RNA BIOLOGY
2024, VOL. 21, NO. 1, 1–6
https://doi.org/10.1080/15476286.2024.2379118

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POINT OF VIEW

Temperature-sensing riboceptors

Savani Anbalagan

Institute of Molecular Biology and Biotechnology, Faculty of Biology, Adam Mickiewicz University, Poznań, Poland

ABSTRACT

Understanding how cells sense temperature is a fundamental question in biology and is pivotal for the evolution of life. In numerous organisms, temperature is not only sensed but also generated due to cellular processes. Consequently, the mechanisms governing temperature sensation in various organisms have been experimentally elucidated. Extending upon others' proposals and demonstration of protein- and nucleic acid-based thermosensors, and utilizing a colonial India 'punkah-wallahs' analogy, I present my rationale for the necessity of temperature sensing in every organelle in a cell. Finally, I propose temperature-sensing **riboceptors** (**ribo**nucleic acid re**ceptors**) to integrate all the RNA molecules (mRNA, non-coding RNA, and so forth) capable of sensing temperature and triggering a signaling event, which I call as thermocrine signaling. This approach could enable the identification of riboceptors in every cell of almost every organism, not only for temperature but also for other classes of ligands, including gaseous solutes, and water.

ARTICLE HISTORY
Revised 19 June 2024
Accepted 8 July 2024

KEYWORDS
Thermoreceptor; temperature sensing; RNA thermometer; ribozyme; Thermocrine signaling

Have we identified all the temperature-sensing protein-based receptors?

Temperature is one of the pivotal regulators of the evolution of molecular machinery and life. The 600 million years of evolutionary conservation of temperature regulation capacity has been suggested to provide a survival benefit in organisms [1]. Temperature can affect growth rates across various cells and organisms [2–6]. Apart from environmental changes in temperature, pathogen infections and toxin exposure in plants and animals can also increase organismal temperatures [1,7–10]. The mechanisms that allow organisms to survive high temperatures have been attributed to heat shock proteins, temperature-sensitive gene cluster architecture, differential osmotic activity, differential antioxidant defense mechanisms, differential sequences that allow the formation of a relatively higher number of protein disulfide bonds, and protein stabilization [11–13].

The mechanisms that allow cells to sense membranal temperature include the temperature-sensing TRP channels (transient receptor potential) that are referred to as sensory thermoreceptors [14–16]. Such temperature-sensing TRP channel proteins have relatively high Q_{10} (temperature coefficient: the fold-increase in rate per 10°C increase) in comparison to other non-temperature sensing channel proteins [17]. In *Drosophila melanogaster*, dTrpA1 in the warmth-activated anterior cell neurons and GR28b.d in the antennal arista are membranal temperature-sensing proteins [18–20]. In the insect triatomine (*Rhodnius prolixus*), TRPA5B is also a temperature-sensing protein that exhibit a high temperature coefficient ($Q_{10} = 25$) [21]. In addition to TRP channels, some GPCRs (G protein-coupled receptors) also exhibit temperature-sensing properties. For instance, light-sensitive rhodopsin in mammals and Drosophila, as well as mouse melanopsin (Opn4), have been identified as membranal temperature-sensing proteins (thermosensors) [22–24].

In addition to membranal proteins, temperature can also be sensed internally via other intracellular proteins (thermosensors or thermometers) that are intrinsically temperature-sensitive. Such proteins either have temperature-sensitive domains or lose their dimerization capabilities at high temperatures. For instance, bacterial GrpE, sigma 32, and DesK are temperature-sensing proteins that exhibit nucleotide exchange factor, transcriptional factor, and kinase activity, respectively [25–27]. In *E. coli*, the dimeric GrpE, at heat shock temperatures, undergoes unfolding of the long N-terminal helix pair, resulting in the loss of its nucleotide exchange factor activity [28]. In Salmonella, the temperature-sensing activity of the DNA-binding autoregulator TlpA depends on the monomer-to-coiled-coil equilibrium [29]. At high temperatures, TlpA loses its DNA binding and *tlpA* repressor activity. Another example is TdcA (thermosensory diguanylate cyclase), a temperature-sensing protein that exhibits a 100-fold increase in the activity of c-di-GMP generation upon a 10°C increase [30]. TdcA diguanylate cyclase is inactive at 22°C and highly active at 37°C. TdcA and some TdcA homologs are thermosensitive via a conserved temperature-sensitive PAS (Per-Arnt-SIM) domain. In yeast, nucleotide exchange factor Mge1, a GrpE homolog, was identified as a thermosensor. At heat-shock temperatures, it loses its dimerization, interaction with Hsp70, and the capability to regulate its ATPase activity [31,32]. Human HSF1 (heat shock factor 1) is also

CONTACT Savani Anbalagan savani.anbalagan@amu.edu.pl Institute of Molecular Biology and Biotechnology, Faculty of Biology, Adam Mickiewicz University, ul. Uniwersytetu Poznanskiego, Poznań 61-614, Poland

a temperature-sensing protein [33]. HSF1 is a transcription factor that trimerizes at increased temperature, binds to promoter sites with heat shock elements, induces gene expression, and confers proteostasis and stress response. In Arabidopsis, TWA1 (Thermo-with abscisic acid-response 1), an intrinsically disordered protein, is a temperature-sensing transcriptional co-regulator that undergoes a conformational change at high temperature, accumulates in the nucleus, and binds to other transcriptional factors that promote the expression of genes that confer thermotolerance [34]. Overall, similar to the gas-sensing gasoreceptor proteins that have diverse signaling domains and activity (kinase, phosphodiesterase, transcription factor, guanylate cyclase, adenylate cyclase, etc.), temperature-sensing proteins or receptors also seem to have diverse signaling domains [35–37]. But are the above-listed proteins the only temperature-sensing proteins in cells? [38,39]

Temperature differences exist internally across different regions and cellular organelles. For instance, the nucleus is marginally hotter than the cytoplasm [40]. In neuron-like cells *in vitro*, cell body temperature is higher than in neurite-like structures [41]. Temperatures in highly energy-active organelles such as mitochondria is around 50°C, and ATP synthesis perturbations in mitochondria can also cause temperature differences [42–44]. Therefore, temperature-sensing must occur in almost all organelles and regions within the cell.

To illustrate the need for region/organelle-specific temperature-sensing mechanisms, I draw an analogy to colonial India. The British, struggling to acclimate to the Indian heat while maintaining their aristocratic attire, employed 'punkah wallahs' – servants or slaves who manually operated ceiling fans called punkahs. These fans, mounted on rectangular wooden frames with cloth, were pulled via a pulley system by the punkah wallahs, cooling the British as they moved between rooms [4546,46. In some cases, the punkah wallahs were completely isolated from the room, as a small hole in the room allowed the rope to be pulled via the pulley. Similar to the punkah wallahs adjusting the cooling in each room, temperature-sensing mechanisms must exist in each cellular organelle and region. The primary function of these mechanisms must be to ensure that the temperature in the cellular microenvironment is tightly regulated probably also by acting along with aquareceptors [47].

Despite the advent of electricity and air conditioners, which require temperature sensors to sense room temperature, cells similarly need internal temperature sensors. Hence, we must identify all temperature-sensing receptors through a systematic approach, akin to research that identifies specific receptors for ligands or transcription factor targets. Although enzyme activity generally decreases at increased temperatures (16-fold per 25°C), proteins with extreme temperature-dependent activity variations are likely candidates for either heat or cold-sensing receptors [48]. Systemically identifying temperature-sensing receptors with unusually high temperature-coefficient will allow us to identify all temperature-sensing receptors. I propose the term 'agnireceptors' ('Agni' in Sanskrit for 'God of fire') for all temperature-sensing proteins (thermoreceptors, thermosensors, and cold-sensing proteins), regardless of their localization and signaling domains and 'thermocrine signaling' for all temperature-dependent signaling events that are sensed and triggered via temperature-sensing receptors [14,49–51]. A unified terminology may facilitate the systemic study of temperature-sensing proteins' functions, especially with advanced deep-learning algorithms that aim to replace animal models in drug discovery [49].

Have we identified all the temperature-sensing nucleic acid-based receptors?

During evolution, temperature sensing was likely crucial for proto-organisms that lacked proteins or with limited protein-based cellular machinery [52,53]. To understand how temperature sensing might have occurred in such organisms, we can study RNA-based temperature-sensing mechanisms observed in microorganisms. These mechanisms often rely on stem-loop-based secondary structures [54,55]. For instance, certain mRNAs contain temperature-sensing elements that regulate the translation of downstream genes, permitting translation only at higher temperatures when ribosome-binding sites are accessible [56–59]. An example is the temperature-sensitive 5' mRNA coding sequence of the bacterial *rpoH* gene, which codes for the heat shock transcription factor sigma 32 [60]. The stability of mRNA secondary structures is temperature-dependent, destabilizing under conditions like heat shock (shift from 30°C to 42°C). Another example is found in *Yersinia pestis* where the *lcrF* Shine-Dalgarno sequence is sequestered in a temperature-sensitive stem-loop. This structure allows ribosome access and initiates translation only after temperature-induced conformational changes [61,62]. Similarly, cold temperature-induced ncRNA (non-coding RNA) *COOLAIR*, *COLDWRAP*, and *COLDAIR* in plants have also been reported but whether these are intrinsically temperature-sensitive is unclear [63,64]. In my view, 'RNA thermometers' or 'RNA thermosensors' can be considered as RNA-based temperature-sensing receptors or proto-receptors. A discussion is warranted on when to categorize these structures as receptors. Riboswitches, for instance, have been proposed as receptors for metabolites and hormones, and temperature-sensing riboswitches have been identified as well [65–67]. The determination of when an RNA thermometer or thermosensor qualifies as a receptor depends on the extent of downstream signaling events it triggers. Analogous to 'ribozymes' for RNA-based enzymes, it would be beneficial to adopt a unifying term for RNA-based receptors [68].

To encompass all RNA molecules (mRNA, non-coding RNA, etc.) capable of directly sensing various stimuli within a cell – such as temperature, gravity, gaseous solutes, water, metal ions, metal clusters, amino acids, pH, and other biological molecules – and triggering a signal, I propose the term 'riboceptors' (**ribo**nucleic acid re**ceptors**). Examples of riboceptors also include RNA-based evolutionarily old proto-receptors, such as the riboswitches sensing lithium, sodium, thiamine, lysine, magnesium, manganese, nickel, cobalt, and others [69–73]. For temperature-sensing riboceptors, temperature *per se* serves as the ligand, with hot and cold temperatures acting as agonists and antagonists, or vice versa (Figure 1).

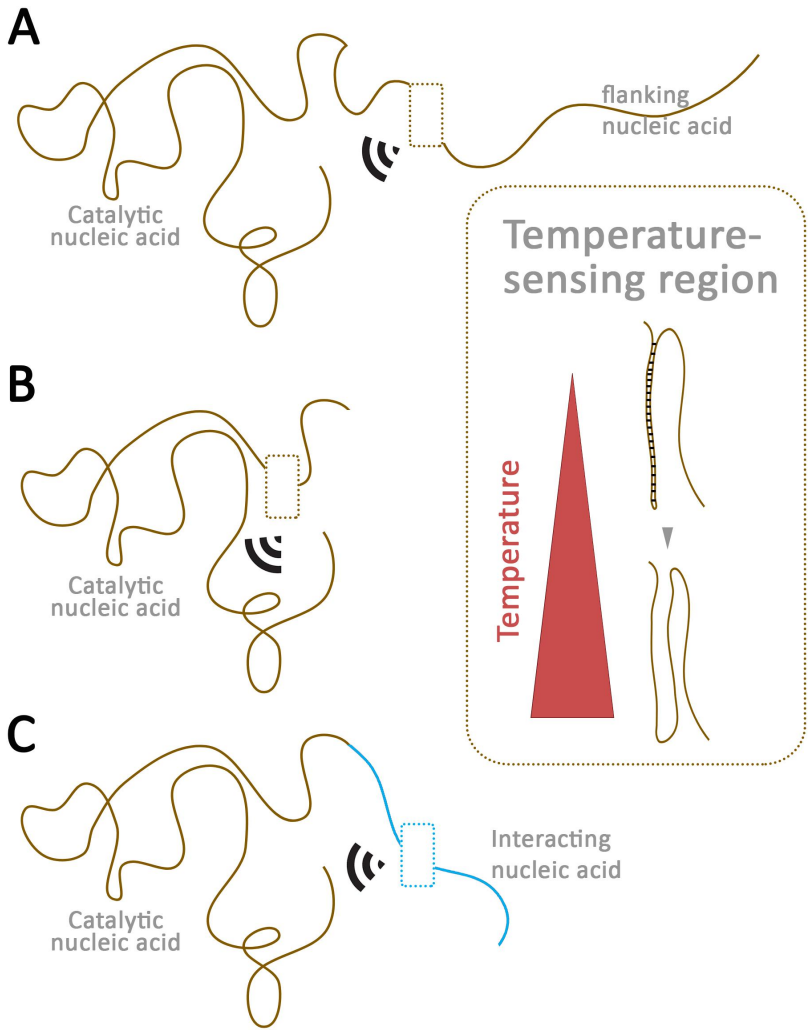

Figure 1. Model of putative temperature-sensing riboceptors.

(A) A ribozyme or deoxyribozyme flanked by sequences that contain temperature-sensitive structures, where temperature-dependent structural changes modulate catalytic activity. (B) A ribozyme or deoxyribozyme containing temperature-sensitive structures, where temperature-dependent structural changes modulate catalytic activity. (C) A ribozyme or deoxyribozyme binding with other nucleic acid sequences that contain temperature-sensitive structures, temperature-dependent structural changes modulate catalytic activity.

How to identify temperature-sensing riboceptors?

To identify temperature-sensing riboceptors, we first need to systematically identify all RNA structures with catalytic (or even transcription factor) activity *in vivo*. In such functional RNA molecules, we need to identify which contain or are flanked with highly temperature-sensitive sequences and structures (Figure 1(A,B)). Several computational tools have been developed and applied to identify such temperature-sensitive structures. However, the predictions made by these tools do not always align closely with *in vivo* temperature sensitivity. This discrepancy is not surprising, as even the binding of ribosomes to specific temperature-sensitive structures can promote RNA unwinding/melting at high temperatures [74–80]. Next, we should determine which ribozymes exhibit an unusually high temperature coefficient (Q_{10}) *in vivo*. Such highly temperature-sensitive ribozymes are likely to be temperature-sensing riboceptors. Mutational studies disrupting temperature-sensitive regions and structural stability should confirm the loss of temperature-sensing activity and modulation of ribozyme activity. We must also debate how distant the temperature-sensitive flanking sequence can be from the ribozyme to still be considered a temperature-sensing riboceptor (Figure 1(A)). Another possibility is that a ribozyme lacking temperature-sensitive regions may interact with a temperature-sensitive nucleic acid, and the resulting complex may act as a temperature-sensing riboceptor (Figure 1(C)).

Is it temperature sensing *per se*, or is it loss of binding partners?

One potential caveat when identifying temperature-sensing riboceptors is determining whether the changes in temperature affect only the nucleic acid structure or also impact the binding of other components necessary for catalytic or signalling activity. However, the question arises: are there any proteins or nucleic acids that function entirely independently without interacting with other molecules? Even the temperature-sensing TRPV1 channel can bind to various classes of endogenous and

exogenous molecules [81–83]. Both TRPV1 and TRPV3 channels seem to require lipid binding or ejection for temperature sensitivity [84,85]. Yet, they are still considered temperature-sensing receptors and not lipid-sensing receptors. Similarly, an adenine-sensing riboswitch was identified as temperature-sensitive due to its 35-nucleotide temperature-sensitive module and has been proposed as a riboswitch-thermostat [67,86,87]. In the case of the RNA thermometer MiniROSE (Repression Of heat Shock gene Expression) RNA and agsA mRNA-based thermometer, the temperature-based 'melting' of RNA is facilitated by ribosome binding [55,59,80]. Overall, temperature-sensing riboceptor activity could be modulated by its binding factors, similar to the above-mentioned examples of temperature-sensing proteins and RNA. Additionally, besides RNA, DNA also contains temperature-sensitive structures, and DNA structures (deoxyribozymes or DNAzyme) can also exhibit catalytic activity [88–94]. Therefore, it is theoretically plausible that temperature-sensing deoxyriboceptors may exist as well.

Overall, until all the putative temperature-sensitive nucleic acid structures have been systemically characterized for their ability to sense temperature *in vivo*, it remains challenging to dismiss the possibility of temperature-sensing riboceptors. Identifying temperature-sensing agnireceptor proteins and riboceptors may help us better understand processes such as RNA editing and the cross-talk with gas-sensing gasoreceptors, water-sensing aquareceptors, and organism physiology [30,35,95–97]. It may also help us understand the evolutionary origins of receptors and cellular signaling. With temperature and gases likely preceding RNA and protein world, thermocrine and gasocrine signaling via riboceptors are likely one of the earliest cellular signaling mechanisms during the evolution of life [98].

Author contributions

Savani Anbalagan: conceptualization, writing of the original draft, and review and editing.

Disclosure statement

The funding agency and institution S.A. is affiliated with was not involved in the contents of the manuscript.

Funding

S.A. is supported by National Science Centre grants (SONATA-BIS 2020/38/E/NZ3/00090 and SONATA 2021/43/D/NZ3/01798).

ORCID

Savani Anbalagan http://orcid.org/0000-0003-4839-9439

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