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Review

Review

Deciphering the relationship between temperature and immunity

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A note on sex and gender: This review discusses population differences, including sex differences. Sex refers to the biological and physiological characteristics of females and males. It is distinct from gender, which is a social, psychological, and cultural construct. Both sex and gender exist on spectrums. This article will only address sex, using the terms 'female' or 'male' to refer to sex assigned at birth. The biological characteristics of sex are not mutually exclusive, as there are individuals who possess both male and female characteristics, and they can be changed. The biology of individuals across the sex spectrum is and should be studied, but we still lack the body of work necessary for the scope for this review [1].

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Summary

Fever is a hallmark symptom of disease across the animal kingdom. Yet, despite the evidence linking temperature fluctuation and immune response, much remains to be discovered about the molecular mechanisms governing these interactions. In patients with rheumatoid arthritis, for instance, it is clinically accepted that joint temperature can predict disease progression. But it was only recently demonstrated that the mitochondria of stimulated T cells can rise to an extreme 50°C, potentially indicating a cellular source of these localized 'fevers'. A challenge to dissecting these mechanisms is a bidirectional interplay between temperature and immunity. Heat shock response is found in virtually all organisms, activating protective pathways when cells are exposed to elevated temperatures. However, the temperature threshold that activates these pathways can vary within the same organism, with human immune cells, in particular, demonstrating differential sensitivity to heat. Such inter-cellular variation may be clinically relevant given the small but significant temperature differences seen between tissues, ages, and sexes. Greater understanding of how such small temperature perturbations mediate immune responses may provide new explanations for persistent questions in disease such as sex disparity in disease prevalence. Notably, the prevalence and severity of many maladies are rising with climate change, suggesting temperature fluctuations can interact with disease on multiple levels. As global temperatures are rising, and our body temperatures are falling, questions regarding temperature–immune interactions are increasingly critical. Here, we review this aspect of environmental interplay to better understand temperature's role in immune variation and subsequent risk of disease.

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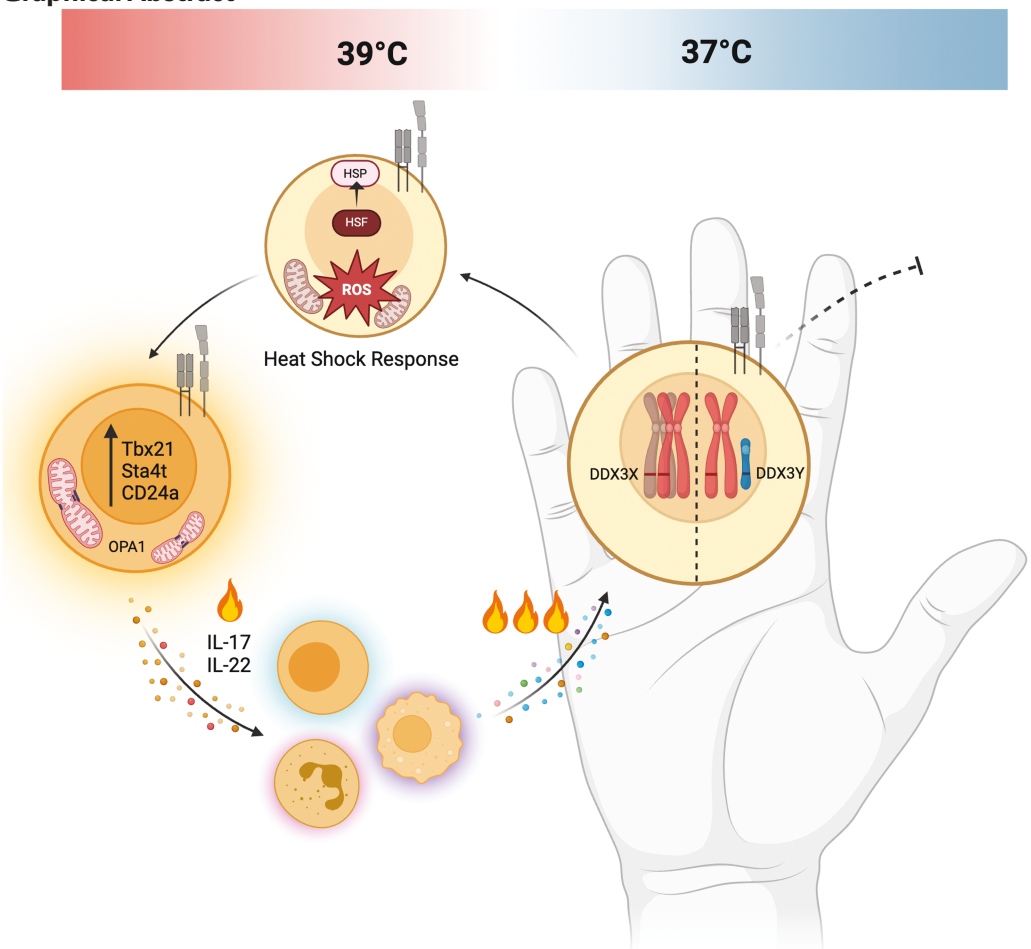
Graphical Abstract



Keywords: temperature, immunity, immune homeostasis, autoimmunity, Th17

Abbreviations: BAT: brown adipose tissue; B.C.E.: before common era; BMAL1: basic helix-loop-helix ARNT like 1; CD24a: cluster of differentiation 24 antigen; DDX3: DEAD-box helicase 3; DDX3X: DEAD-box helicase 3 X-linked; DDX3Y: DEAD-box helicase 3 Y-linked; Ded1: ATP-dependent DEAD-box RNA helicase; FCAS: familial cold autoinflammatory syndrome; GLUT1: glucose transporter 1; HIV: human immunodeficiency virus; HMGB1: high mobility group box 1; HSF: heat shock response; HSP: heat shock proteins; HSR: heat shock response; IFN-γ: interferon gamma; IL-1β: interleukin 1 beta; IL-6: interleukin 6; IL-7: interleukin 17; LKB1: liver kinase B1; LPS: lipopolysaccharides; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3: NOD-like receptor protein 3; OPA-1: optic atrophy 1; PER2: period circadian regulator 2; RA: rheumatoid arthritis; ROS: reactive oxygen species; SLC2A1: solute carrier family 2 member 1; STAT: signal transducer and activator of transcription; STAT4: signal transduction and activator of transcription 4; TBX21: T-box transcription factor 21; Th17: T-helper 17; TNF-α: tumor necrosis factor alpha; UBA1: ubiquitin-like modifier activating enzyme 1; UCP1: uncoupling protein 1; VEXAS: vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic.

Introduction

Fundamental temperature and immune interactions

What is a healthy human body temperature? The common answer, 37°C, was established in 1851 by averaging over 1 million samples from 25 000 patients in Germany [2, 3], but more recent cross-sectional studies have found the mean to be closer to 36.6°C [2, 4, 5]. This modest difference may be physiologically relevant given that sweating can be induced with a +0.4°C increase in core body temperature [6], and may warrant reassessment of fever thresholds. Around the mean, body temperature varies significantly and systematically with factors such as age, sex, and time of day [2, 4, 5, 7–11], the same factors seen to correlate with differences in immune response and disease disparity [12–17]. Even controlling for this variability, a longitudinal study of over 20 000 patients found a +1°C increase in temperature correlated with 3.5% higher mortality after one year [18], making the clinical implications of temperature–immune interactions clear. What remains to be elucidated are the mechanisms underlying temperature–immune interplay and how they may contribute to population variability and disease disparity. In pursuit of these questions, we examine temperature and immune interactions conserved across evolution.

Heat shock response (HSR) is a fundamental example of temperature-affecting immunity found in virtually all living organisms. From bacteria to humans, HSR is a protective function triggered when cells are exposed to environmental stressors such as heat, cold, or hypoxia [19]. These environmental stressors can cause protein misfolding and loss of function within the cell, inducing rapid upregulation of heat shock proteins (HSPs), which act as molecular chaperones to mitigate these adverse effects [19]. In humans and other mammals, HSR modulates immune pathways through the hypothalamic–pituitary–adrenal axis, a complex neuroendocrine feedback loop controlling stress response [20]. The

hypothalamic–pituitary–adrenal axis directly modulates immune responses through glucocorticoids [21], the same steroid hormones used therapeutically to suppress allergic, inflammatory, and autoimmune disorders [22]. Further linking the pathways, intracellular glucocorticoid receptors are stabilized by chaperones including hsp90 and hsp56 in their steroid-free state [23]. A growing body of evidence indicates that HSR-induced immune modulations can also be mediated through immunometabolism, with specific requirements for each cell type and subset [19]. Therefore, metabolic pathways are receiving renewed focus as potential mediators for immune modulations observed in response to smaller temperature changes, such as daily circadian rhythms [13, 24–32], as well as during increased temperatures caused by inflammation and fever [25, 33].

Fever, a prime illustration of immunity impacting temperature, has been conserved over 550 million years of animal evolution [24] (Fig. 1). Fish exhibit behavioral fever, swimming to warmer water (+2–3°C) when challenged with bacterial infection and subsequentially resolve infections faster [24, 36]. Uninfected goldfish moved to +2°C warmer water activated similar immune pathways to infected fish, although to a lesser degree [24]. This indicates temperature alone, in the absence of immune challenge, can activate immune defences. Behavioral fever can also be seen on a eusocial scale, often referred to as social fever. Honeybees will begin rapid movement, raising the overall temperature of their hive in response to a colonial infection by a heat-sensitive pathogen [37, 38]. While fever is often synonymous with elevated temperature, temperature can also decrease following an immune challenge. For example, mice become hyperthermic or hypothermic depending on the dose and location of a challenge with bacterial lipopolysaccharides (LPS) [39]. Environmental temperature can also affect this response, as mice housed at a thermoneutral 31°C respond to intravenous injection with LPS with hyperthermic fever, while the same treatment at 26°C results in transient hypothermia [40]. These phenomena add complexity to the proposed survival advantage of fever, with many questions remaining about the role of cold and environmental temperature in immune responses.

The well-established theory for the conservation of fever is that it provides a survival advantage through defence against environmental pathogens. There is evidence that this defence derives directly from higher body temperatures, creating a thermal exclusion zone where pathogens adapted to environmental temperatures are not able to grow [41]. Febrile temperatures (40–41°C) reduce the replication rate of poliovirus in mammalian cells by 200-fold [42] and inhibit Gram-negative bacteria such as *E. coli* and *Salmonella* from synthesizing LPS, thereby making them more susceptible to serum-induced lysis [42, 43]. A thermal tolerance study of 4802 fungal strains representing 144 genera, showed that 95% of fungal species were inhibited by human core temperatures [35]. Every 1°C increase in the 30–40°C range halted the growth of an additional 6% of fungal isolates, indicating fever could significantly bolster the defence provided by a thermal exclusion zone [35]. For humans and other endotherms, mounting a thermal defence comes at a high metabolic cost as our body heat is primarily generated through mitochondrial oxidative metabolism [16]. Every 1°C increase in body temperature is estimated to require a 10% increase in metabolic rates, a striking figure that has yet to be reexamined in diverse populations [34].

Metabolism may be especially pertinent to how environmental temperature affects human health. Climate hazards provoke or heighten the severity of an estimated 58% of infectious diseases and increasingly frequent heat waves are disproportionally harming our most vulnerable communities [44]. With global temperatures rising around us, it is more important than ever to understand the impact of this ubiquitous environmental factor. With a better understanding of the role of body temperature in diseases beyond infection, its variation among healthy populations, and how it may underlie disparities in disease prevalence, we may be better able to address growing global health concerns that arise with climate change. To do so, it will be necessary to examine temperature at each level; cellular, systemic, and environmental, to identify possible unifying mechanisms and opportunities for exploration.

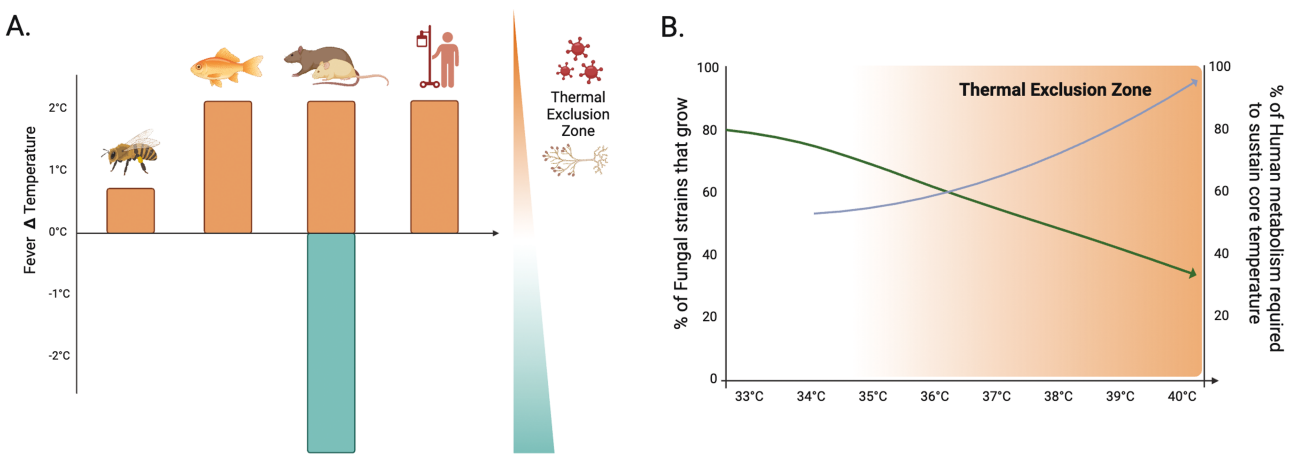


Figure 1: Conserved evolutionary advantage of fever. (A) A wide variety of animal species use changes in temperature as a defense mechanism against infection. This creates a thermal exclusion zone in which the growth of viruses, bacteria, and fungi, adapted to healthy host body temperature, is inhibited. (B) Thermal exclusion zones are metabolically costly for endotherms, such as humans. Each degree increase in human body temperature demands ~10% more metabolic resources [34] (gray line), but also inhibits the growth of 6% more fungal strains [35] (green line).

Healthy body temperature variation

While fever is the most common example of changing body temperature, our homeostatic body temperatures undergo many fluctuations that influence immunity which are less well understood. Throughout a day, a month, or a lifetime, these cycles and trends can be seen within and across individuals (Fig. 2). Further exploration into temperature variances in a healthy context could uncover new explanations for population differences in immune responses and mechanisms underlying disease disparity.

The rhythm of body temperature

Daily cycles in environmental temperature are an important cue for many organisms to synchronize their endogenous circadian clock [45]. However, humans do not respond as strongly to these cues since we are endothermic, meaning our body temperature is regulated independently from our environment [45]. Instead, a central biological clock located in the hypothalamus dictates the cycles of many systems, including the hypothalamic–pituitary–adrenal axis, the immune system, and body temperature, which fluctuates ~1°C in a daily sinusoidal rhythm [4, 16]. The thermoregulatory center, also located in the hypothalamus, uses cues from the clock and thermoreceptor nerve cells throughout the body to activate mechanisms of heat gain (cellular oxidative metabolism, muscle contraction) or heat loss (sweating, increased blood flow to the skin) and keep the body at its set point [16].

Recent studies suggest this control is bidirectional, as experimental fluctuations mimicking humans' 1°C daily temperature cycle have successfully retrained the cellular clocks of cultured mouse fibroblasts [21]. Indicating HSR pathways are involved, this retraining required heat shock factor-1 to synchronize *PER2* gene expression and in turn phase-reset other clock genes such as *BMAL1* [21]. These clock genes also affect immunity, as *PER2* mutant mice are relatively resistant to LPS-induced endotoxic shock, in part due to decreases in proinflammatory cytokines, IFN-γ, and IL-1β, while *BMAL1* deficient mice have poor B cell development [17]. Also reflective of HSR mechanisms, there is evidence that temperature–clock–immune interactions are mediated through the hypothalamic–pituitary–adrenal axis, with STAT and NF-κB as potential interface pathways [17].

Further connecting to HSR, metabolism is proposed as a link between circadian rhythm, immunity, and body temperature. Redox, bioenergetic, and temperature regulation is critical in maintaining cellular circadian rhythms; wakefulness is mainly 'nucleorestorative', whereas sleep is mainly 'mitorestorative' [29]. Keeping circadian homeostasis, including immune and thermal homeostasis, is considered the largest component of human energy expenditure, comprising around 65% for a sedentary individual [46]. However, this calculation was first derived from a case study of one 70-kg, 40-year-old man, and recent analyses of more diverse populations show our accepted resting metabolic rate is overestimated by 20% on average [47]. This marked metabolic variance adds new consequences to differences in circadian temperature between tissues and across populations [17, 48].

Body temperature varies with age and sex

While temperature rhythms can be seen across individuals, the observed set point varies depending on intrinsic factors such as age and sex. Females are +0.1–0.5°C warmer than males on average, and body temperatures decrease with age for both sexes [2, 49]. The mechanisms underlying these conserved patterns still require investigation, but one

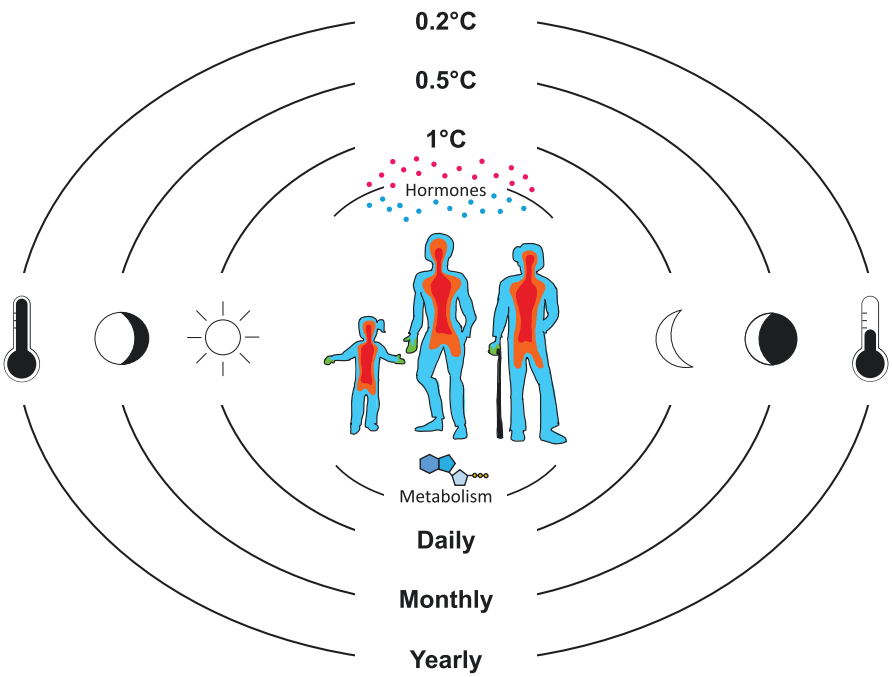


Figure 2: Core body temperature follows daily, monthly (for menstruating females), and seasonal rhythms. Body temperature also fluctuates throughout the body, with the warmest point at the core, and the coldest point at the extremities. An individual's mean body temperature and distribution of heat are affected by intrinsic factors such as age and sex. Interactions between body temperature and circadian and immune pathways are mediated by hormones and metabolism.

hypothesis is hormone levels directly influence body temperature. This is supported by the observation of temperature changes coinciding with the start and cessation of menses in a lifetime, monthly menstrual cycles, and use of daily hormonal contraception [7]. Emerging around menarche (first menses), females have monthly circadian temperature cycles, with a peak of +0.6°C at ovulation [50]. Leveraging this pattern along with sleeping heart rate, modern wearables accurately predicted the preovulatory surge of luteinizing hormone with 100% accuracy in a study of 20 premenopausal and 5 peri-menopausal females [51]. Also coinciding with ovulation, aspects of the innate, humoral, and cell-mediated immune system are suppressed by sex hormones in the female reproductive tract to optimize conditions for procreation [52]. Unfortunately, this immune suppression also creates a 'window of vulnerability' for increased risk of contracting sexually transmitted infections such as HIV [52]. Importantly, hormonal contraceptives disrupt typical monthly rhythms by maintaining elevated hormone levels akin to the post-ovulatory luteal phase, consequently sustaining the associated temperature peak and creating an continuous 'window of vulnerability' for infection, characterized by a suppression of immunoglobulins and lactoferrin [7, 10, 52]. Hormonal contraceptives have also been linked to an increased risk of developing autoimmune diseases such as Crohn's disease, systemic lupus erythematosus, and multiple sclerosis [53], which could be due to a confluence of hormone-mediated temperature and immune effects and may warrant the revaluation of prescribing this form of contraception when alternatives are available.

At the other end of fertility, menopause represents an underexplored avenue of investigation for hormone–temperature–immune interactions given its association with immune changes and hot flashes [54, 55]. As most immune cells in the female reproductive tract are estrogen responsive, the loss of estrogen with menopause results in a loss of toll-like receptor function, secretory antimicrobial components, and commensal lactobacilli [54, 56]. By contrast with premenopausal females whose uterine T cell activity varies in concert with their menstrual cycle, postmenopausal females show significantly higher uterine cytotoxic lymphocyte activity and low constant numbers of regulatory T cells [54, 57–60]. Systemically, menopausal females show elevated plasma levels of the proinflammatory cytokines TNF-α, IFN-γ, and IL-6, which can be reduced with hormone replacement therapy [54, 61]. Much remains to be discovered about how these immune differences affect postmenopausal health, and how to distinguish their influence from temperature and non-hormonal aging effects.

These menopausal immune changes are concurrent with temperature dysregulation in the form of hot flashes, transient increases in core body temperature which may recur for >7 years [62]. Cross-cultural meta-studies report the proportions of menopausal females affected by hot flashes range from 18% (South Africa) to 97% (Turkey) [62, 63]. Most males do not experience hot flash since testosterone levels slowly decrease ~1% per year after age 40, staying within a normal range [64]. By contrast, females experience a more drastic hormonal decline. While this phenomenon primarily affects females, similar symptoms are present in 70–80% of men treated with androgen deprivation therapy for prostate cancer [64]. Though much remains to be discovered about the variable incidence of hot flashes, this cooccurrence of hormonal change and temperature dysregulation lends credence to the hypothesis that hormone levels and body temperature are linked. This hypothesis is further evidenced by the clinical observation that estrogen therapy virtually eliminates hot flashes in both sexes [55]. By contrast, older studies did not find relationships between hot flashes and estrogen levels in plasma, urine, or vaginal secretions, or differences in plasma levels in females with or without hot flash [65]. This leaves additional questions of how estrogen acts as a treatment, but not a biomarker for hot flashes, and what additional research into this hormonal–temperature link could tell us about their interplay in all populations.

While the symptoms and treatments are the same in both sexes, the exact pathophysiological basis of hot flashes still lacks consensus [66]. Menopausal body temperatures, measured by ingested radiotelemetry pills, showed that postmenopausal females without hot flashes initiate vasodilatory mechanisms of heat loss when their core body temperature increases by only +0.4°C [6]. Postmenopausal females with hot flashes initiate these mechanisms with a significantly smaller increase in core body temperature—only +0.12°C [55]. Interestingly, these different cooling thresholds are not present during exercise, and no hot flashes occurred during exercise in this study, potentially indicating an alternate pathway for hormone-decoupled cooling. Although findings that core body temperatures increase by +0.12°C seem small, it actually represents an average change of +3.9°C at the extremities, highlighting strong variation in temperatures between tissues [55, 67, 68]. Incidentally, this research may provide insight into the physiological response and relevance of temperature changes and subsequent impact on immunity.

Body temperature varies between tissues

Increasing evidence shows tissue microenvironments profoundly influence immune function. A study of 13 tissue types from 632 donors found ~50% of protein-coding genes display circadian patterns of expression without considerable overlap among tissues [69]. Temperatures fluctuate extensively within a body, with as much as a 10°C difference between the warmest central organs and coldest extremities [41, 70]. As with core body temperature, this distribution of heat differs between sexes. A systemic review of 36 articles showed that depending on the temperature measurement site, females were colder (skin), comparable (oral & rectal), or warmer (ear canal) than their male counterparts [5]. These readings illustrate that males display more even heat distribution while females display more pronounced gradation between their core and extremities [41]. Greater heat loss in females is observed in children as young as age 8 [71], and, therefore, may be uncoupled from the hormone-mediated temperature changes seen in puberty that compound this inter-sex variability.

Greater understanding of population differences in heat distribution has gained new significance with the rise of personalized medicine and new medical approaches like temperature-sensitive vaccines. Temperature-sensitive vaccines harness body heat distribution and the thermal exclusion zone to build immunity with less virulent, cold-adapted pathogens. Cold-adapted pathogens are introduced at a cool peripheral tissue, allowing the pathogen to multiply before encountering warmer, lethal temperatures at the body's

core [41]. The most recent example is FluMist, an influenza vaccine introduced through droplets in the nose (~33°C), which uses a cold-passaged strain with 2–5 log-fold restricted growth at warmer core temperatures (~39°C) [41, 72]. This strategy can generate the optimal protection provided by inoculation with live, replicating organisms or viruses, while reducing their pathogenicity [41]. But as evidenced by age restrictions for FluMist (only available to people 2–49 years old [73]), expanding access to temperature-sensitive vaccines will require characterizing inter-population temperature variation to ensure efficacy and safety. Furthermore, elucidating the mechanisms that underlie temperature differences could help explain disease disparities and inform safer, more effective personalized care over an individual's entire lifetime.

Temperature variation in disease

As far back as 3000 B.C.E., fever was described as a symptom of disease and inflammation in medical records from ancient Egypt, Mesopotamia, China, and India [74]. Hippocrates and other Greek scholars even considered fever to be beneficial to the host and recommended against treating it [74]. It was not until 2000 years later, that bacteriology demonstrated infectious disease as a cause of fever with the discovery of pyrogenic typhoid and tubercle bacillus [74]. Today, fever is a recognized clinical symptom in a wide range of diseases including viral and bacterial infection, autoinflammation, and autoimmunity, as well as certain cancers and drug reactions [75]. Ancient medicine also described systemic fever as a distinct phenomenon from localized tissue-specific fevers due to inflammation [74], a delineation that persists to this day and warrants distinct consideration. Despite this firmly established association between temperature and immunity, the mechanisms underlying it remain elusive and can have broad effects. These questions have renewed urgency with the emergence of noninfectious diseases defined by fever, such as autoinflammation. Beyond a symptom or defence mechanism, artificial fever has long been used as a therapy, a strategy that modern medical research continues to innovate.

Systemic fever in noninfectious disease

While fever is most often associated with infectious disease, it is a hallmark symptom of many maladies including penicillin reactions, blood-borne cancers, and autoinflammatory diseases. In fact, autoinflammatory and autoimmune diseases were the leading cause of classic fevers of unknown origin in a retrospective study of 602 Chinese patients (fevers defined by ≥38.3°C at least twice over >3-week period, unknown cause after 3 outpatient visits or during 3 inpatient days) [75]. The most common disease in this category, adult-onset Still's disease, rose in incidence in these clinical cohorts from 38% to 75% over the 15-year study (1998–2012). This rise is part of a larger trend of growing prevalence in autoinflammatory disease, a delineation of disorders that often present with recurrent fever [76]. In contrast to autoimmune diseases, which are primarily dysregulation of the adaptive immune system, autoinflammatory diseases stem from dysregulation of the innate immune system [14, 15, 76–78]. Clinically, they differ markedly in that 78% of those diagnosed with autoimmune diseases are female [77], while some autoinflammatory diseases, such as FCAS (familial cold autoinflammatory syndrome), can disproportionately affect males 2:1 [78].

Autoinflammatory diseases can be divided into two main categories: polygenic diseases, such as adult-onset Still's disease, and monogenic diseases, such as FCAS. Research in monogenic diseases is rapidly growing due to more widespread availability of whole exome sequencing, in fact >50 new monogenic autoinflammatory disorders have been described in the last 10 years [76]. Notably among these, VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) was discovered in 2020 and is now recognized as one of the most frequent monogenic causes of recurrent fevers, worldwide [76]. Unique in its pathology, VEXAS is not inherited but acquired through somatic mutations in the *UBA1* gene [79]. Given that *UBA1* is located on the X-chromosome, the majority of VEXAS patients are male, but it is also diagnosed in females with constitutional or acquired X monosomy through age-related mosaicism [79, 80]. Also of note, while autoinflammatory disorders all exemplify the connection between body temperature and immunity, FCAS additionally demonstrates the influence of environmental temperature on immunity. As first described in 1940, exposure to cold triggers recurrent fever, urticaria (skin rash), and arthralgia (joint pain) [81]. This reaction is due to gain-of-function point mutations in the *NLRP3* gene (1q44), which help regulate inflammation [81].

Glucocorticoids are currently the primary therapy for autoinflammatory diseases, and in addition to their anti-inflammatory role, their effect on tissues is primarily catabolic [82]. This lends credence to metabolism as a mediator between fever and immune function. Immunometabolism may also account for the only other unifying symptom of autoinflammatory diseases, malaise (general feeling of illness and fatigue), as it may represent a syphoning of resources from growth and reproduction toward immune pathways and temperature increase [33]. Further immunometabolic studies of these diseases may help to identify more precise treatments, as glucocorticoids have wide-ranging impacts on the hypothalamic–pituitary–adrenal axis, resulting in numerous side effects, mixed results, and risk of resistance.

Localized fever in noninfectious disease

Clinically distinct from systemic fever, *calor*, or heat, is one of the four cardinal signs of inflammation [83]. A key example, noted over a century ago, is found when comparing unharmed versus fractured arms during the healing process. During this phenomenon, local temperatures at the femur fracture locations in hamsters increased 1–4°C compared to uninjured limbs [84]. With modern technological advances such as infrared cameras, the association between inflammation and temperature can be studied with greater granularity. In a recent study of 25 patients, infrared cameras measured the mean temperature difference between healthy and fractured sites of the distal radius, which peaked 3 weeks after fracture (1.42°C) and slowly decreased to 0.22°C between the groups at 23 weeks after fracture [85].

Increased temperature at inflammation sites is also observed in chronic inflammatory diseases, such as rheumatoid arthritis (RA), where joint temperature can exceed core body temperature and predict disease progression [86, 87]. In an observational study of 104 patients, the average difference between these progressive 'hot joints' and stable 'cool joints' was +3°C, reflective of febrile responses [86]. These 'site fevers' can have a large impact on a tissue microenvironment, as cell

types have different sensitivities to heat. Immune cells differently activate HSR pathways *in vivo*, with B cells expressing temperature-inducible proteins such as heat shock factor-1 (HSF1) at 42°C, while T cells are induced at just 39°C [25, 88, 89]. This heightened temperature sensitivity, coupled with evidence of elevated temperatures promoting T cell activation, proliferation, differentiation, and trafficking, suggests T cells have specialized functions at inflammation sites during febrile temperatures [25].

Temperature as a therapy

Apart from its role as a symptom of fever and biomarker of inflammation, temperature fluctuation can also be therapeutic. Virtually all cultures use artificial fever therapy, or hyperthermia, in the form of saunas, steam baths, or sweat lodges [74]. Clinically, hyperthermia is especially effective in rheumatic diseases such as ankylosing spondylitis, and the immune mechanisms underlying its beneficial effects are just now being elucidated [90]. In a pilot study of 12 male ankylosing spondylitis patients, mild hyperthermia (38.5°C) induced by hot baths led to a 40–50% reduction in proinflammatory cytokines, TNF-α, IL-1β, and IL-6 over the subsequent 24 h [90]. These results were confirmed over nine serial sessions and represent suppression of the same pathways targeted by approved therapies such as infliximab [90]. If recapitulated in a larger and more diverse cohort, these findings could represent a therapeutic alternative to patients who cannot tolerate or access these medicines which are expensive and must be delivered intravenously. This correlation between hyperthermia and decreased inflammatory signaling exemplifies how a mechanistic understanding of temperature–immune interactions could benefit patients if utilized properly.

Growing interest in the ability of temperature to modulate host responses has also led to exciting results in treating infectious disease. For example, preliminary findings show thermal cycling between healthy (37°C) and hyperthermic (42°C) temperatures can reduce secretion of proinflammatory cytokines and increase macrophage clearing of herpes simplex virus type 1 in comparison with constant artificial fever *in vitro* [91]. These cycles consisting of 3 min at hyperthermia punctuated by 2 min of thermoneutral recovery also diminish the damage caused by sustained high temperatures over 24 h [91] and may allow broader patient populations to benefit from hyperthermia. More broadly for disease treatment, the next generation of gene therapies are being developed with inducible HSP promoters [92]. HSPs are induced by HSR [93], so gene therapies with their promoters would require a heat trigger, allowing for spatial and temporal control over therapeutic expression. This exquisitely simple and precise control technique could have wide-ranging applications from vaccination to immunotherapy.

Body temperature variations may underlie disease disparity

A growing body of evidence indicates small temperature changes can have significant effects. Exploring this local and systemic role in both health and disease may lead to new discoveries about the underlying mechanisms of disease. A case study for this relevance may be sex disparity in autoimmune disease prevalence. As previously discussed, autoimmune and autoinflammatory diseases are both characterized by immune dysfunction, but of different parts of the immune system. Many studies have explored how sex affects immune responses both directly and indirectly, but the precise factors mediating these differences still lacks consensus [12, 14, 15]. Considering that this most likely entails complex interactions between hormones, genes, and our environment, the significant sex differences in body temperature and heat distribution should be explored as a possible contributing factor (Fig. 3).

Heat may be the activator

A potential pathway for these heat-mediated physiological effects is HSPs, a large family of chaperone proteins induced by HSR that mitigate adverse stress effects such as protein misfolding. In yeast, the translational switch from housekeeping to HSP production is promoted by the DED1 protein [94]. *DED1* is conserved in humans as *DDX3X* on the X-chromosome in females, and *DDX3Y* on the Y-chromosome in males. The *DDX3X* gene escapes X-linked inactivation and has two active alleles in most females [95, 96]. Its male paralog, *DDX3Y*, shows lower and more variable expression in somatic tissues, as well as mosaic depletion with age in hematopoietic stem and progenitor cells through loss of Y [97, 98]. The DDX3X and DDX3Y protein sequences share 92% similarity, though their expression and function can be quite different [99]. Given DDX3's wide-ranging impact, its paralogs are implicated in the progression of many diseases, including viral infection, inflammation, intellectual disabilities, and cancer [98, 99]. These sex differences in DDX3 paralog expression may be primed to trigger dysfunction in HSR pathways when taken in the context of differing temperature ranges, distribution, and cycling, as outlined in the previous section.

HSP dysfunction may be triggered most easily in T cells, which are the central drivers of autoimmune disease [25, 88, 89]. Temperatures as low as 38.5°C selectively enhance T cell differentiation to the proinflammatory T-helper 17 (Th17) subtype almost 2-fold *ex vivo* [25, 100, 101]. *In vivo* treatment with anti-pyretic drugs not only reduces fever and fever-related gene expression but also decreases Th17 cell differentiation in treated mice [101]. Furthermore, differentiated Th17 T cells are more sensitive to temperature than other T cell effector subtypes, exhibiting increased pathogenic gene transcription (e.g. *TBX21, STAT4, CD24a*) and recruitment of neutrophils [101]. These studies highlight that not only are T cells able to respond biochemically to elevated temperatures, but that this biochemical response could have subset-specific effects on immunity and inflammation.

Significantly, an imbalance of Th17 cells is a key factor in the pathology of autoimmune patients with systemic lupus erythematosus, Sjogren's syndrome, and RA [102, 103]. In RA, Th17 cells play a central role in disease pathogenesis, cooperating with synovial fibroblasts in a proinflammatory feedback loop in patients with early RA [104–106]. Circulating Th17 cells and serum IL-17 are consistently elevated in patient serum compared to healthy individuals and their levels positively correlate with RA disease progression [104, 107]. Altogether, Th17 T cell temperature sensitivity, their role in RA, and sex differences in body temperature raise the hypothesis that temperature fluctuation may activate these cells in pre-disposed females with two active DDX3X alleles. If so, immunometabolism may be the fundamental mechanism underlying this phenomenon [13].

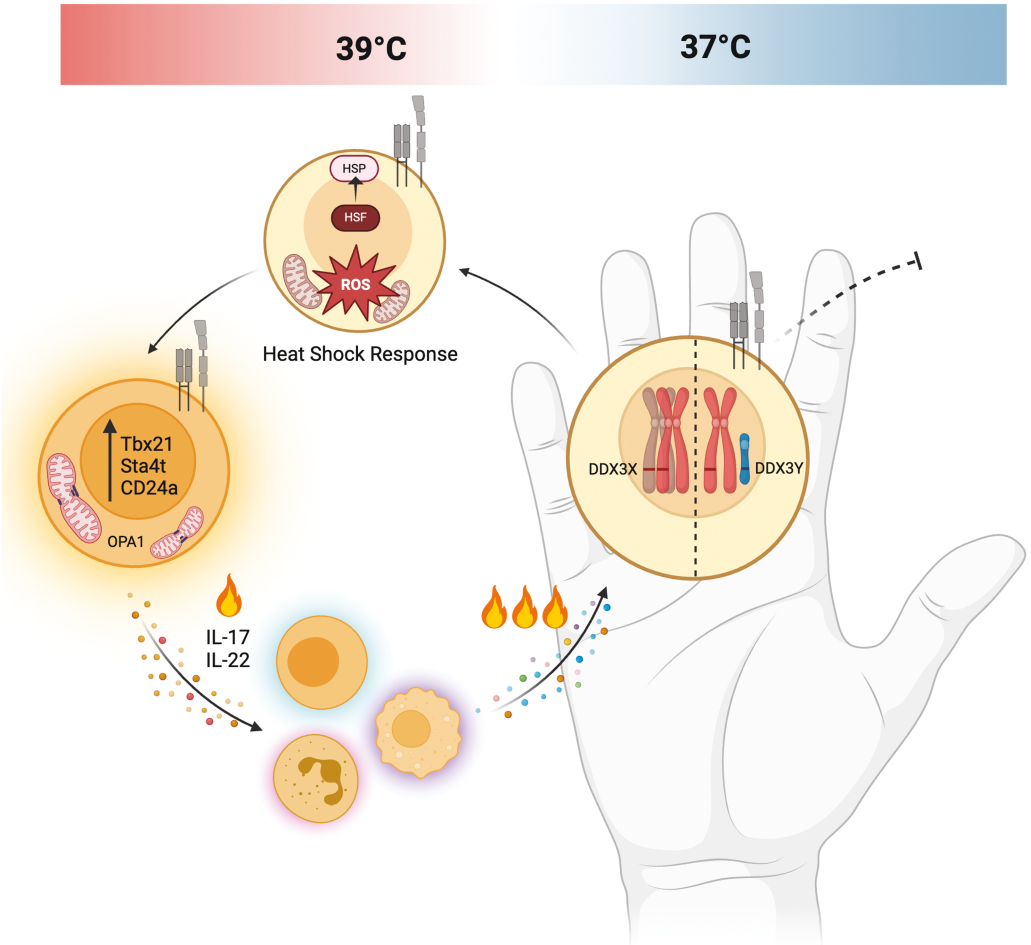


Figure 3: Temperature–immune mechanisms may underlie sex disparity in rheumatoid arthritis. Females have warmer core body temperatures and more drastic fluctuations in their extremities. A temperature increase above 38.5°C in a joint could preferentially activate Th17 T cells, inducing HSR exacerbated by two active DDX3X alleles. These metabolically active Th17 cells subsequently generate more heat, HSPs, and inflammatory cytokines, activating other immune cell types and starting an inflammatory feedback loop.

Immunometabolism may be the mediator

Once activated, Th17 cells shift to aerobic glycolysis. In fact, mitochondrial oxidative phosphorylation is required for Th17 effector function *in vivo*, with the liver kinase B1 enzyme as the proposed link between mitochondrial function and cytokine expression [108, 109]. Uniquely among CD4+ T cell subsets, Th17 cells have fused mitochondria with tight cristae, and recent studies suggest OPA-1-mediated mitochondrial fusion is critical for their apoptotic resistance [108, 109]. Interestingly, OPA-1 and mitochondrial fusion are also essential for thermogenic activity of mitochondria in brown adipose tissue (BAT) *in vivo* [110]. BAT thermogenesis can also be activated through mitochondrial reactive oxygen species (ROS) [110], whose levels can increase in the face of environment stressors such as heat and even radio frequency radiation emitted by cell phones [111, 112]. Furthermore, UCP1 also controls ROS levels in BAT and could represent another mechanism to explore in autoimmune Th17 T cells [27, 113].

Along with Th17 T cell mitochondrial similarities to thermogenic BAT, recent studies using internal cellular thermometers suggest that mitochondrial metabolism generates large amounts of heat, though to what degree remains under investigation [27, 28, 114]. Dissipation of this heat may subsequently activate immune cells with higher heat shock thresholds, thereby initiating a temperature-activation feedback loop. This is molecularly evident through HSPs and HMGB1 found in the synovial fluid of RA patients [115, 116]. Clinically, it may manifest as joint site fevers which are a biomarker of disease severity [86, 87].

Metabolic targets

If immunometabolism is the mechanism of pathology, it may represent a promising therapeutic target. The reliance of Th17 T cells on glucose for their metabolism is evidenced by the inhibition of inflammatory responses *in vivo* through genetic deletion of the glucose transporter *Slc2a1* (GLUT1) or glucose restriction [25]. Glucose restriction causes mitochondrial dysfunction and increased ROS levels in freshly resected tumor-infiltrating T cells [25, 30]. This pathway could represent a driver of sex disparity, as DDX3 and its homologs play a central role in mitochondrial protein quality control by preventing ROS-mediated damage [26, 117, 118]. Moreover, inhibition of DDX3X and its subsequent ROS protection, induced apoptosis in breast cancer cell lines [117]. This study suggests that DDX3X could be used as a co-therapeutic target due to the metabolic dependence of breast cancer on aerobic glycolysis [117], a principle that could also be explored for RA and other autoimmune diseases in which Th17 cells play

a role. DDX3X inhibition could be especially promising for RA patients who receive benefit from first-line therapy methotrexate, a folic acid metabolism disruptor, but cannot tolerate its side effects [119].

As we strive to unravel this temperature–metabolism–immune interplay, we are working against the clock. Average body temperature in the USA has been decreasing 0.03°C per decade since the Industrial Revolution [8]. More recently, this trend was found to be accelerated in a Bolivian cohort of almost 18 000 Tsimane Ameridians [9]. Coinciding with changing epidemiological and socioeconomic conditions, Tsimane body temperature dropped steeply in 16 years on a trajectory observed in the USA over 160 years. While the exact cause of body temperature decrease remains to be seen, the trend may endanger our thermal exclusion protection against pathogens as environmental temperatures are on the rise and exacerbating disease [44, 120]. Moreover, the drastic rate difference between Bolivia and the USA harbingers how rapidly changing environments exacerbate global disparities due to thermal inequality between low- and high-income countries [121]. Likewise, sex disparities are also exacerbated, as Europe's 2022 heat waves caused 56% more heat-related deaths in females than males, a phenomenon likely caused by a confluence of biologic and societal factors [122]. Physiological differences due to body temperature and heat response may illuminate the biological mechanisms underlying these disparities. Therefore, accelerating these research avenues is necessary to prepare public health for our changing world.

Environmental temperature and disease

Temperature can impact humanity on every level, evidenced by seasonal patterns in both health and disease. Influenza epidemics peak every winter in temperate climates. Environmental models show temperature to be the strongest predictor of Influenza peaks, with accuracy up to 84% in high altitudes [123]. These phenomena are becoming more pronounced with increased temperatures worldwide, highlighting both the direct and indirect effects human-caused climate change will have on our health.

Heat waves have increased in frequency, duration, and intensity since the 1960s, and the United Nations considers heat as the deadliest weather-related hazard, worldwide [121]. Beyond the direct threat of heat, rising ambient temperatures are associated with increased rates of maladies from infectious diarrhea [124] to COVID-19 [44], and the risk of new epidemics may increase 20–50% in highly populated regions [125]. One proposed mechanism for these associations is that extreme temperature places increased pressure on immunometabolic resources to maintain homeostasis [44, 124, 125]. The increase in new epidemics is exacerbated by the expanded distribution of known disease vectors, such as the mosquito *Aedes albopictus*, which have expanded their distribution range due to warming, bringing pathogens such as Chikungunya virus and Dengue virus to previously unaffected regions [126].

Outside of infectious disease, associations have been found between increased temperature and increased risk of stillbirth and shorter gestation [127]. Rapid temperature fluctuations have also been linked to worsening of dementia hospitalizations, with the greatest impact felt by already high-risk cohorts (low-income, elderly) [128]. Mental health deserves special consideration since chronic stress has been linked to decreased immunity through glucocorticoid receptor resistance, with broad implications for disease resistance and severity [22, 44].

Along with exacerbating known maladies, higher temperatures are leading to new classes of diseases. Scientists hypothesize higher environmental temperatures are selecting for fungi that can replicate within our thermal exclusion zone [129]. This may be seen in the emergence of *Candida auris*, a multidrug-resistant fungus identified in 2009 that is capable of causing severe infections in hospitalized patients [130]. Experts hypothesize that this strain recently became pathogenic for humans due to thermal adaption in response to climate change [131]. This is supported by findings that wild strains grow slower at mammalian temperatures than the clinical strains now recognized on all human-inhabited continents [132]. This represents a heightened threat to all species that use fever as a defense mechanism.

No matter the method of action, the correlation persists: with more extreme temperatures, health suffers. These consequences fall disproportionately on lands, countries, and communities who have contributed the least to the problem and are least able to mitigate the harms due to centuries of colonial appropriation and resource depletion [120, 133, 134]. Yet despite extensive evidence and decades of warnings from experts, dominant structures of power are not preparing for the impact that the biospheric emergency will have on global public health [120, 133, 134]. In the face of this failure to act, as scientists, we must extend beyond advisement to embrace advocacy and activism. Though a daunting task on an individual scale, a group of academic activists released an inspiring road map for integrating activism into our work [134]. Their conclusion is ours as well, 'Let us not turn ourselves into passive witness of mass death and extinction. We are life scientists after all—let us stand up for life'.

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Conflicts of Interest

None declared.

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Data availability

This article did not entail the generation or analysis of new data.

Author contributions

All authors contributed to this article.

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