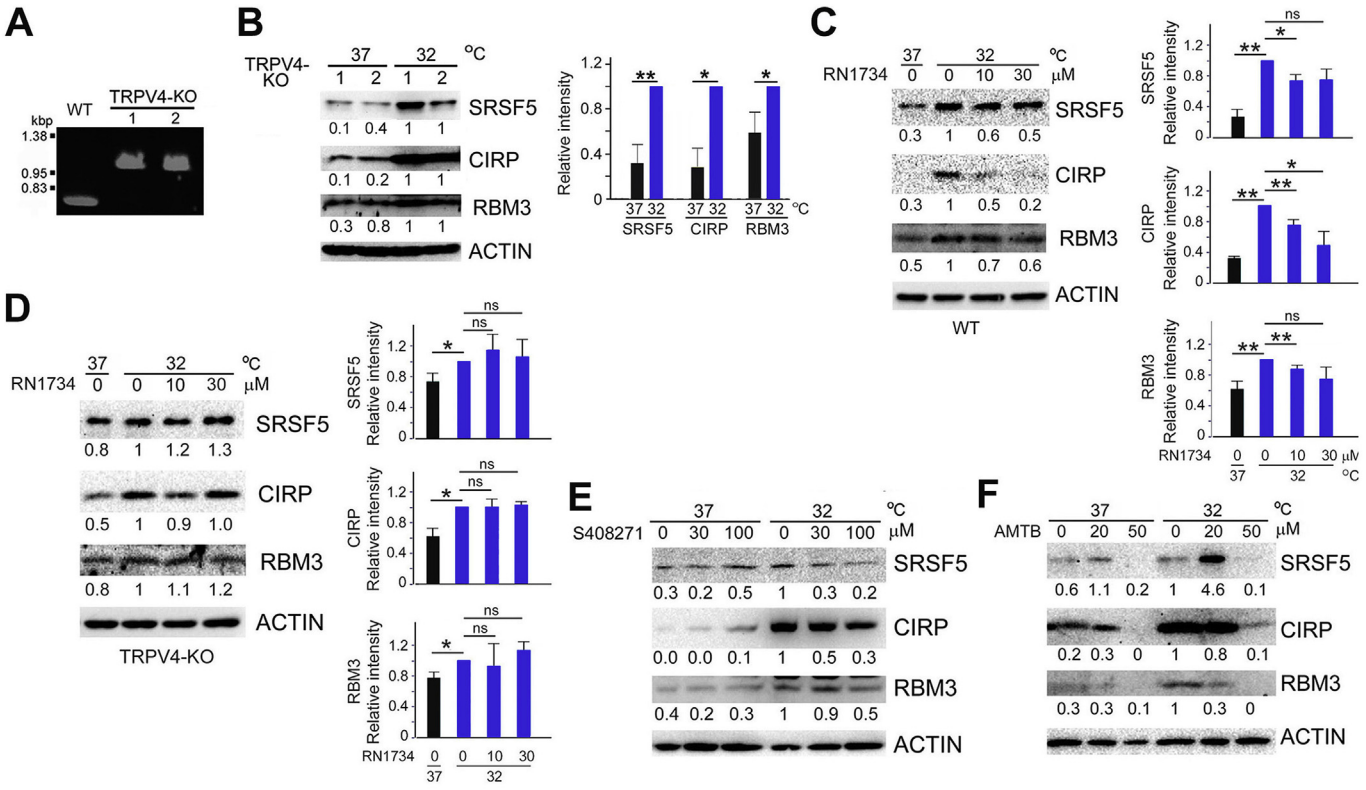

Fig. 2. Induction of CIPs by hypothermia in the absence of TRPV4. (A) Genotyping of cell lines derived from wild-type mouse (WT) and TRPV4-knockout (KO) mouse (cell lines 1 and 2) by PCR. (B) TRPV4-KO cells were cultured at 37 °C or 32 °C for 24 h, and analyzed by western blot. Band intensities relative to those at 32 °C were determined after normalization to ACTIN (left, representative results. Right, data indicate mean ± SEM; n = 3). *, $P < 0.05$. **, $P < 0.01$. (C, D) WT (C) and TRPV4-KO (D) cells were cultured in the presence of RN1734 and analyzed as in (B) (left, representative results. Right, data indicate mean ± SEM; n = 3). ns, not significant. (E, F) TRPV4-KO cells were cultured in the presence of S408271 (E) or AMTB (F) and analyzed as in (B) (representative of 2 independent experiments).

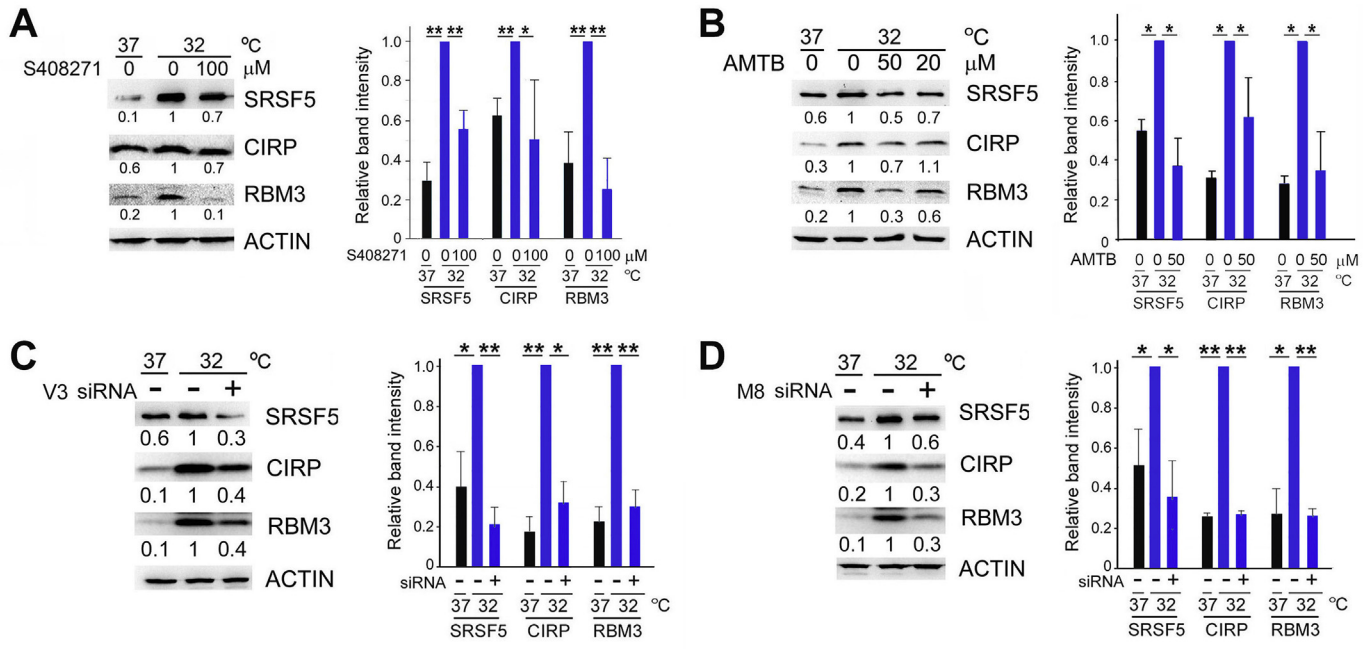

Fig. 3. Effects of antagonists against TRPV3 and TRPM8 channels on CIP induction. (A, B) U-2 OS cells were cultured at 37 °C or 32 °C in the presence of S408271 (A) or AMTB (B) for 24 h, and analyzed by western blot. Band intensities relative to those at 32 °C were determined after normalization to ACTIN (left, representative results. Right, data indicate mean ± SEM; n = 3 or 4). *, $P < 0.05$. **, $P < 0.01$. (C, D) U-2 OS cells were transfected with siRNAs against TRPV3 (C, +), TRPM8 (D, +) or control siRNAs (-). 48 h after transfection, cells were transferred to the indicated temperatures and protein levels were determined after further 24-h incubation as in (A) (left, representative results. Right, data indicate mean ± SEM; n = 3).

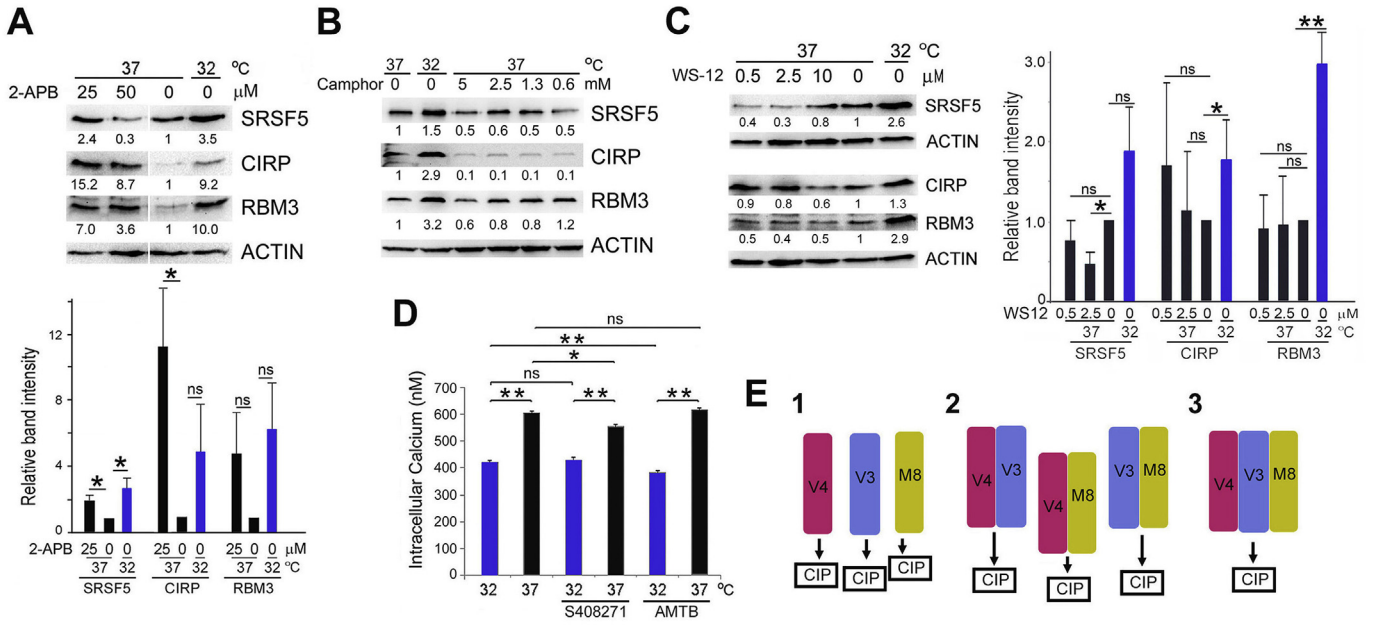

Fig. 4. TRPV3 and TRPM8 ion channel activities and induction of CIPs. (A, B, C) U-2 OS cells were cultured at 37 °C or 32 °C in the presence of 2-APB (A), camphor (B) or WS-12 (C) for 24 h, and analyzed by western blot. Band intensities relative to those at 37 °C were determined after normalization to ACTIN. Representative results and graphs are shown (data indicate mean ± SEM; n = 3). *, $P < 0.05$. **, $P < 0.01$. ns, not significant. (D) Quantification of $[Ca^{2+}]i$ by Fura-2 in U-2 OS cells. Cells were cultured at 37 °C or 32 °C for 24 h in the presence or absence of 100 μM S408271 or 40 μM AMTB as indicated (data indicate mean ± SEM; n = 6). (E) Possible combinations of thermo-TRPs necessary for CIP induction.

the shRNA-resistant TRPV4, excluding possible off-target effects of the shRNA knockdown. Since a TRPV4 antagonist RN1734 suppressed induction of CIP transcripts by hypothermia, TRPV4 is most probably involved in hypothermia-induced expression of CIPs at or before the transcript-level rather than the protein-level.

Homozygotes for a null allele of TRPV4 show abnormal touch/nociception and late-onset hearing loss [20]. Homozygotes for a different null allele show impaired bladder voiding, abnormalities in touch/nociception, osmotic regulation and vasodilation, ocular hypertension but no hearing or vestibular deficits or temperature phenotypes. In cell lines derived from TRPV4-KO mice, we observed induction of CIPs by hypothermia, and consistent with TRPV4-deficiency the induction was not suppressed by RN1734. This may not be so surprising, because many temperature-sensitive TRP and non-TRP receptors detect overlapping temperatures in the warm to hot range, and therefore, individual TRP channel KO mouse models do not always display strong temperature phenotypes as compensation by redundant temperature detectors takes place [7,21]. In TRPV4-KO cells, antagonists and shRNAs against TRPV3 and TRPM8 suppressed induction of CIPs by hypothermia. TRPV3 is highly expressed in skin, where it is involved in skin barrier formation and hair growth, and mediates the cutaneous sensation of itch and pain [15,22]. TRPM8 was discovered as prostate-specific gene upregulated in cancer and a menthol receptor, and is the main detector of environmental cold [23]. How much do TRPV3 and TRPM8 contribute to the compensation remains to be clarified.

Although induction of CIPs by hypothermia is dependent on TRPV4, effects of the TRPV4 channel antagonists and agonists [24] are not consistent with their effects on the ion channel activity [13]. For example, Gd^{3+}, a general TRPV antagonist, and ruthenium red, a non-competitive pan inhibitor of all TRP channels including TRPV1-4, show no suppressive effects on CIRP and RBM3. A potent TRPV4 agonist GSK1016790A does not induce expression of CIPs. Herein, camphor and WS-12 which activate TRPV3 and TRPM8 channels, respectively [15,16], did not induce CIPs, although antagonists against TRPV3 and TRPM8 channels suppressed hypothermia-induced expression of CIPs, and a TRPV3 channel agonist 2-APB induced expression of CIPs. Previously, we observed higher $[Ca^{2+}]i$ in TRPV4-expressing cells at 37 °C than 32 °C, and the differences disappeared in the presence of TRPV4 inhibitors [13]. Present analysis of $[Ca^{2+}]i$ suggested that TRPV3 ion channel is open at 37 °C and closed at 32 °C like TRPV4, whereas TRPM8 is open at 32 °C and closed at 37 °C, and that the difference in $[Ca^{2+}]i$ at these temperatures is mainly due to TRPV4 ion channel activity. Ca^{2+} chelator BAPTA-AM has been shown to decrease the $[Ca^{2+}]i$ and increase expression of CIPs at 37 °C [13]. Since a TRPM8 antagonist AMTB suppressed induction of CIPs when it further decreased the $[Ca^{2+}]i$ at 32 °C, the possibility that a decrease in $[Ca^{2+}]i$ mediates CIP induction by hypothermia could be negated. Taken together, these results suggest that TRPV4, TRPV3 and TRPM8 proteins, but not their ion channel activities are necessary for induction of CIPs at 32 °C. Interestingly, a non-channel function of TRPM8 has recently been reported [25]. TRPM8 interacts with Rap1 intracellularly and prevents its cytoplasm-plasma membrane trafficking, thus inhibiting cell migration. Identification of proteins that differentially interact with TRPV3, TRPV4 and TRPM8 at 37 °C and 32 °C would help elucidate the underlying mechanisms of CIP induction by hypothermia.

Most TRP channels permeate cations through central nonselective cation entry pores that are symmetrically located in the plasma membrane [26]. TRP channels are also located in the membrane of various organelles, and mainly formed from four subunits [22,23,27,28]. As the TRP ion channel activity seems independent of the CIP-inducing activity, whether localization at the plasma membrane and formation of multimers are necessary for the CIP-inducing activity is presently unknown. TRPV4, TRPV3 and TRPM8 share the same basic topology, consisting of six transmembrane domains, a pore-forming loop between domains 5–6, and cytoplasmic N and C termini [2,3,22,23]. They form functional channels as homotetramers, but heteromultimerization has also been observed [29]. These channels may display properties different from those of homomultimeric channels. TRPV4-TRPC1

heteromeric channels mediate flow-induced endothelial [Ca^{2+}]i influx and subsequent vascular relaxation [30]. TRPV4 and TRPP2 assemble to form a 23-pS divalent cation-permeable non-selective ion channel in renal principal cells [31]. TRPV3-TRPV1 heteromeric channels exhibit unique activation threshold temperature [32]. Hetero-tetrameric channels composed of subunits of 3 different subfamilies, TRPV4, TRPC1, and TRPP2 have been reported [33]. TRPM8 tunes sensory neurons to a range of different temperatures in combination with other (potassium) ion channels [5]. It will be interesting to examine whether TRPV4 participates in the response to mild hypothermia alone or in combination with TRPV3, TRPM8 and possibly non-TRP temperature-sensitive proteins (Fig. 4E).

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