

1

Temperature for Living Things

Temperature is one of the most influential physical parameters in our daily lives. For example, in Tokyo, where the author lives, there are four seasons throughout the year. When it is cold in the winter, people travel to tropical countries to search for warmth. The arrival of spring can be recognized by the warmth of the sunshine filtering through the leaves of trees and the gentle breeze. On the other hand, recent summers have been too hot to relax without an air conditioner. A French chef always pays attention to the temperature of a frying pan and an oven, and a Japanese chef checks the oil temperature in a pot to deep-fry crispy tempura.

In the same way, temperature is intensely involved in the activity of living things from a biological viewpoint (Cossins and Bowler, 1987). Humans sweat in summer and shiver in winter to maintain their body temperature. When we feel ill, we measure the body temperature first. When I was a child, we used a mercury-filled thermometer to measure the body temperature, but now a thermistor has replaced it. Accordingly, it is only natural that there is a long history of comprehending temperature and measuring it. Some intriguing literature is available for the historical background on temperature measurements from the 16th century (Middleton, 1966; Chang, 2004). Here, as the first chapter of this textbook, the relationships between temperature and organisms are summarized. As indicated in Figure 1.1, temperature-related biological phenomena can be categorized into “spontaneous thermogenesis” and “response to environmental temperature” at both an individual body level and a single cell level. Each category will be introduced with relevant examples. Of them all, the spontaneous thermogenesis in single living cells will be highlighted in Chapter 3 as a new outcome brought about by intracellular thermometry.

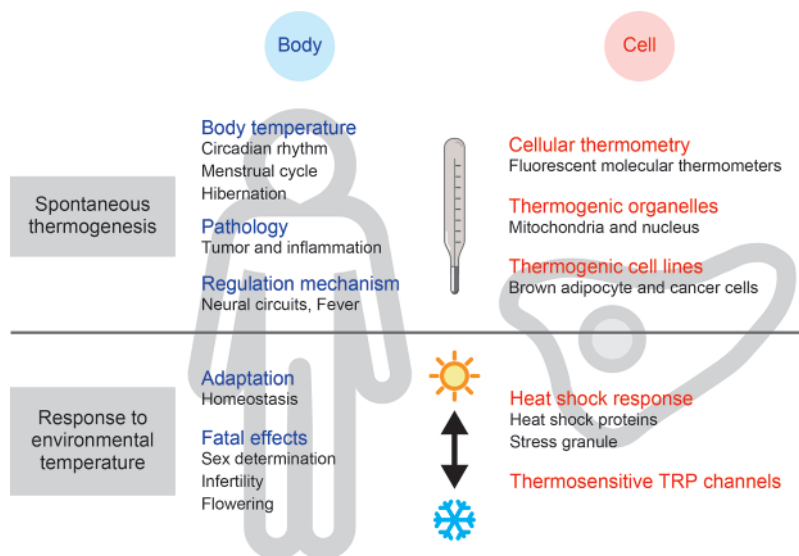


Figure 1.1 Keywords in biological studies that correlate temperature with physiological events. The original figure is from Okabe and Uchiyama (2021) *Commun. Biol.*, 4, 1377 and is updated here.

1.1

Temperature of Individuals

1.1.1

Spontaneous Heat Generation

1.1.1.1 Human

A human with a body temperature of 36–37 °C is a representative of an endotherm; the body temperature of endotherms is kept higher than that of the environment by spontaneous heat generation (called thermogenesis) (Geneva et al., 2019). Although we were told that humans are homeotherms in our childhood, the actual body temperature of humans considerably varies within a few degrees in relation to circadian rhythms, including ultradian and infradian rhythms (Figure 1.2a) (Zulley et al., 1981). Misconceptions by the use of the terms “endotherm” and “warm-blooded” for mammals have been pointed out for correct comprehension of organismal thermoregulation (Brack Jr. et al., 2022). Women have another circadian rhythm of basal body temperature due to the ovulation cycle (Figure 1.2b) (Lee, 1988; Baker et al., 2020). The menstrual cycle-dependent variability in basal body temperature is affected by aging. However, seasonal variation is slight, and thus, basal body temperature is being proposed as a non-invasive diagnostic indicator of ovulation (Tatsumi et al., 2020). The body temperature of humans is also influenced by race, age, voluntary exercise, and disease (Refinetti and Menaker, 1992).

Body temperature is one of the most basic vital signs in clinical diagnosis and routine human health care. To measure human body temperature with high

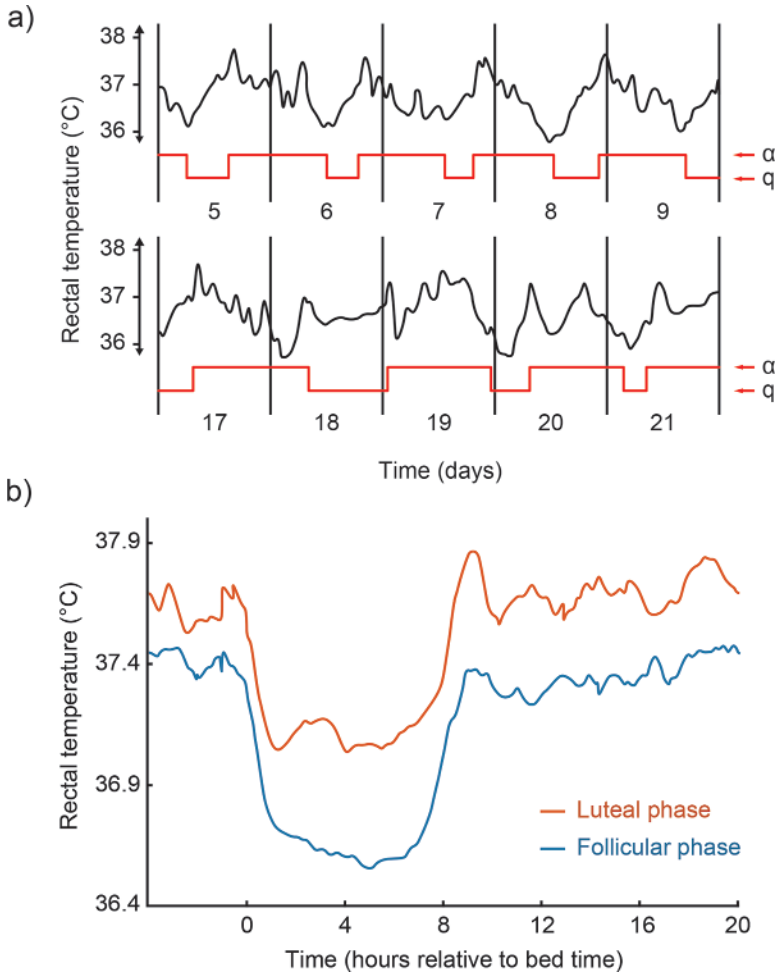


Figure 1.2 Variation in human body temperature. (a) Rectal temperature (black) and sleep-wake cycle (red) recorded in an isolated subject during internal synchronization (upper) and internal desynchronization (lower). α : wakefulness; q : bedrest. Adapted from Zulley et al. (1981) *Pflügers Arch.*, **391**, 314–318. (b) Averaged rectal temperatures of 15 young women (age: 22 ± 4 years) at the mid-follicular and mid-luteal phases in their menstrual cycles. Subjects followed their usual daytime schedules and spent the nights in a sleep laboratory. Adapted from Baker et al. (2020) *Temperature*, **7**, 226–262.

accuracy, actual and predictive measurements using instruments or mathematics, either invasive or non-invasive, are used (Childs, 2018; Chen, 2019). The methods for measuring the human body temperature involve wearable temperature sensors, and information technology-based real-time and long-term recording and expand to the application of life-critical decision-making and mass screening of diseases.

The regulation of human body temperature has been the central subject of physiology (Houdas and Ring, 1982; Jessen, 2001). It functions with the nervous system. Some molecules involved in temperature sensing in the periphery and the neural circuits that transmit temperature information to the brain, as well as the

central circuits for maintaining body temperature homeostasis, have been identified, whereas the detailed thermoregulatory mechanisms are still unclear (Tan and Knight, 2018). Fever is an uncomfortable, ill status for us, but it is even controlled under a thermoregulation system with identified neural circuits. In addition to the inflammatory response induced by pathogen infection (Roth et al., 2006), fever can also be caused by social stress (Kataoka et al., 2020).

In contrast to heat generation for a healthy life, cancers and tumors significantly increase the focus temperature, which has been empirically accepted since the 1960s (Lawson and Chughtai, 1963). Now, infrared thermography of skin temperature is considered adequate for the diagnosis of malignant soft-tissue tumors (Figure 1.3a, 1.3b) (Shimatani et al., 2022). Microcalorimetric investigation using a mass of cells confirmed that the heat production rate of tumor cells depends on their malignancy (Figure 1.3c) (Monti et al., 1986).

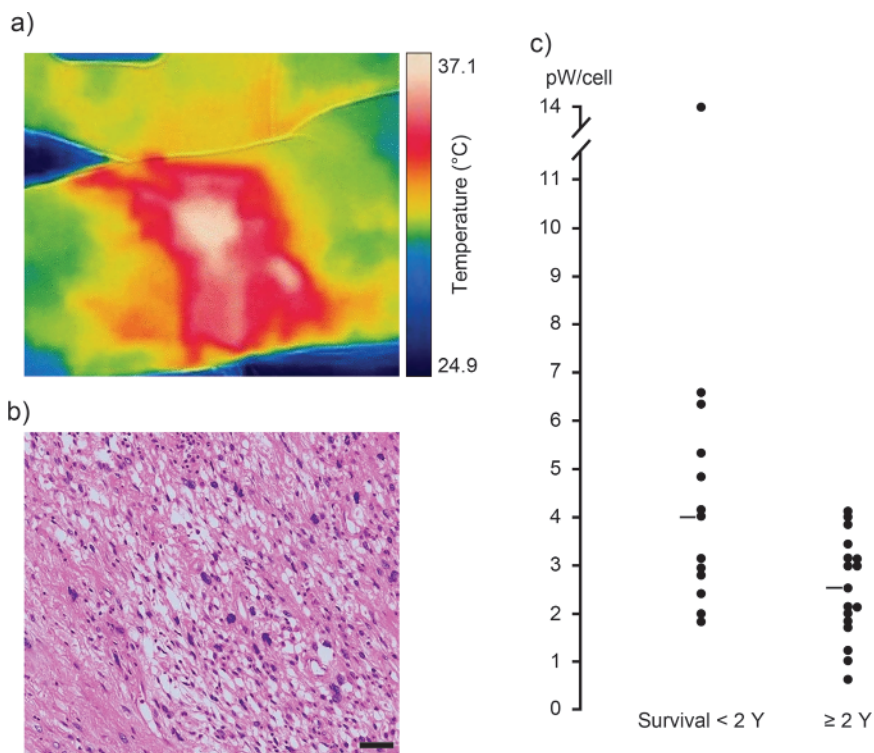


Figure 1.3 Heat production in tumors. (a,b) Representative case of myxofibrosarcoma. (a) Skin temperature map by infrared thermography. A malignant soft-tissue tumor in the right thigh was diagnosed as myxofibrosarcoma. The skin temperature on the affected part is higher than the surrounding areas. (b) Sections of the myxofibrosarcoma stained with hematoxylin and eosin (magnification: $\times 200$). Panels (a,b) are adapted from Shimatani et al. (2022) *Int. J. Clin. Oncol.*, **27**, 234–243. (c) Heat production rate per lymphoma cell from non-Hodgkin lymphoma patients. The left group of 13 patients died within two years, while the right group of 17 patients survived two years or longer. Horizontal bars indicate median values. Panel (c) Monti et al. (1986) *Scand. J. Haematol.*, **36**, 353–357 / John Wiley & Sons.

1.1.1.2 Bear

An extreme case of animal spontaneous thermogenesis is found in hibernation (Kosara, 2011), especially in bears (Harlow et al., 2004). The body temperature of a hibernating black bear (*Ursus americanus*) is displayed in Figure 1.4 (Tøien et al., 2011). During hibernation in winter, even in cold environments (-40 – 0 °C) where metabolic activity is markedly suppressed, *Ursus americanus* maintains a body temperature of 32 – 38 °C by performing regular muscular exercises without waking up from sleep.

1.1.1.3 Oceanic Lives

Due to the high thermal conductivity of water, it is harder for marine creatures to keep their body temperature higher than their surroundings compared to animals living on land. Nevertheless, various fish maintain their body temperature higher than the surrounding sea. Figure 1.5 shows the relationship between the ambient temperature and the body temperature of bigeye tuna (*Thunnus obesus*) (Holland et al., 1992). The ambient temperature fluctuations were due to vertical excursions of *Thunnus obesus* of more than 100 meters. Analyzing these temperature data suggested that the whole-body thermal conductivity of *Thunnus obesus* was altered by two orders of magnitude between the warming and cooling phases. A mesopelagic fish, opah (*Lampris guttatus*),

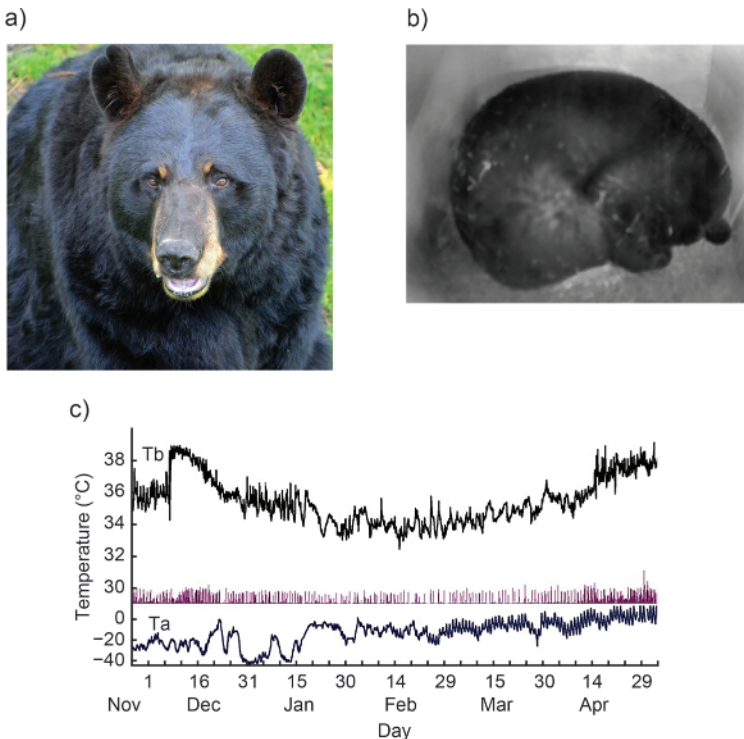


Figure 1.4 Thermogenesis of a hibernating bear. (a) A black bear, *Ursus americanus* (© Meunierd). (b) Hibernation of *Ursus americanus* in an artificial den. (c) Temperature patterns of the core body temperature of a hibernating *Ursus americanus* (Tb, black) and the outside of a cave (Ta, dark blue). Purple lines indicate the movements of the black bear. Panels (b,c) Tøien et al. (2011) *Science*, **331**, 906–909 / American Association for the Advancement of Science.

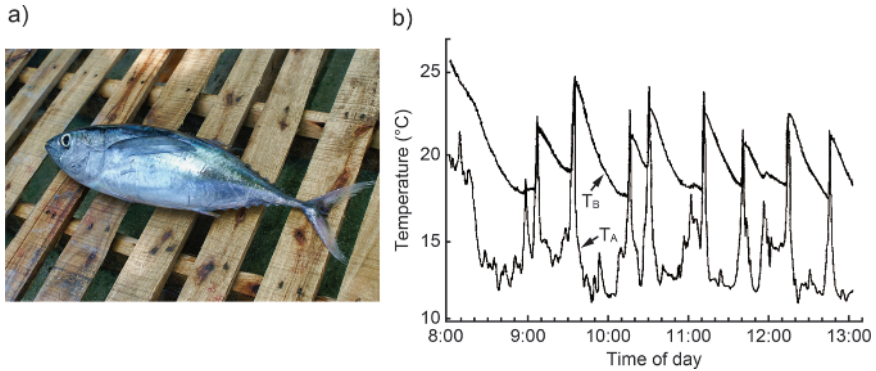


Figure 1.5 Thermoregulation of a tuna. (a) A bigeye tuna, *Thunnus obesus* (© MikeCloud). (b) The body temperature of a swimming *Thunnus obesus* (T_B) and ambient temperature (T_A). Panel (b) is adapted from Holland et al. (1992) *Nature*, **358**, 410–412.

also shows temperature elevations above ambient by 3.2–6.0 °C in its heart, viscera, cranial region, and pectoral muscle (Wegner et al., 2015). It has been assumed that the endothermic properties of these living things are beneficial for enhancing physiological performance in cold oceans. Temperature regulation to keep the body temperatures higher, or occasionally lower, than their environment has also been observed in king penguins (Handrich et al., 1997) and sea turtles (Sato, 2014).

1.1.1.4 Plants

It might be surprising to readers that some plant species also produce remarkable heat (Knutson, 1979; Seymour, 2001). The first example is the garden philodendron, *Philodendron selloum* (Figure 1.6a) (Nagy et al., 1972). The inflorescence of *Philodendron selloum* produces heat during the flowering sequence and remains at maximum temperature for 0.3 to 4 hours before cooling. A core temperature of 38–46 °C is maintained in air temperatures in the range 4–39 °C through a variable metabolic (i.e., oxygen consumption) rate (Figure 1.6b). Another thermogenic

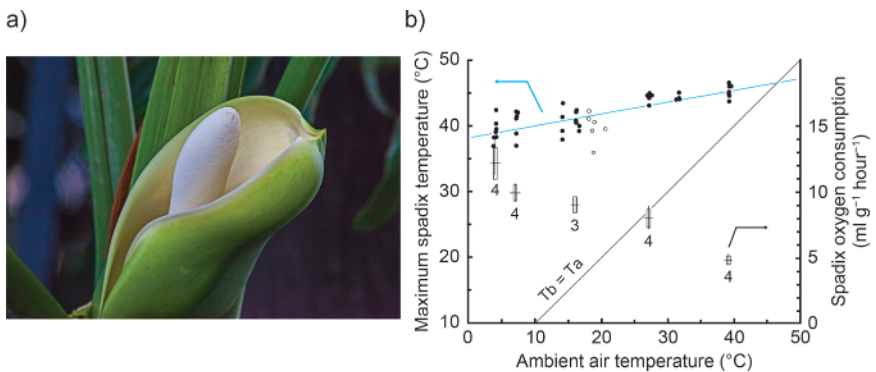


Figure 1.6 Thermogenesis of the inflorescence of philodendrons. (a) A garden philodendron, *Philodendron selloum* (© Kobus Peché). (b) Core temperatures (T_b) of philodendron inflorescences outdoors (open circle) and in incubators (closed circle) at different ambient temperatures (T_a). Solid horizontal lines indicate the mean spadix oxygen consumption rates. Vertical lines show the ranges. Rectangles are \pm standard deviations. The numbers below the rectangles are sample sizes. Panel (b) is adapted from Nagy et al. (1972) *Science*, **178**, 1195–1197.

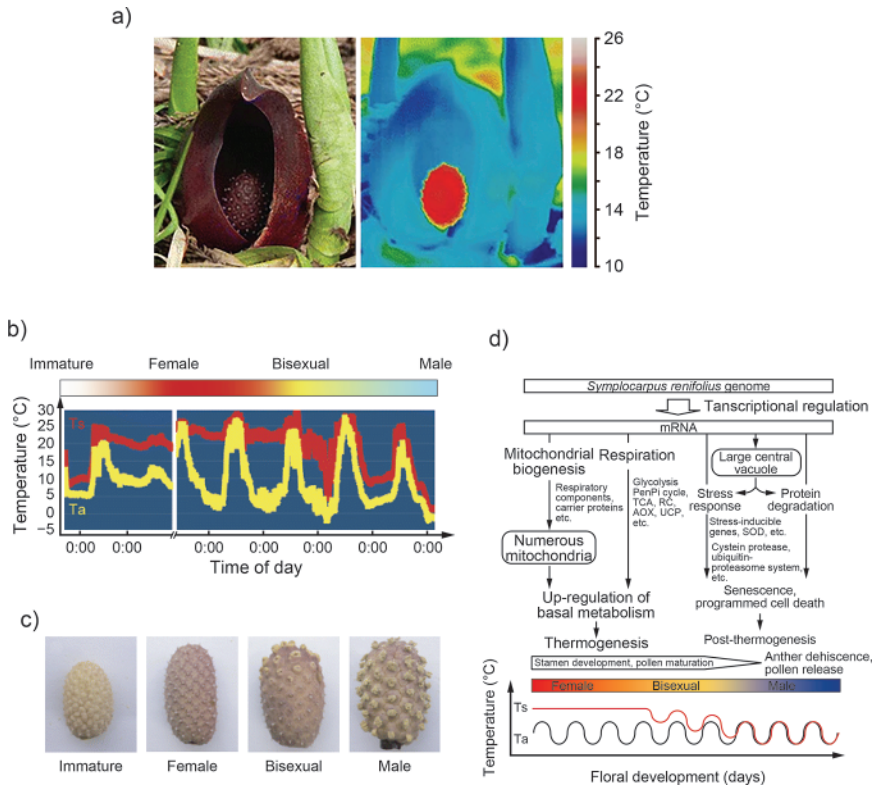


Figure 1.7 Thermogenesis of the spadix of skunk cabbages. (a) Visible image (left) and thermographic image (right) of a skunk cabbage, *Symplocarpus renifolius*. Adapted from Ito-Inaba et al. (2009) *Planta*, **231**, 121–130 / Springer Nature. (b) Variations in ambient air temperature (T_a , yellow) and the spadix temperature (T_s , red) of *Symplocarpus renifolius* during floral development. (c) Visible images of the spadices of *Symplocarpus renifolius* during floral development (immature, female, bisexual, and male). Panels (b,c) are adapted from Ito-Inaba et al. (2009) *J. Exp. Bot.*, **60**, 3909–3922 / Oxford University Press. (d) Hypothetical model of floral thermoregulations. PenPi: pentose phosphate, TCA: tricarboxylic acid, RC: respiratory chain, AOC: alternative oxidase, UCP: uncoupling protein, SOD: superoxide dismutase. Adapted from Ito-Inaba et al. (2012) *Plant Cell Environ.*, **35**, 554–566.

plant is the skunk cabbage (*Symplocarpus renifolius*) (Figure 1.7a) (Ito-Inaba et al., 2009a). The development of an inflorescence of skunk cabbage is divided into four stages: immature, female, bisexual, and male. Within these four stages, only at the female stage, the spadix generates massive heat and can maintain its internal temperature at 20–25 °C despite the environmental temperature at night falling to almost 0 °C (Figure 1.7b, 1.7c) (Ito-Inaba et al., 2009b). Studies on mitochondrial activity and protein and gene expression hypothesized thermoregulation mechanisms of *Symplocarpus renifolius*, as indicated in Figure 1.7d. However, the exact mechanisms by which the plant senses changes in ambient temperature, produces heat, and stops thermogenesis have not yet been elucidated (Ito-Inaba et al., 2012).

1.1.2

Responses to Environmental Temperature Change

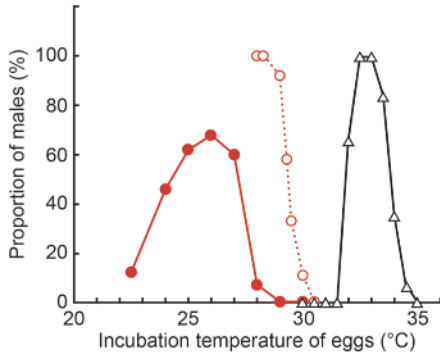
The adaptation of body temperature in response to environmental temperature variation is an essential function of life for endotherms and is remarkably diverse

		Cold-defense	Heat-defense
Physiological	Non-shivering (BAT) thermogenesis	Activated	Inhibited
	Skin blood flow	Vasoconstriction	Vasodilation
	Water evaporation	Inhibited	Sweating Panting Saliva spreading
	Shivering thermogenesis	Activated	Inhibited
Behavioral	Postural changes	Reduced exposed surface	Increased exposed surface
	Temperature choice	Heat-seeking	Cool-seeking
	Altering microenvironment	Nesting Social huddling	Air conditioning

Figure 1.8 Physiological and behavioral strategies for controlling body temperature under cold and hot environments. BAT: brown adipose tissue; UCP1: uncoupling protein-1. Adapted from Tan and Knight (2018) *Neuron*, **98**, 31–48.

(Figure 1.8) (Tan and Knight, 2018). Mechanisms of adaptive non-shivering thermogenesis have been discussed in the molecular level (Lowell and Spiegelman, 2000). Humans can maintain homeostasis even in a cold, aqueous environment such as a swimming pool by generating heat (Fox et al., 1979). The body temperature is not vastly changeable even in a hot aqueous environment like a bath (Ohnaka et al., 1995). The disruption of homeostasis can lead to serious threats to life.

There are some biological phenomena in which environmental temperature is utilized to determine fate. Temperature-dependent sex determination in reptiles is an example (Bull and Vogt, 1979; Crain and Guillette Jr., 1998). As displayed in Figure 1.9, the temperature at which eggs are incubated determines gender in three reptiles: alligator snapping turtle (*Macrolemys temminckii*) (Ewert et al., 1994), a false map turtle (*Graptemys pseudogeographica*) (Bull et al., 1982), and the American alligator (*Alligator mississippiensis*) (Lang and Andrews, 1994). A slight shift in incubation temperature can cause a dramatic change in their sex ratio. Due to temperature-dependent sex determination and environmental warming, serious feminization has been observed in turtle populations in the Great Barrier Reef in Australia (Jensen et al., 2018). In a red-eared slider turtle (*Trachemys scripta elegans*),



△ *Alligator mississippiensis*



● *Macrolemys temminckii*



○ *Graptemys pseudogeographica*

Figure 1.9 Temperature-dependent sex determination in three reptiles, an alligator snapping turtle, *Macrolemys temminckii* (© Matthijs Kuijpers) (closed red circle), a false map turtle, *Graptemys pseudogeographica* (© pisces2386) (open red circle), and an American alligator, *Alligator mississippiensis* (© Richard Mcmillin) (open black triangle). Adapted from Ewert et al. (1994) *J. Exp. Zool.*, **270**, 3–15 (alligator snapping turtle), Bull et al. (1982) *Evolution*, **36**, 326–332 (false map turtle), and Lang and Andrews (1994) *J. Exp. Zool.*, **270**, 28–44 (American alligator).

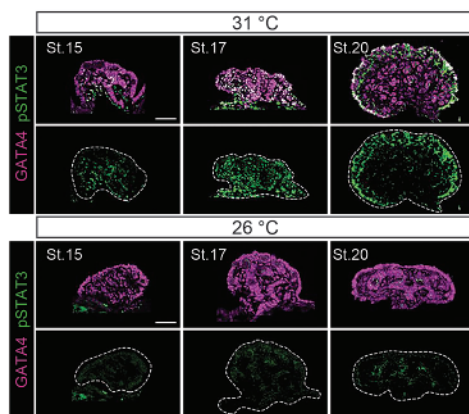
the corresponding gene responsible for the temperature-dependent sex determination has been identified: under warmer environments, signal transducer and activator of transcription 3 (STAT3) is more phosphorylated through a Ca^{2+} ion influx, then represses *Kdm6b* transcription to block the male pathway (Figure 1.10) (Weber et al., 2020). In a short-lived lizard jacky dragon (*Amphibolurus muricatus*), the effect of incubation temperature on the reproductive success of males differs from the effect on females (Warner and Shine, 2008). The temperature-dependent sex determination is also observed in certain fish (Shen and Wang, 2014).

Infertility is another reproduction matter that is sensitive to environmental temperatures (Mieusset and Bujan, 1995). In mammalian species, spermatogenesis is a heat-vulnerable process, and the scrotal temperature is maintained at 2–8°C lower than that of the core body (Moore and Quick, 1924). If the testes go through a temperature elevation beyond a threshold, spermatogenesis is interrupted, resulting in male infertility. Recently, it was revealed that heat-induced meiotic failure is one of the reasons for heat vulnerability in mouse spermatogenesis (Hirano et al., 2022).

a)



b)



c)

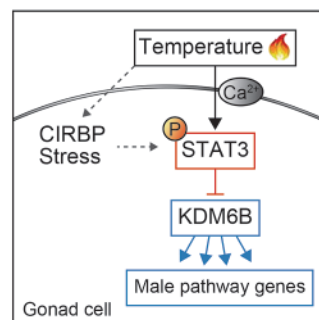


Figure 1.10 Molecular mechanisms of temperature-dependent sex determination in red-eared slider turtles. (a) A red-eared slider turtle, *Trachemys scripta elegans* (© Slowmotiongli). (b) Immunofluorescence images of phosphorylated STAT3 (pSTAT3) (green) and GATA4 (magenta, somatic gonad marker) in gonadal cross sections from embryos at 26 and 31 °C throughout the temperature-sensing window (from stage (St.) 14 to 20). pSTAT3 expression is nuclear and restricted to the sex cords and cortical domain. Dotted lines are outlines of embryonic gonads. Scale bars: 50 μ m. (c) A molecular model for temperature-dependent sex determination in *T. scripta*. High temperatures initiate a rise in intracellular calcium ions that promotes STAT3 phosphorylation. pSTAT3 binds *Kdm6b* to repress activation of *Dmrt1* and the male pathway. Low temperature may activate cold-inducible RNA-binding protein (CIRBP) and stress response pathways, activating STAT3. Panels (b,c) are adapted from Weber et al. (2020) *Science*, **368**, 303–306.

Cherry blossoms (Figure 1.11) are symbolic flowers in Japan. People look forward to their short bloom as a sign of warm spring. Interestingly, the flowering day of cherry blossoms (e.g., *Prunus serrulata*) can be accurately estimated by temperature sums during February and March, implying that the flowering of cherry blossoms is a temperature-dependent phenomenon (Lindsey, 1963). In general, plants have evolved excellent plasticity to adapt to their surrounding temperature environment (Patel and Franklin, 2009; Wigge, 2013). The modulation of plant architecture by environmental temperature is an essential issue concerning crop productivity and global climate change. Gene expression is induced in plants' low-temperature perception for chilling and freezing tolerance (Knight and Knight, 2012). Nevertheless, the mechanisms through which plants sense ambient temperature variation remain elusive.



Figure 1.11 Yoshino cherry, *Prunus* × *Yedoensis*. © Monika Baumbach.

1.2

Responses to Temperature Variation at the Cellular Level

Disclosed responses to environmental temperature variations are not exclusive to individuals, which are described in Section 1.1.2, but also inclusive of live cells in diverse ways. For example, circadian gene expression in peripheral cells is synchronized with rhythms of host body temperature (Brown et al., 2002). Nucleic acids, proteins, and membranes are representative biomacromolecules that sense temperature variations within cells (Sengupta and Garrity, 2013).

When living organisms are subjected to an environmental temperature change, temperature-sensitive proteins initially respond to it within cells. One of the typical thermal responses in living cells is the heat shock response (Richter et al., 2010). When an organism is exposed to an excessive temperature of 5–20 °C above the normal growth temperature, the expression of heat shock proteins is induced in the cell. The heat shock proteins protect cells from heat damage by preventing the aggregation of functional proteins through modulation of the transcription of related genes.

The cellular response to thermal stimuli also includes fast translational regulation by changes in the state of translating mRNAs, which are mediated by stress granule formation (Kedersha et al., 1999). RNA-binding proteins, TIAR and TIA-1, concentrated in the nuclei of DU145 (human prostate carcinoma) cells rapidly accumulate into stress granules in the cytoplasm in response to a mild heat shock at 44 °C for 20 minutes (Figure 1.12).

Thermosensitive transient receptor potential (TRP) channels also play important roles in temperature sensing at cell membranes exposed to large temperature fluctuations (Figure 1.13a) (Clapham, 2003; Castillo et al., 2018). Three-dimensional structures of the TRP channel family have been clarified one after another to yield mechanistic insights (Figure 1.13b). Noticeably, the Nobel Prize in Physiology or Medicine 2021 was given for discoveries of a TRP channel member, TRPV1, as well as mechanically activated ion channels (Ernfors et al., 2021). A variety of TRP family proteins are activated either by molecules in stimulating foodstuffs such as capsaicin and menthol or by temperature variations in specific ranges. The latter activations are considered implicated in temperature-related physiological functions.

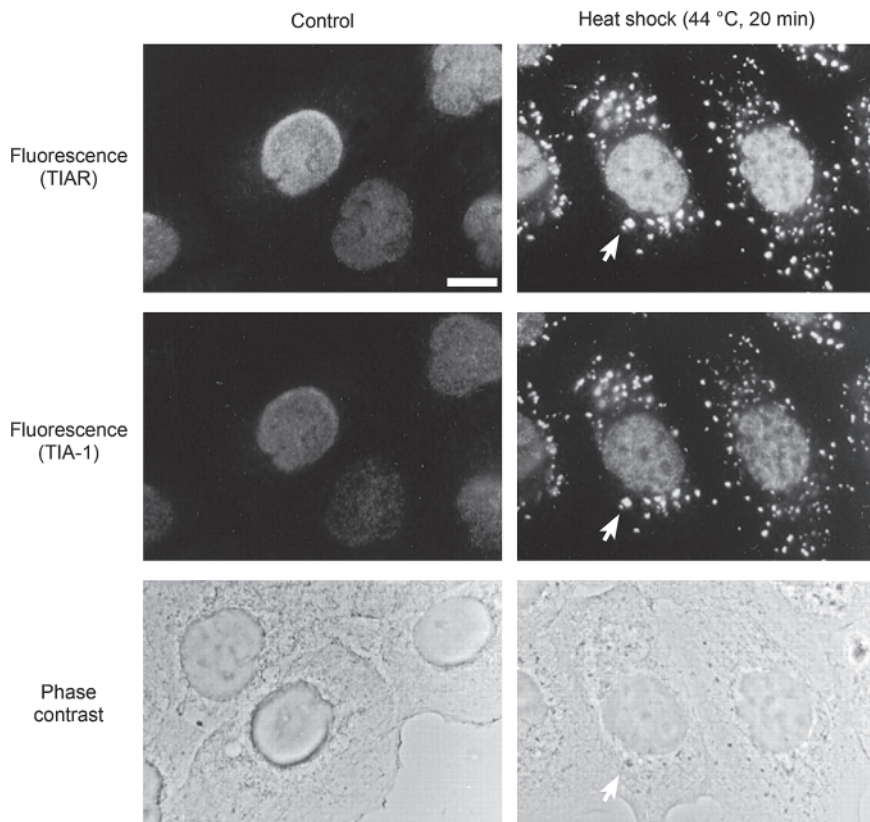
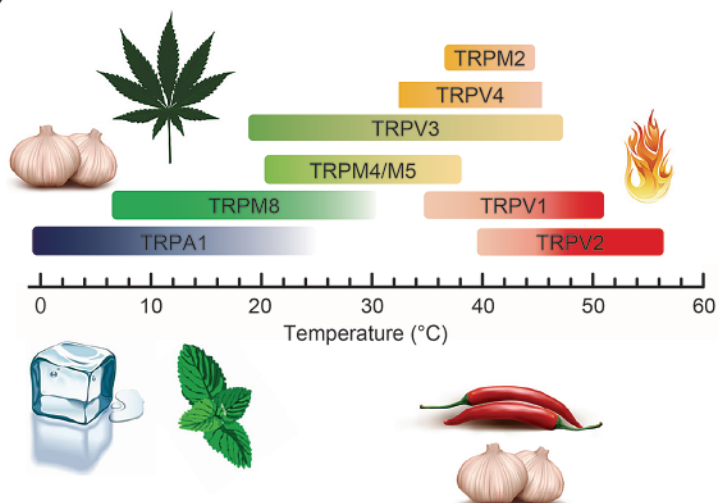


Figure 1.12 Coaggregation of TIAR and TIA-1 at stress granules. Fluorescence images of TIAR-specific antibody 6E3 (upper) and TIA-1-specific antibody ML29 (middle) and phase-contrast images (lower) of DU145 cells without (left) and with (right) mild heat shock (44 °C for 20 min). Cells were immediately fixed after the heat shock and processed for immunostainings. TIAR and TIA-1 colocalized at stress granules (arrows). Scale bar: 10 μ m. Adapted from Kedersha et al. (1999) *J. Cell. Biol.*, **147**, 1431–1441.

Another interesting temperature-responsive protein discovered is the splicing factor (Preußner et al., 2017). This protein can detect a temperature change of 1 °C for use as an input factor in regulating gene expression. In cellular biotechnology, spatiotemporally controlled heating within a cell has been applied for gene induction based on a heat shock promoter (Kamei et al., 2009) and manipulation of a temperature-sensitive mutant protein that functions depending on temperature (Hirsch et al., 2018).

Neural developments are also temperature-dependent; the significant effects of environmental temperatures were reported on axonal outgrowth of cortical neurons isolated from rat embryos (Black et al., 2016) and proliferation and differentiation of neural stem/progenitor cells isolated from forebrain cortices of rat fetuses (Hossain et al., 2017). In addition, temperature-dependent migration was observed in neutrophil-differentiated HL-60 cells (derived from human peripheral blood leukocytes) (Khachatryan et al., 2022).

a)



b)

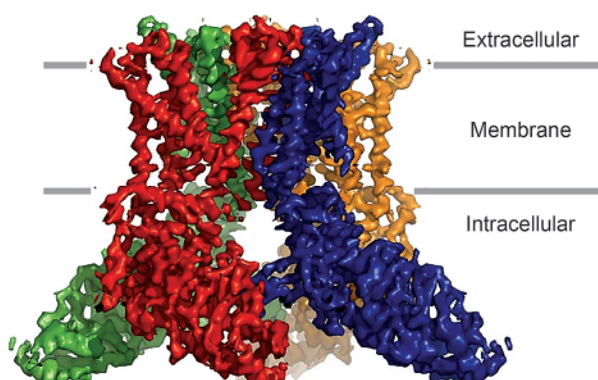


Figure 1.13 Temperature-sensitive TRP channels. (a) Sensitive temperature ranges for open probabilities of TRP channels. The TRP channels are also activated by chemical ligands, including active ingredients such as allicin (in garlic), cannabinoids (in cannabis), menthol (in mint), and capsaicin (in chili pepper). Adapted from Castillo et al. (2018) *Phys. Biol.*, **15**, 021001 / IOP Publishing. (b) Cryo-electron microscopy reconstruction of TRPV4 as a representative. Deng et al. (2018) *Nat. Struct. Mol. Biol.*, **25**, 252–260 / Springer Nature.

1.3

Significance of Intracellular Thermometry

Just as humans maintain a body temperature higher than the environment, so do cells spontaneously produce heat. Heat-induced formation of stress granules in the cytoplasm and expressions of TRP channels in the plasma membrane hint that a detectable temperature variation might take place within a single cell. Accurate intracellular temperature measurements will enable the comparison of temperature-involving biological events between individuals and cells and the monitoring

of temperature-related biological phenomena at the single-cell level. The elucidation of profound mechanisms of thermal biology described in Sections 1.1 and 1.2 has motivated us to explore the temperature inside living cells.

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