



REVIEW

Sympathetic nerve-adipocyte interactions in response to acute stress

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Abstract

Psychological stress predisposes our body to several disorders. Understanding the cellular and molecular mechanisms involved in the physiological responses to psychological stress is essential for the success of therapeutic applications. New studies show, by using *in vivo* inducible Cre/loxP-mediated approaches in combination with pharmacological blockage, that sympathetic nerves, activated by psychological stress, induce brown adipocytes to produce IL-6. Strikingly, this cytokine promotes gluconeogenesis in hepatocytes, that results in the decline of tolerance to inflammatory organ damage. The comprehension arising from this research will be crucial for the handling of many inflammatory diseases. Here, we review recent advances in our comprehension of the sympathetic nerve-adipocyte axis in the tissue microenvironment.

Keywords Sympathetic nerves · IL-6 · Adipocytes · Microenvironment · Hepatocytes

Introduction

Stressful psychological circumstances are frequent in our daily life. The “fight or flight response” is presently well-defined as an evolutionary conserved physiological reaction of the organism to the eminent encounter with a stressor (threat or harmful event) [1]. This process was initially described at the first half of the twentieth century by the American physiologist Walter Bradford Cannon [2]. This phenomenon aims to preserve or restore organism homeostasis in vertebrates [3]. It is characterized by several physiological manifestations, including increase of respiratory and heart rates, rise in temperature, release of stocked energy, elevation in blood supply to skeletal muscles, dilation of eye pupils, among other changes [2, 4]. Nonetheless, although the consequences of this response are usually adaptive [5], they can also be damaging, affecting organ integrity and being detrimental to health [5, 6]. Hence, a unified in-depth mechanistic comprehension of the “fight or flight response” is crucial for discriminating pathological from physiological outcomes to which it leads, and for improving therapies designed to prevent organ damage resulting from this phenomenon.

The most well-studied effector organ that responds to stress is the adrenal gland, which releases catecholamines and glucocorticoids into the bloodstream [7]. Nonetheless,

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the fight or flight response also activates the sympathetic nervous system, which has been historically less explored partially due to its diffuse anatomy [8, 9]. Sympathetic nerves innervate most organs and are also involved in various pathophysiological responses to psychological stress [10, 11]. Sympathetic neurotransmitters released by these innervations, such as norepinephrine, ATP, neuropeptide Y, and nitric oxide, may affect the behavior of specific cell types in diverse tissue microenvironments [12, 13]. Albeit sympathetic nerves activated by psychological stress have long been suspected of participating in the origin of many disorders, the cellular and molecular mechanisms involved still remain incompletely understood. Understanding the role of sympathetic nerves and the signaling mechanisms involved during psychological stress may be crucial for the success of clinical applications.

In a recent article in *Cell*, Qing and colleagues demonstrated elegantly that sympathetic nerves play a central role in the inflammatory organ damage that can be caused by psychological stress [14]. Using state-of-the-art technologies, such as sophisticated *in vivo* inducible genetic methods, including Cre/loxP-mediated systems, in combination with pharmacological approaches, the authors selectively eliminated different components from the tissue microenvironment to dissect the cellular and molecular mechanisms involved in acute stress-derived organ damage. The authors found that the level of interleukin-6 (IL-6) induced after psychological stress was higher than of all other cytokines tested. This level was sustained for several hours, and it was independent of circadian oscillations [14]. Interestingly, surgical removal of brown adipose tissue eliminated the increase in IL-6 after psychological stress. Additionally, Qing and colleagues, by using UCP1-Cre/IL-6-floxed mice in which IL-6 is deleted specifically from brown adipocytes, revealed that IL-6 levels after psychological stress decreased significantly in those mice [14]. These data indicated that the major source of IL-6 after psychological stress was brown adipocytes.

Remarkably, the authors discovered that pharmacological sympathetic denervation reduced IL-6 levels induced by psychological stress. Also, specific genetic ablation of β 3 adrenergic receptors in brown adipocytes attenuated the levels of stress-induced IL-6, demonstrating that sympathetic nerves control brown adipocytes IL-6 release by β 3 adrenergic signaling during acute stress. Moreover, Qing and colleagues showed that sympathetic nerve activation of adipocyte IL-6 secretion leads to hyperglycemia through gluconeogenesis in response to psychological stress [14]. Notably, pharmacologic blockade or genetic deletion of IL-6 receptors in hepatocytes suppressed hepatic gluconeogenesis after psychological stress. Overall, these results indicate that sympathetic

nerves induce hyperglycemia in response to acute stress via adipocyte-derived interleukin-6 acting on hepatocytes [14].

Qing and colleagues demonstrated that lipopolysaccharide-induced inflammation can cause mortality in stressed animals. Strikingly, this mortality was dependent of sympathetic nerves signaling through β 3-adrenergic receptors in adipocytes, of IL-6 release by those adipocytes, and of glucose production by hepatocytes in response to IL-6 [14]. Importantly, the mortality in stressed animals was caused by renal and cardiac damage. Altogether, this study reveals a key role of sympathetic nerves in decreasing tolerance to inflammatory organ damage via adipocyte-derived IL-6 (Fig. 1).

This study reveals details of cellular and molecular mechanisms involved in the organism response to acute stress. It also identifies a systemic communication between the peripheral nervous system, brown adipocytes, and hepatocytes. These findings also offer novel therapeutic targets for treatments of disorders characterized by inflammatory organ damage. Here, we discuss the discoveries from this work and evaluate recent advances in our understanding of the influence of sympathetic nerve-adipocyte-hepatocyte axis in the tissue microenvironment.

Perspectives/future directions

Specificity of transgenic cre/loxP models

Qing and colleagues analyzed cell-specific null mutant mice models (Ucp1-CreER/ β 3-adrenergic receptor-floxed, Ucp1-CreER/IL-6-floxed, and Alb-Cre/IL-6 receptor a-floxed mice), and the principal discoveries from this study are based on the experimental results collected from these mice [14]. A limitation of such approaches is that they rely on the induction of the Cre recombinase [15–17]. Thus, caveats, that need to be given attention when using these models, include inadequate recombination leading to insufficient gene deletion, off-target Cre expression, and compensatory upregulation of other genes [18, 19]. Therefore, examination of gene expression levels in the targeted cells will clarify the level of achieved gene deletion, and whether there are compensatory changes in the expression of other genes in these specific cells.

Traditionally, it is well established that Ucp1 is expressed by adipocytes [20]. Nevertheless, not all adipocytes have this protein [21], and Cre-mediated expression based on this gene can be detected in other cells as well, for instance in renal collecting ducts [22]. Additionally, Ucp1 expression was previously detected outside of the adipose tissue as well [23]. Thus, in Ucp1-CreER/ β 3-adrenergic receptor-floxed and Ucp1-CreER/IL-6-floxed mice, β 3-adrenergic receptor and IL-6 may be also eliminated from other cell types

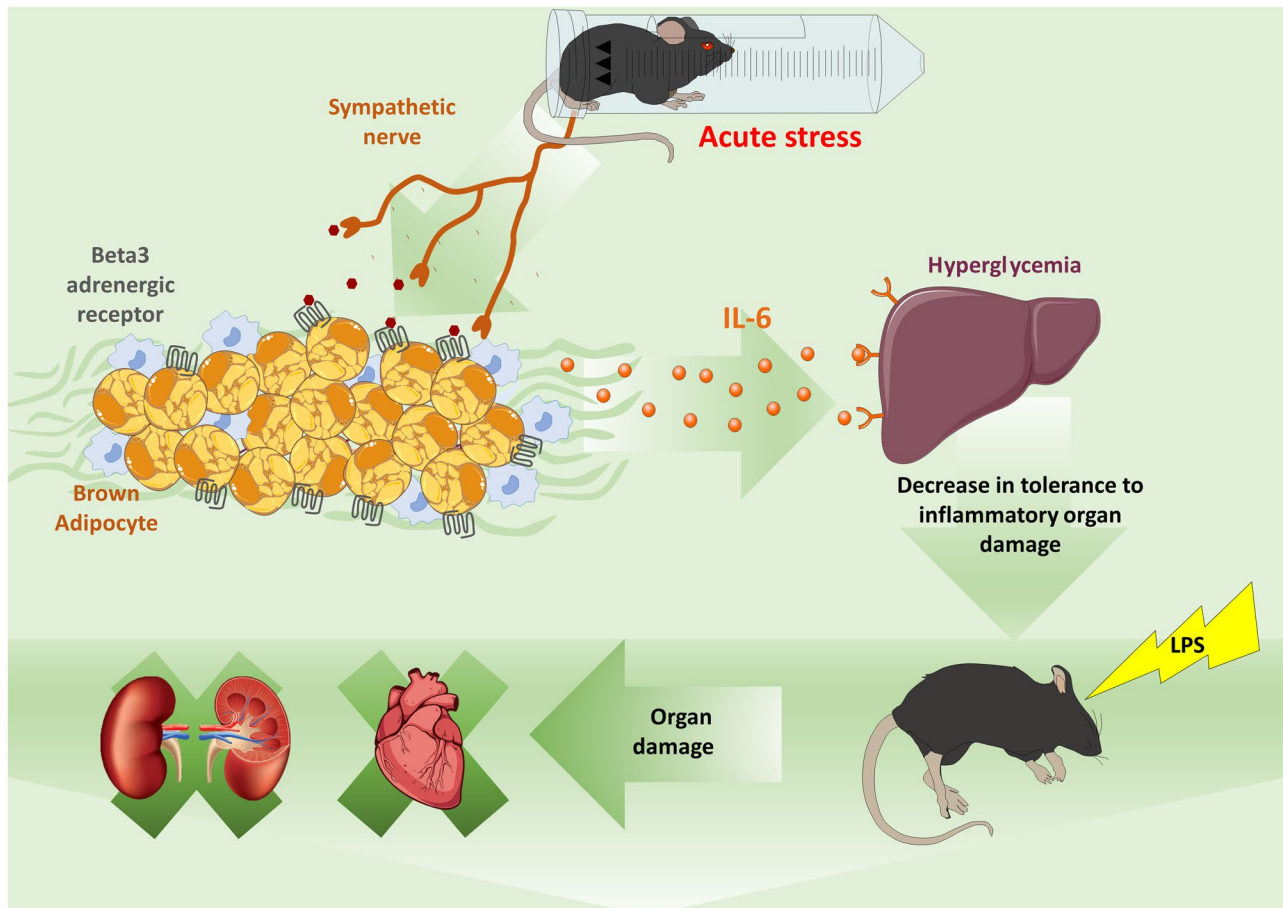


Fig. 1 Sympathetic nerve-adipocyte-hepatocyte axis dictates physiologic response to acute psychological stress. Using state-of-the-art technologies, Qing and colleagues demonstrated that, after acute psychological stress, sympathetic nerves induce brown adipocytes

to increase circulatory IL-6 levels. IL-6 signals to hepatocytes to increase glucose production via gluconeogenesis leading to hyperglycemia. This results in a decline in the organism tolerance to inflammatory organ damage [14]

outside of the brown adipose tissue. Although these concerns do not change the outcome of this study, it is possible that some of the effects observed in those models are not exclusively due to brown adipocytes.

Brown adipocytes are present in diverse anatomical locations in mice and humans, including dorsal back of the interscapular and subscapular regions, cervical region between scapula and head, supraclavicular region, associated to kidneys, and attached to the thoracic aorta [24–27]. Additionally, they can be found also within the epididymal and inguinal white adipose tissue [28, 29] as beige/brite adipocyte. Qing and colleagues surgically removed intrascapular fat pads, suggesting the importance of brown adipocytes from this site [14]. Nevertheless, in all transgenic models analyzed, genetic deletions of β_3 -adrenergic receptor and IL-6 were done in brown adipocytes from all locations where they are present. Therefore, it remains to be explored whether the observed phenotype in these transgenic models is due to brown adipocytes from

a specific anatomical location, or whether all brown adipocytes contribute to this phenomenon.

Heterogeneity within the sympathetic nerve-adipocyte axis

Mature adipocytes are the typical residents of the adipose tissue [30–32] and are classified into three distinct types: white, brown, and beige/brite (<https://doi.org/10.1016/j.cmet.2016.10.005>). White adipocytes are related to storing triacylglycerides (TGs). The brown adipocytes oxidize lipids to produce heat in part through a UCP1 associated uncoupling of electron transport from ATP production. Beige adipocytes (“brown-like”) can also support UCP1-independent thermogenesis (<https://doi.org/10.1042/BCJ20200298>). Beige cells resemble white adipocytes with a shallow basal expression of UCP1, but, like classical brown fat, they respond to cyclic AMP stimulation with high UCP1

expression and respiration rates (<https://doi.org/10.1016/j.cell.2012.05.016>). Nevertheless, this tissue comprises a variety of other components with important physiological roles, such as pre-adipocytes, mesenchymal stem cells, nerves, macrophages, neutrophils, lymphocytes, fibroblasts, pericytes, endothelial cells, and others [33–36]. The proportions of the different adipose tissue constituents may vary depending on the pathophysiological condition and the anatomical location [37]. Interestingly, most of these cells produce IL-6 [38]. Qing and colleagues demonstrated that adipocytes are the main source of IL-6 after psychological stress [14]. Future studies will reveal whether other sources of IL-6 also may be activated by sympathetic nerves and play important roles during the “fight or flight response”.

Adipocytes have been shown to be heterogeneous, based on molecular markers, embryonic origins, and anatomical locations [39–41]. Qing and colleagues consider brown adipocytes as a homogeneous population in their study [14]. Nonetheless, a recent study revealed the existence of two brown adipocyte subpopulations based on adiponectin expression [42]. This study showed that the two subtypes differ in their functions and metabolic signatures, characterizing them as low and high thermogenic brown adipocytes. Elegantly, by single-brown adipocyte RNA sequencing, it was revealed that there is molecular heterogeneity based on the transcriptomic patterns of the two brown adipocyte subtypes [42]. Curiously, only one of the subpopulations declined in number with aging. Thus, whether only a fraction of brown adipocytes responds, by producing IL-6, to sympathetic nerves in response to acute stress still needs to be elucidated. It would be important to examine whether different brown adipocytes’ subsets behave distinctly during sympathetic nerve activation.

Although all rodent brown adipose tissue depots receive sympathetic innervations [43], the tissue microenvironments of these depots differ [44, 45]. For instance, only the pericardial and minor mediastinal brown adipose tissue depots are innervated by parasympathetic nerve fibers [44, 45]. The sympathetic innervations may also vary in their morphologies and functions in different species [46–51]. Thus, the role of sympathetic neurons in the brown adipose tissue of distinct anatomical locations in particular species should be investigated in future studies.

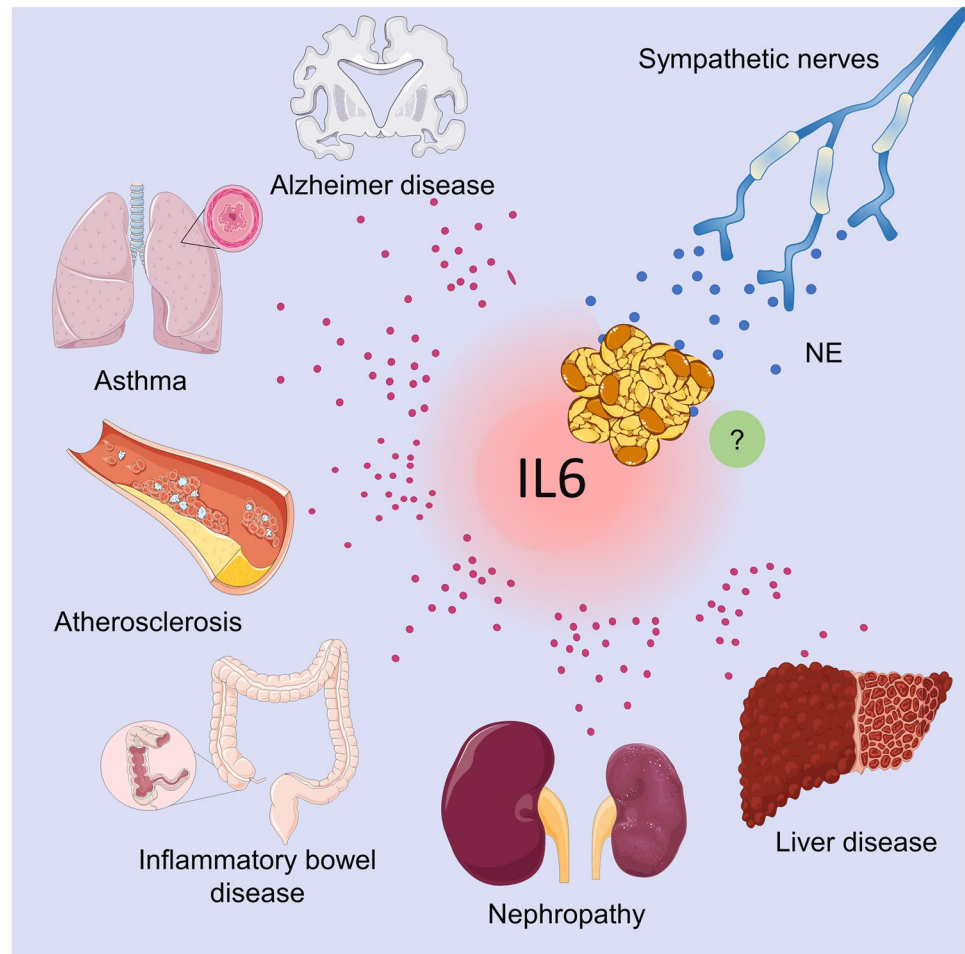
Other roles of IL-6 signaling

IL-6 is a prototypical cytokine involved in the enhancement of multiple inflammatory pathways [52]. It can be induced by diverse stimuli, such as invasion of pathogens or other types of inflammation-linked damage [53]. IL-6 has been shown to be involved in both the innate and adaptive immune responses [38, 54]. It also activates the leukocytic

chemotaxis towards the injured site [55, 56]. Importantly, decontrolled IL-6 release results in constant inflammation leading to tissue damage [57, 58]. IL-6 signaling involves canonical and non-canonical molecular mechanisms via a membrane bound or a soluble receptor, respectively. In canonical signaling, IL-6 binds to a membrane-anchored IL-6 receptor (IL-6R). This binding promotes an association with gp130, which activates signal transduction [59]. Non-canonical IL-6 signaling is mediated by the binding to a soluble form of IL-6R (sIL-6R) and forming the complex with gp130 [58]. The differences between downstream signaling mechanisms of IL-6 in canonical versus non-canonical pathways depend on the affected cells, leading to the activation of JAK/STAT3 and/or SHP2/Gab/MAPK pathways [59]. Canonical IL-6 signaling is essential in the chemoresistance of ovarian cancer [60], autoimmune diseases [61], colitis [62], and hepatic inflammation [63], while non-canonical IL-6 signaling influences rheumatoid arthritis, Castleman disease [64], osteoclastogenesis [65], and type 2 diabetes [66]. Increased IL-6 levels have been related to a series of stressors such as cold, infection, restraint, fatigue, sleep deprivation, and psychosocial stressors [67–71]. Thus, IL-6 increase may affect different tissues differently during psychological stress [72]. Future studies should explore whether canonical, non-canonical IL-6 signaling, or both are involved during psychological stress pathogenesis.

IL6 is expressed as distinct isoforms that may be responsible for different functions associated with IL6 signaling. For example, four IL-6 variants were detected in the human lung tissue: *native IL-6*, *IL-6 missing exon 2 (IL-6Δ2)*, *IL-6 missing exon 4 (IL-6Δ4)*, and *IL-6 missing both exons 2 and 4 (IL-6Δ2,4)*. Nevertheless, proteins were coded exclusively by *native IL-6* and *IL-6Δ4*. The *IL-6Δ4* isoform can form a stable complex with IL-6R α like *native IL-6*, but not with IL-6R β . Thus, *IL-6Δ4* might have a regulatory influence on IL-6 signaling [73]. A spliced isoform of IL-6 was also detected in renal cell carcinoma which acts as IL-6 inhibitor [74]. Recently, there were also reported two IL-6 isoforms in turtles subjected to stress homologous to the mammalian IL-6 [67]. The two IL-6 transcripts were named *psIL6* and *psIL6ns*. Future studies should explore whether different IL-6 isoforms act differently in stress-related contexts. Qing and colleagues demonstrate that after acute stress sympathetic nerves induce the increase in the levels of IL-6 which leads to other pathophysiological effects [14]. It will be interesting to determine whether sympathetic nerves are also responsible for IL-6 increase in other pathological conditions, in which the role of this cytokine is well characterized, such as Alzheimer’s disease [75–77], Asthma [78, 79], atherosclerosis [80, 81], inflammatory bowel disease [82, 83], nephropathy [84], liver diseases [85], and others [38] (Fig. 2).

Fig. 2 Schematic illustration summarizing the possible role of sympathetic nerves on multiple inflammatory diseases via IL-6. After acute psychological stress, sympathetic nerves induce the increase in the levels of IL-6 which leads to other pathophysiologic effects [14]. IL-6 plays important roles in the pathogenesis of multiple disorders. Future studies will reveal whether sympathetic nerves are also responsible for IL-6 production in these pathological conditions



Intriguingly, high levels of circulating IL-6 were associated with worse outcomes in COVID-19 patients, bringing attractive possibilities in terms of treatments [86]. An excessive inflammatory reaction is observed in patients infected by the SARS-CoV-2 virus [87–90]. COVID-19 infection can be characterized as a “cytokine storm” because the infection is followed by an intense inflammatory response with the release of a copious pro-inflammatory cytokines. The cytokine storm can be characterized by destructive systemic inflammation, hyperferritinemia, hemodynamic instability, and multiple organ failure that can lead to death. Multiple pro-inflammatory cytokines, including IFN- γ , TNF- α , IL-1, IL-6, and IL-18, participate in this uncontrolled immune response [87, 91]. IL-6 plays a fundamental role in the harmful systemic hyperactivated immune status, characterized as “cytokine storm”. IL-6-induced immune dysregulation is an important feature of SARS-CoV-2 infection, and the increase of this and other cytokines, including TNF- α , is associated with augmented viral load found in the severe form of the disease [91–93].

Three drugs that block IL-6 signaling, tocilizumab, sarilumab, and siltuximab, have been proposed to be used

against COVID-19 [94, 95]. Yet, the cellular and molecular players involved in COVID-19 pathophysiology still remain poorly understood. It will be interesting to examine whether SARS-Cov-2 virus activates the sympathetic nerves–brown adipocytes axis to produce IL-6. During the pandemic, patients also suffer with social isolation what leads to acute psychological stress, with the possible involvement of sympathetic nerves in the production of IL-6. COVID-19 disease brought fear, lockdown, and precautionary measures that led to psychosocial stress which may result in depression [96–98]. Acute stress is related to isolated episodic events while chronic stress is associated with an accumulation of several episodic psychological stress events [99]. The prolongation of pandemic restrictions could lead to chronic stress. Although Qing et al. discussed IL-6 regulation of acute stress, IL-6 has been shown to be involved in both acute and chronic stress [71]. High levels of IL-6 are detected in patients with depression [100]. Furthermore, increased IL-6 concentration and systemic inflammation have been reported in psychosocial stress, similar to the observed after COVID-19 infection [100]. In spite of major epidemiological studies, stress

has not yet been singled out as an essential risk factor in COVID-19 disease. Nevertheless, reports have shown that psychological stress and depression in COVID-19 patients may worsen disease prognosis [101, 102]. Interestingly, infants and children, which have more abundant brown adipose tissue [103–106], are the ones least affected by COVID-19 [107, 108]. This may be due to a variety of reasons, including lower expression of angiotensin-converting enzyme 2 (ACE2) receptors in children [109, 110], higher COVID-19 comorbidities in adults [111], increased chronic pro-inflammatory status with age [112–115], and others. Thus, it will be important to investigate in depth the mechanisms involved in the production of IL-6 in COVID-19 patients at different ages, exploring the possible cross-talk between sympathetic nerves and brown adipocytes (Fig. 3).

IL-6 signaling induces distinct acute and chronic pathophysiological effects. Initially, IL-6 is produced in the site of inflammation by the skeletal muscle, adipose tissue, adrenal gland, endothelial cells, and others [71], leading to the production of C-reactive protein, serum amyloid A, fibrinogen, and other acute-phase proteins [116, 117]. On the other hand, during the chronic response, IL-6 is produced by a variety of leukocytes mediating the switch from innate to adaptive immunity which restores the body homeostasis after inflammation [117, 118]. In obesity, although the main focus of studies has been the targeting of the white adipose tissue, increase in brown adipose tissue has emerged as a promising strategy against this

pathology as well [119]. Indeed, ablation of UCP1, the brown-fat-specific uncoupling protein, has been shown sufficient to induce obesity, suggesting that brown adipose tissue may protect against this disease [120]. Nevertheless, an increase in IL-6 has been detected in the circulation and adipose tissue of obese patients [121–123], indicating that possibly this increase in IL-6 may be coming from a different source than during acute psychological stress. Interestingly, findings point to different and even sometimes contradictory outcomes when using IL-6 knockout mice. While some showed that these mice develop spontaneous obesity [124], other studies found different results [125, 126]. Such contradictory findings could be explained only in the frame of a more in-depth investigation on the role of IL-6 coming from different sources (cells/tissues).

Interactions within the tumor microenvironment

In addition to key roles of peripheral innervations within different organs, nerves infiltrate also inside tumors in several tissues, affecting cancer development in different ways [127–134]. Specifically, sympathetic nerves have been shown necessary for cancer progression [131]. Importantly, clinical studies reveal beneficial effects of treatments that affect the sympathetic nervous system in human cancer patients [135]. Still, the detailed molecular mechanisms by which sympathetic nerves influence cancer progression

Fig. 3 Possible role of sympathetic nerves and brown adipocytes in COVID-19 pathogenesis. High levels of circulating IL-6 are associated with worse outcomes in COVID-19 patients. It will be interesting to examine whether SARS-Cov-2 virus activates the sympathetic nerve-brown adipocyte axis to produce IL-6. During the pandemic, patients also suffer with social isolation what leads to acute psychological stress, with the possible involvement of sympathetic nerves in the production of IL-6

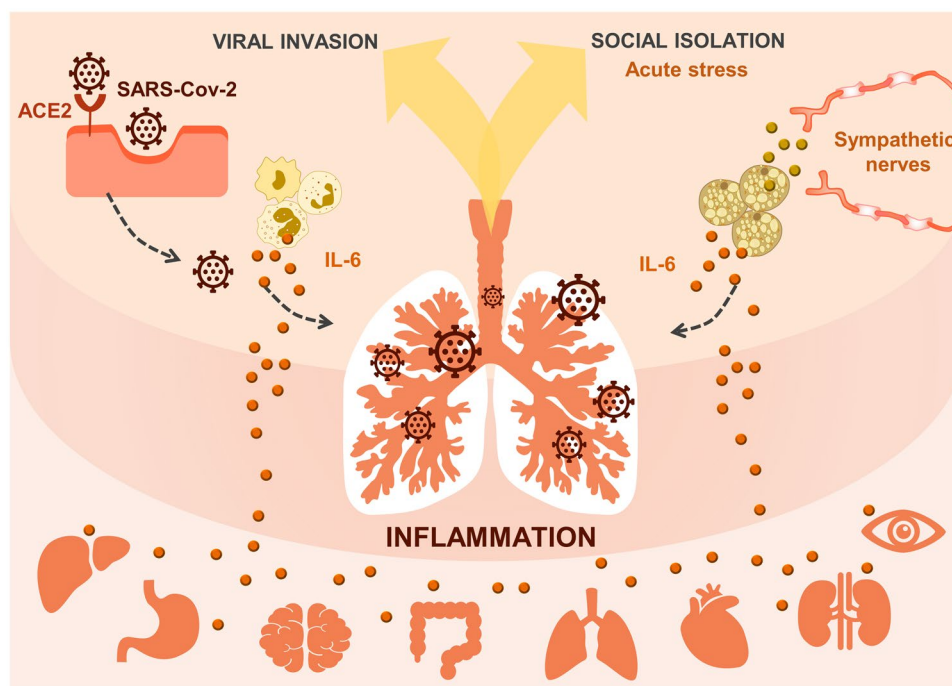
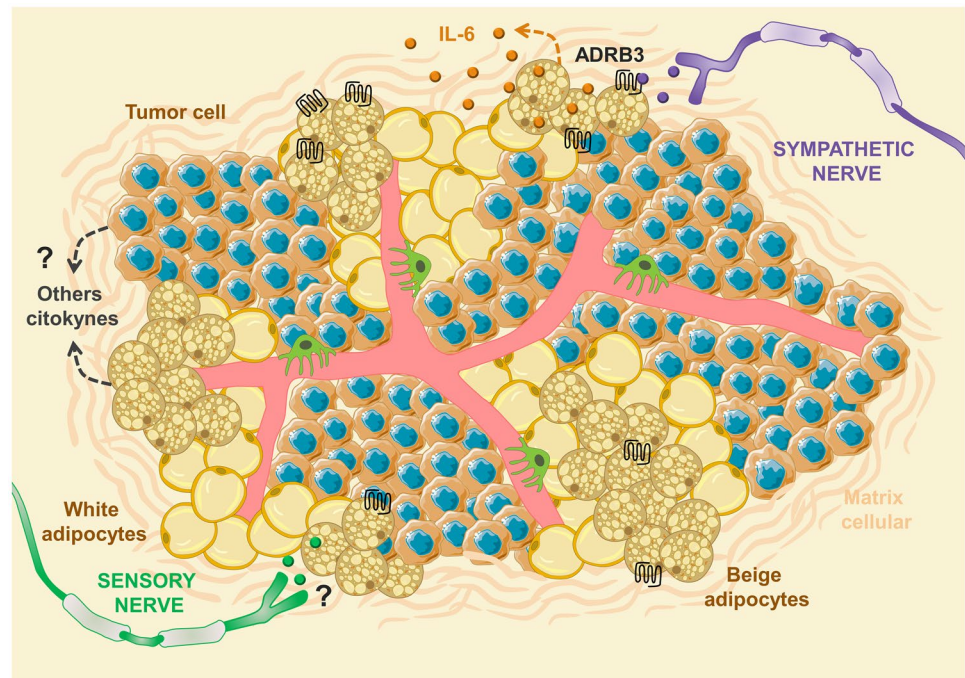


Fig. 4 Potential new mechanism of sympathetic nerve role within the tumor microenvironment. Different nerve fibers, including sympathetic innervations, infiltrate the tumors, and affect their development. The detailed molecular mechanisms by which sympathetic nerves influence cancer progression remain incompletely understood. Future studies should examine whether sympathetic nerves also act within tumors via IL-6 derived from intra-tumoral adipocytes



remain incompletely understood within the complexity of the tumor microenvironment [133, 136].

When adipose tissue is invaded by cancer cells, adipocytes act as a supply of lipids for neoplastic cells [137, 138]. Additionally, adipocytes directly interact with malignant cells affecting their behavior, including their proliferation and invasion capacities [139–143]. Adipocytes may also affect other components within the tumor microenvironment, such as newly formed blood vessels [144–157]. White and beige adipocytes, within the tumor microenvironment, also produce IL-6, and some of their effects on cancer cells have been attributed to IL-6 signaling [158, 159]. Additionally, brown adipocytes can transform and secrete IL-6 upon other different stimulations [160, 161]. Cancer-associated cachexia is associated with switch from WAT to BAT [162] (<https://doi.org/10.1038/s41598-018-36626-3>). Increased circulating IL-6 levels have been associated with WAT browning, as consequence of the upregulation of the uncoupling protein-1 (UCP1) [162, 163] (<https://doi.org/10.20900/immunometab20200032>). Experiments blocking IL-6 production by cancer cells show a reduction in browning [162], which limits cachexia [164]. Additionally, treatment with anti-IL-6 blocks WAT atrophy [162]. The role of the sympathetic nervous system in IL-6 induction of cancer-associated cachexia remains to be explored.

Thus, it will be compelling to examine whether sympathetic nerves also act within tumors via IL-6 derived from intra-tumoral adipocytes (Fig. 4). New treatments targeting this possible mechanism could potentially be used in the anti-cancer fight, improving patient survival.

Translating mouse research into humans

Qing and colleagues reveal a novel role of sympathetic nerves increasing circulatory IL-6 via brown adipocytes after psychological stress [14]. Mouse models aim to recreate features of human biology as closely as possible. Nevertheless, to translate animal research into human patients, these discoveries should be in the future validated in human tissues. Although it is known that in humans IL-6 levels increase after stress [14, 165, 166], the mechanisms involved in this phenomenon remain to be confirmed. It has been implied that β 3-adrenergic response in the adipose tissue varies between species [167]. Comparing rodent and human brown adipose tissues, differences have been detected in composition, gene expression profiles, and anatomical location, being more widely dispersed in humans [168, 169]. IL-6 also presents species-specific characteristics, such as binding specificity [170, 171]. Also, the human and rodent IL-6 receptors differ, and tocilizumab does not activate the rodent receptors [172–176]. It is not yet clear whether these findings could be translated into clinic, thus future studies should examine whether the mechanistic discoveries by Qing et al. (2020) are also valid in humans. Enhancing the accessibility to human biopsies will be essential to achieve this aim. Importantly, although some BAT deposits have been reported [161, 177–180], the WAT is the predominant fat type in humans. IL-6 production by WAT has been suggested to participate in the pathophysiology of type 2 diabetes and obesity in humans [66, 181, 182]. Moreover, the white adipose tissue is also innervated by the sympathetic nervous

Table 1 Ongoing clinical trials for multiple disorders targeting IL-6 biology registered on <https://clinicaltrials.gov>

NCT number	Title	Conditions	Interventions	Start year
1	NCT03288584 Effects of interleukin-6 inhibition on vascular, endothelial and left ventricular function in rheumatoid arthritis	Rheumatoid arthritis, inflammation	Drug: tocilizumab, corticosteroid	2017
2	NCT04544033 IL-6 gene (174G/C) single nucleotide polymorphism as an indicator of COVID-19 severity in Egyptian patients	COVID-19	Diagnostic test: IL-6 level measurement, IL-6 gene-174C detection	2020
3	NCT03882307 Levels of interleukin-6 and transforming growth factor beta in hepatitis C virus (HCV) patients sera	Chronic hepatitis C	Drug: sofosbuvir, daclatasvir (HCV drugs)	2021
4	NCT04842981 Interleukin-6 inhibitors and drug-drug interactions in patients with rheumatoid arthritis	Rheumatoid arthritis	Drug: tocilizumab, sarilumab	2021
5	NCT04359667 Serum IL-6 and soluble IL-6 receptor in severe COVID-19 pneumonia treated with tocilizumab	COVID-19, severe pneumonia	Drug: tocilizumab	2020
6	NCT03999749 A phase II study of the interleukin-6 receptor inhibitor tocilizumab in combination with ipilimumab and nivolumab in patients with unresectable stage III or stage IV melanoma	Melanoma	Drug: ipilimumab, nivolumab, tocilizumab	2019
7	NCT04387201 GLP-1 therapy: the role of IL-6 signaling and adipose tissue remodeling in metabolic response	Glucose intolerance, overweight, obesity, adiposity	Drug: dulaglutide cyanocobalamin	2020
8	NCT04363502 Use of the interleukin-6 inhibitor clazakizumab in patients with life-threatening COVID-19 infection	COVID-19	Drug: clazakizumab placebo	2020
9	NCT04078035 Biological response to brief psychological challenge	Acute inflammatory response to psychological stress	Behavioral: socio-evaluative speech task	2020
10	NCT04626505 Trial to evaluate reduction in inflammation in patients with advanced chronic renal disease utilizing antibody mediated IL-6 inhibition in Japan	Chronic kidney disease inflammation, cardiovascular risk	Drug: ziltekimab placebo	2020
11	NCT04616235 Acute exercise and NK cell regulation in tissue and circulation after IL-6R blockade	IL-6 inhibition, physical stress, appetitive behavior	Drug: tocilizumab	2021
12	NCT04729959 Testing the addition of the immune therapy drugs, tocilizumab and atezolizumab, to radiation therapy for recurrent glioblastoma	Diffuse astrocytoma, IDH-wildtype, recurrent glioblastoma	Biological: atezolizumab, conventional surgery Radiation: fractionated stereotactic radiation therapy Biological: tocilizumab	2021
13	NCT04687540 Meal-regulated substrate metabolism, influence of obesity and IL-6	Obesity	Drug: tocilizumab	2021

system [180, 183, 184] and has been shown to secrete IL-6 [66]. This brings the question of whether the production of IL-6 in humans is activated in the WAT through sympathetic innervations stimulation as well. Thus, albeit IL-6 is secreted in humans from WAT, BAT and beige adipocytes, future work will explore whether and how the sympathetic nervous system is involved in these processes. Interestingly, several ongoing clinical trials are exploring the role of IL-6 biology in multiple human disorders including inflammation, rheumatoid arthritis, COVID-19, pneumonia, cardiovascular diseases, cancer, adipose tissue remodeling, stress, exercise, immune cell regulation, and obesity (Table 1).

Conclusion

Qing and colleagues provide a new and important insight into the cellular and molecular mechanisms involved in the response to acute psychological stress: Sympathetic nerves induce adipocytes to release IL-6 which activate hepatocytes for gluconeogenesis [14]. This new concept places sympathetic nerves, brown adipocytes, and hepatocytes as central players that might be pharmacologically targeted to alter the physiologic effects of acute psychological stress and improve the organism reactions. Future studies will reveal whether these cross-talks are important also in other physiopathologic conditions.

Author contribution GSPS, ACC, CCP, BGSR, SOS, DCR, MCXP, MLBJ, JHA, VACA, RRR, NOSC, AM, and AB performed the literature search, reviewed the content, edited the text, and critically revised the work. GSPS, ACC, CCP, BGSR, and SOS created the figures and table. AB wrote and approved the final manuscript. All the authors commented on the manuscript.

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Availability of data and materials Not applicable.

Declarations

Ethics approval and consent to participate Not applicable.

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Competing interests The authors declare no competing interests.

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