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Review

Stimulator of Interferon Genes (STING)-Type I Interferon Signaling: Bridging Immunity and Pain

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Abstract

Interferons (IFNs) are cytokines with diverse functions, possessing antiviral, antiproliferative, and immunomodulatory effects. IFN-α and IFN-β, key members of the type I interferon (IFN-I) family, are widely used in the treatment of diseases such as hepatitis and multiple sclerosis. In the nervous system, microglia, astrocytes, and neurons express IFN-I receptors. Beyond their classical transcriptional roles, IFN-Is can suppress neuronal activity and synaptic transmission through nongenomic mechanisms, producing potent analgesic effects. However, IFN-Is are active in signaling pathways such as phosphoinositide 3-kinase (PI3K), mitogen-activated protein kinase (MAPK), and the MAPK-interacting serine/threonine-protein kinase (MNK)-eukaryotic initiation factor 4E (eIF4E) pathway, which can sensitize peripheral nociceptors and contribute to nociceptive responses. This narrative review explores recent advances in understanding the roles of IFN-I and the cyclic-GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) signaling cascade in acute and chronic nociceptive responses, which are increasingly recognized but remain a subject of debate. Recent studies suggest that the STING–IFN-I pathway has complex, stage-dependent effects on nociception. In the middle to late stages of the nociceptive response, this pathway can activate signal transducer and activator of transcription (STAT) signaling, as well as microglial mediated STING pathways and tumor necrosis factor (TNF) receptor-associated factor (TRAF) family member-associated nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB activator) collectively referred to as TANK. These pathways increase pro- and anti-inflammatory cytokine production, promote microglial M1 polarization, and inhibit endoplasmic reticulum-phagy (ER-phagy) in the central nervous system (CNS). These mechanisms contribute to central sensitization while modulating the analgesic effects of IFN-Is. Thus, the STING-IFN-I pathway plays a dual role in nociception, with both pro-nociceptive and analgesic effects that are dependent on the stage of the nociceptive response. Understanding the differential roles of STING–IFN-I signaling in nociceptors under physiological and pathological conditions could pave the way for the development of targeted nociceptive response management therapies.

Keywords: nociceptive response; type I interferon; STING; IFN-α; IFN-β; type I interferon receptor

1. Introduction

Interferons (IFNs) were first discovered in 1957 and named for their ability to “interfere” with viral replication [1]. Over the years, significant progress has been made in understanding their mechanisms of action and therapeutic potential. Recent studies have elucidated the pivotal role of IFNs in combating viral infections with hepatitis B and C, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and various emerging viral pathogens [2–5]. For example, type I IFNs (IFN-Is), including IFN-α and IFN-β, are now recognized for their ability to modulate the antiviral state through the induction of hundreds of interferon-stimulated genes (ISGs) that target multiple stages of the viral lifecycle. Advances in IFN-based therapies include the development of polyethylene glycol (PEG)ylated IFN formulations, improvements in pharmacokinetics and efficacy in chronic viral infections such as hepatitis C, and the strategic use of recombinant IFNs in combination with direct-acting antivirals [2,3]. Additionally, the critical contributions of IFNs to innate and adaptive immunity have been harnessed in antiviral vaccine development and immune modulation during pandemics [4,5]. In addition to their antiviral functions, IFNs influence the endocrine, immune, and nervous systems, including the central nervous system (CNS). The IFN family is divided into three main subfamilies: IFN-Is, type II IFNs (comprising IFN-γ), and type III IFNs (comprising IFN-λ1–3). Type I IFNs include several subtypes, such as IFN-α (13 human and 14 mouse homologs), IFN-β, IFN-ε, IFN-κ, IFN-τ, and IFN-ω1–3. This review focuses on IFN-α and IFN-β, versatile type I cytokines that bridge innate and adaptive immunity while serving as mediators of antimicrobial, antitumor, and nociceptive response-regulating responses [6–9].

Following viral or bacterial infections or tissue injury, pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs) detect pathogen- and damage-associated molecular patterns (PAMPs and DAMPs). This activation triggers the release of cytokines and chemokines, including tIFN-Is, through neuroimmune interactions, alerting the host immune system to potential threats [10,11]. TLRs 2, 4, and 5, which are located on the cell surface, primarily detect bacterial PAMPs. TLR4 can also be found to a lesser extent in endosomes, whereas TLR3 and TLR7/8 are endosomal receptors that respond mainly to viral and bacterial nucleic acids, specifically, double-stranded RNA (dsRNA) and single-stranded RNA (ssRNA), respectively [12,13]. For example, TLR3 detects viral dsRNA and its synthetic analog poly (I:C), whereas TLR7/8 can be activated by imidazoquinoline-like molecules (imiquimod and resiquimod). TLR9, another endosomal TLR, recognizes dsDNA and unmethylated cytidine-phosphate-guanine deoxyribonucleic acid (CpG) DNA. The activation of TLRs such as TLR4 by bacterial lipopolysaccharides (LPS) and viral proteins induces robust IFN-I production and triggers specific intracellular signaling cascades [10]. When a ligand binds to a TLR, adaptor proteins such as TIR-domain-containing adapter-inducing IFN-β (TRIF) (for TLR3) and myeloid differentiation primary response 88 (MyD88) (for TLR7/8/9) are recruited, triggering a signaling cascade. This cascade results in the phosphorylation of interferon regulatory factors (IRFs) 3 and 7 by tumor necrosis factor (TNF) receptor-associated factor (TRAF) family member-associated nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activator (TANK)-binding kinase 1 (TBK1) and NF-κB. This cascade promotes the transcription of *IFN-I* genes via the binding of IRFs to enhancer regions, amplifying the immune response [14] (Fig. 1).

The signaling pathways involved in the production of IFN-Is through the activation of toll-like receptors (TLRs), melanoma differentiation-associated protein 5 (MDA5) and retinoic acid-inducible gene I (RIG-I)-like receptors are shown. TLRs, which are key pattern recognition receptors, detect pathogens and are located on the cell surface or within intracellular compartments such as endosomes (e.g., TLR3 and TLR7-9) in immune and glial cells. The induction of IFN-Is occurs via distinct intracellular signaling molecules: TRIF mediates signaling for TLR3 and TLR4, while MyD88 facilitates signaling for TLR7-9. Additionally, IFN-Is are produced through the activation of the stimulator of interferon genes (STING) signaling cascade. STING, an adaptor protein in the endoplasmic reticulum, responds to viruses and intracellular DNA by activating TBK1. This, in turn, stimulates the transcription factors NF-κB and interferon regulatory factor 3 (IRF3), driving type I IFN production. Type I IFNs and the activation and inhibition of STING exert both antinociceptive (blue arrows) and pronociceptive (red arrows) effects, modulating nociceptive response signaling.

In addition to TLRs, cytoplasmic sensors such as Asp-Glu-x-Asp (DExD)/H-box RNA helicases and STING detect microbial RNA and DNA to induce IFN-I production [6]. This pathway includes receptors such as retinoic acid-inducible gene I (RIG-I)-like helicases, melanoma differentiation-associated protein 5 (MDA5) and cGAS, which synthesizes cyclic guanosine monophosphate–adenosine monophosphate (cGAMP) upon the detection of cytosolic DNA [14–16]. STING is a transmembrane protein in the endoplasmic reticulum (ER) that responds to cGAMP or other bacterial cyclic dinucleotides (CDNs). In the Golgi, STING interacts with TBK1 once it is translocated from the ER to the ER-Golgi intermediate compartment (ERGIC). STING and IRF3 are phosphorylated by TBK1, promoting IRF3 nuclear translocation and inducing IFN-I production [12,17–19] (Fig. 1). IFN-I production supports immune responses by activating cells such as macrophages and natural killer (NK) cells. Plasmacytoid dendritic cells (pDCs) are key producers of IFN-Is, particularly during viral infections [20–22]. Additionally, STING can activate NF-κB, contributing to inflammation by inducing the expression of proinflammatory cytokines [23] and inflammasome-related genes [24] (Fig. 1). The cGAS-STING signaling cascade also plays a role in antinociception, with intracellular dsDNA triggering IFN-I production via this pathway [8] (Fig. 1). In the context of nociceptive neurons, mitochondrial DNA (mtDNA) is a plausible endogenous source of cytosolic DNA that activates STING. Under physiological conditions, mtDNA is typically confined within mitochondria. However, during cellular stress or damage, as might occur under conditions such as nerve injury or inflammation, mtDNA can be released into the cytosol. This release is facilitated by mitochondrial dysfunction and increased membrane permeability, potentially driven by reactive oxygen species (ROS) or other stress-induced factors [25]. mtDNA is highly immunogenic due to its unmethylated CpG motifs, making it a potent activator of the cGAS-STING pathway. Nuclear DNA fragments resulting from cellular damage or apoptosis may also contribute to STING activation, but their specific role in nociceptive neurons requires further exploration. However, the role of the cGAS-STING signaling cascade in the chronic nociceptive response remains complex and may have diverse effects, requiring further investigation.

2. Signaling Pathway of the Type I Interferon Receptor

IFN-α and IFN-β bind to the interferon-α receptor (IFNAR), a cell surface receptor complex comprising the IFNAR1 and IFNAR2 subunits [7]. IFNAR is widely expressed in diverse cell types, including immune cells, neu-

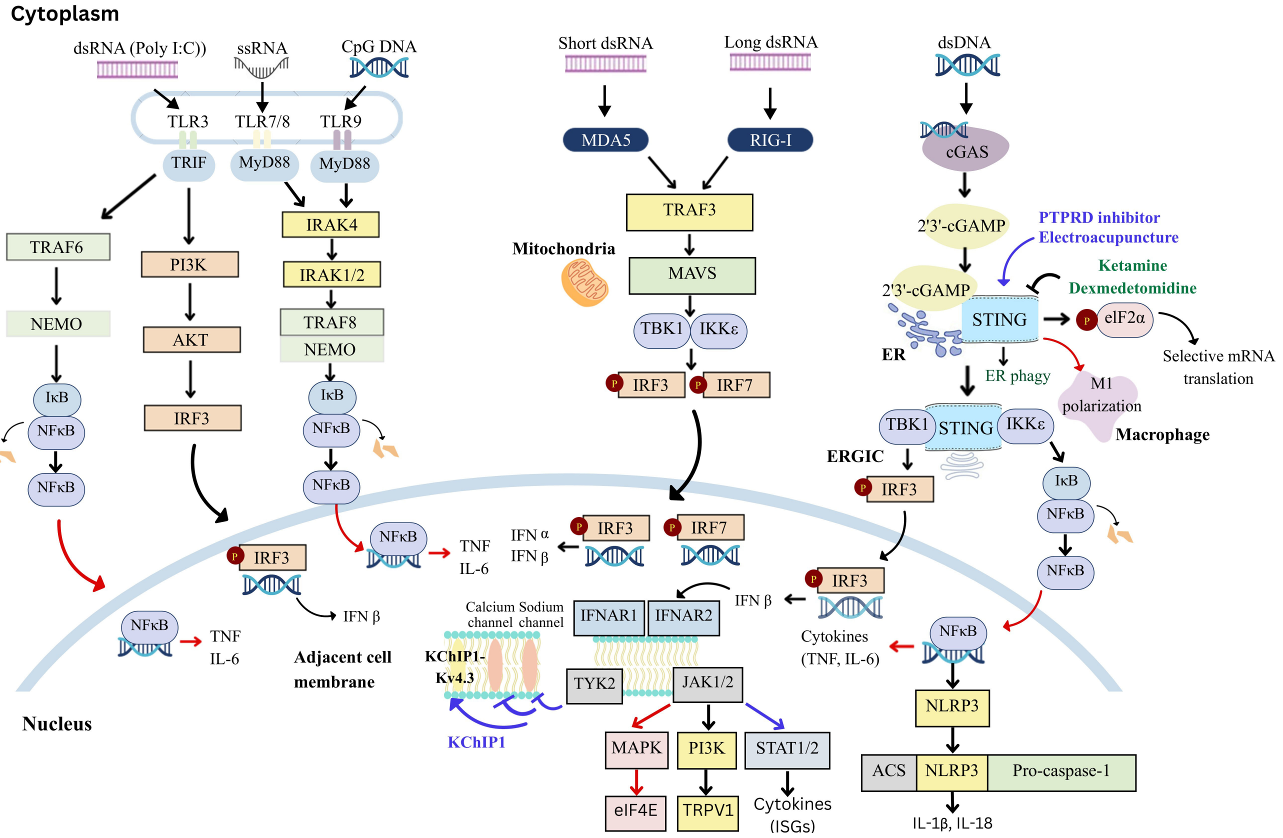

Fig. 1. Pattern recognition and type I interferon (IFN-I) signaling pathways. IRF3, interferon regulatory factor 3; IRF7, interferon regulatory factor 7; RIG-I, retinoic acid-inducible gene I; MDA5, melanoma differentiation-associated protein 5; MAVS, mitochondrial antiviral signaling protein; MYD88, myeloid differentiation primary response 88; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; STING, stimulator of interferon genes; TBK1, TNF receptor-associated factor (TRAF) family member-associated NF-κB activator (TANK)-binding kinase 1; TRIF, TIR-domain-containing adapter-inducing IFN-β; NEMO, NF-κB essential modulator; NLRP, NOD-like receptor pyrin domain-containing; cGAMP, cyclic guanosine monophosphate–adenosine monophosphate; IRAK, interleukin-1 receptor-associated kinase; dsRNA, double stranded RNA; ssRNA, single stranded RNA; mRNA, messenger RNA; CpG DNA, cytosine-phosphate-guanine DNA; cGAS, cyclic-GMP-AMP synthase; ER, endoplasmic reticulum; TNF, tumor necrosis factor; TYK, tyrosine kinase; JAK, janus kinase; ACS, caspase recruitment domain; MAPK, mitogen-activated protein kinase; STAT3, signal transducer and activator of transcription 3; TRPV, transient receptor potential vanilloid; PTPRD, protein tyrosine phosphatase receptor type D; KChIP1-Kv4.3, Kv channel interacting protein 1-K$^+$ (Potassium) voltage-gated channel, subfamily 4, member 3; IκB, inhibitor of nuclear factor kappa B; IKKε, IκB kinase ε; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; IL, interleukin. IFNIs and the activation and inhibition of STING exert both antinociceptive (blue arrows) and pronociceptive (red arrows) effects, modulating nociceptive response signaling. Fig. 1 was created by PowerPoint 2019 (Microsoft Corporation, Redmond, WA, USA.)

rons, and glial cells in the spinal cord [26]. This ubiquitous distribution highlights its critical role in integrating innate and adaptive immune responses across tissues. In humans, *IFN-I* genes are located on chromosome 9, and in mice, they are located on chromosome 4 [26].

Upon ligand binding, IFNAR1 associates with tyrosine kinase (TYK)2, and IFNAR2 interacts with janus kinase (JAK)1, triggering receptor subunit rearrangement and dimerization. This conformational change activates receptor-associated JAKs, leading to the phosphorylation of tyrosine residues on IFNAR, which serve as docking sites for signal transducer and activator of transcription (STAT) proteins. Activated JAKs phosphorylate STAT1 and STAT2, initiating the JAK-STAT signaling cascade [27] (Fig. 1). Phosphorylated STAT1 and STAT2 dimerize and recruit IRF9 to form the interferon-stimulated gene factor 3 (ISGF3) complex. This complex translocates to the nucleus and binds interferon-stimulated response elements (ISREs) in the promoters of ISGs, driving their transcription. ISGs encode proteins with antiviral, immunomodulatory, and apoptotic functions that are essential for effective host defense. In parallel, phosphorylated STAT1 homodimers bind gamma-activated sequence (GAS) elements in ISG promoters, providing an additional layer of regulation. The ISGF3 complex and STAT1 homodimers act synergistically to amplify ISG expression, ensuring a robust and tailored response to type I IFN signaling. This dual mechanism allows fine-tuning of gene expression depending on the cellular context and external stimuli. Notably, some ISGs further enhance IFN signaling, establishing positive feedback loops that amplify the antiviral response [28]. These ISGs inhibit viral replication in infected cells and provide protection to adjacent uninfected cells [29]. ISG15, viperin, ribonuclease L (RNase L), myxovirus resistance (Mx), and 2′-5′-oligoadenylate synthetase (OAS) are key antiviral ISGs. Many of the biological effects of IFN-I are mediated by the JAK-STAT signaling cascade. Studies [27,28] have shown that IFN-Is can regulate hundreds to thousands of genes via this canonical pathway (Fig. 1). In addition to the JAK-STAT pathway, IFNAR1/2 activation also engages noncanonical signaling cascades, such as the phosphoinositide 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK) pathways, expanding the biological effects of IFN-Is [6] (Fig. 1).

Regulatory mechanisms involve suppressor of cytokine signaling (SOCS) proteins, such as SOCS1 and SOCS3. SOCS1 dampens IFN-I responses by directly inhibiting JAK2 and STAT1α signaling, preventing prolonged or excessive activation [30]. Although SOCS3 is a less potent inhibitor of IFN-I signaling, it can suppress other pathways, including the STAT3 signaling pathway, thereby modulating immune cell differentiation and cytokine responses [7].

IFN-Is have been successfully used to treat various viral infections, including hepatitis B and C, as well as autoimmune diseases such as multiple sclerosis (MS), where they reduce inflammation and disease activity [31]. In cancer therapy, IFN-Is enhance cytotoxic T lymphocyte and natural killer cell activation, promote tumor cell apoptosis, and inhibit angiogenesis, with evidence demonstrating improved disease-free survival in melanoma patients [32]. In addition to these therapeutic effects, IFN-Is modulate immune responses by inducing anti-inflammatory cytokines such as interleukin-10 (IL-10) [19] and programmed cell death-ligand 1 (PD-L1) [33] while simultaneously suppressing proinflammatory mediators such as matrix metalloproteinase-9 (MMP-9) and tumor necrosis factor-α (TNF-α) [34]. However, these therapies are associated with significant adverse effects, collectively termed “type I interferonopathies”. These include neurological and neuropsychiatric issues such as depression, cognitive disturbances, and neuroinflammation, as well as systemic autoimmune diseases such as systemic lupus erythematosus and systemic sclerosis, which are often linked to prolonged IFN-I activity [35]. While IFN-Is offer significant therapeutic benefits, their pleiotropic effects necessitate careful management to minimize these adverse outcomes.

3. The Role of IFN-Is in Neuroinflammation and Pain

IFN-Is, particularly IFN-β, play a vital role in maintaining CNS homeostasis and modulating neuroinflammatory processes. IFN-β exerts neuroprotective effects by promoting the secretion of nerve growth factor (NGF), enhancing neuronal survival, and supporting neurite outgrowth and branching. A deficiency in IFN-β has been linked to neurodegeneration, as observed in Parkinson’s disease models [36,37]. In the context of neuroinflammation, IFN-Is regulate interactions between glial cells and neurons. Microglia and astrocytes, the principal glial cell types in the CNS, respond to IFN-Is by modulating their activation states. IFN-β suppresses proinflammatory cytokines such as IL-17 while promoting anti-inflammatory mediators such as IL-10, thereby reducing glial-induced neurotoxicity. IFN-Is also regulate the expression of chemokines, such as C-C Motif Chemokine Ligand 2 (CCL2) and C-X-C Motif Chemokine Ligand 10 (CXCL10), to recruit peripheral immune cells, including NK cells and T cells, into the CNS. Importantly, IFN-Is primarily recruit NK cells from the periphery rather than increasing their absolute number within the CNS. This recruitment aids in clearing damaged cells and modulating neuroinflammatory cascades [38]. Pathogen sensing and IFN-I production in the CNS rely on resident cells, including neurons, microglia, and astrocytes, as plasmacytoid dendritic cells (pDCs), the primary IFN-I producers, are absent in the brain parenchyma [20,22,39,40]. These glial cells produce IFN-Is in response to pathogenic stimuli or damage-associated molecular patterns (DAMPs) via pattern recognition receptors (PRRs). The resulting IFN-I signaling amplifies neuroprotective pathways and limits excessive inflammation, stabilizing the inflammatory environment and preventing neurodegeneration [40].

Neuroinflammation, a hallmark of various CNS disorders such as strokes, injuries, neurodegenerative diseases, and chronic pain syndromes, is characterized by blood-brain barrier (BBB) disruption, immune cell infiltration, and the activation of glial cells. Activated microglia and astrocytes release proinflammatory mediators, including cytokines, chemokines, and matrix metalloproteinases (e.g., MMP-9), which exacerbate inflammation and tissue damage [41–47]. IFN-Is play dual roles in these pathological processes. They stabilize the BBB by modulating endothelial cell function and reducing inflammatory mediator-induced permeability. Additionally, they attenuate the proinflammatory responses of glial cells while promoting anti-inflammatory pathways, fostering a neuroprotective environment. By orchestrating the expression of chemokines such as CCL5 and CXCL10, IFN-Is regulate immune cell trafficking and activation, facilitating the resolution of neuroinflammation and tissue repair. These multifaceted actions highlight the pivotal role of IFN-Is in balancing protective and pathological responses during neuroinflammatory events.

Extensive preclinical research highlights the pivotal role of neuroinflammation, which is characterized by glial activation and the release of proinflammatory mediators, in the development and maintenance of the chronic nociceptive response [48–50]. This neuroinflammatory response is also evident in clinical chronic nociceptive response conditions, supporting the findings from preclinical studies. IFN-α has shown notable antinociceptive effects within the CNS, partly through interactions with opioid receptors (Table 1, Ref. [8,9,51–67]). Early investigations, such as those by Blalock and Smith in 1981, indicated that human leukocyte interferons (but not fibroblast interferons) could bind to opioid receptors [51,68]. Later study reported that IFN-α elicits an analgesic effect by activating mu-opioid receptors, but not delta or kappa receptors, in the nucleus submedius [69]. Additionally, IFN-α exhibits pharmacological properties similar to those of the opioid peptide β-endorphin, contributing to its antinociceptive actions [52]. IFN-α was further demonstrated to compete with naloxone at membrane binding sites [68]. However, the direct binding of IFN-α to opioid receptors requires further validation.

We reported in 2012 that high-dose intrathecal injections of short interfering RNAs (siRNAs) (10 or 20 µg) produced IFN-α-mediated analgesia in a rat model of persistent inflammatory nociceptive response [9] (Table 1). This unexpected finding, which used nontargeting siRNAs as controls without specific gene targets, marked the first evidence that nontargeting dsRNAs could elicit analgesic effects in the spinal cord, emphasizing the need for caution in designing siRNAs for target validation in nociceptive response research. Mammalian cells can be stimulated to produce IFN-I reactions by short dsRNAs and short hairpin RNAs [70]. Our study revealed that high-dose administration of short dsRNAs ($<$21 bp) significantly upregulated IFN-α in the spinal cord [9]. The analgesic effects of the nontargeting siRNAs were abolished by the intrathecal administration of an IFN-α neutralizing antibody, underscoring the essential role of IFN-α in mediating these effects. Moreover, the intrathecal administration of IFN-α significantly increased the paw withdrawal latency in both naïve and inflamed rats, further demonstrating its antinociceptive properties [9].

In the rat spinal cord, IFN-α is expressed by reactive astrocytes, as indicated by its colocalization with glial fibrillary acidic protein (GFAP). It is found within vesicle-like structures in astrocytic processes, suggesting a vesicle-mediated release mechanism [9,53]. The administration of IFN-α to spinal cord slices rapidly inhibits excitatory synaptic transmission, as evidenced by a decrease in the frequency of spontaneous excitatory postsynaptic currents (sEPSCs) in somatostatin-expressing excitatory interneurons of outer lamina II (IIo) [53]. Additionally, IFN-α inhibits capsaicin-induced internalization of the neurokinin-1 (NK-1) receptor and ERK phosphorylation in superficial dorsal horn neurons via IFNAR signaling, effectively blocking capsaicin-induced central sensitization [53]. The IFN-α/β receptor was found on spinal cord axonal terminals coexpressing calcitonin gene-related peptide (CGRP), indicating its presynaptic neuronal localization, although its expression in other cell types cannot be excluded [53] (Table 1). Moreover, direct administration of IFN-α modulated nociceptive synaptic transmission, as demonstrated by *ex vivo* electrophysiology in spinal cord slices [40].

In vivo, intrathecal administration of a neutralizing antibody to endogenous IFN-α or IFN-β caused hyperalgesia in naïve mice [8,9,71], whereas TLR3 activation by poly (I:C) promoted the release of IFN-β in primary cultures of microglia and astrocytes [56]. Compared with wild-type mice, Ifnar1-null mice presented increased excitatory postsynaptic currents (EPSCs). RNA sequencing of single cells (scRNA-seq) revealed widespread expression of Ifnar1 and Ifnar2 in myelinated, peptidergic, and nonpeptidergic neurons of the mouse dorsal root ganglia (DRG). Similar expression patterns have been observed in the trigeminal neurons of both mice and humans [72]. Interestingly, IFNAR1 and IFNAR2 expression was detected in human trigeminal neurons via scRNA-seq [73]. These findings collectively highlight a cellular framework in which IFN-α and IFNAR expression in glial cells and neurons facilitates neuro-glial interactions that modulate nociception. Under naïve and inflamed conditions, intrathecal IFN-α administration increased nociceptive response thresholds, whereas neutralizing endogenous IFN-α led to hyperalgesia, underscoring the role of IFN-α in modulating nociceptive transmission in the nociceptive response circuitry of the spinal cord [40].

In a murine arthritis model, the intrathecal administration of IFN-β provided transient nociceptive response relief, which was significantly prolonged to several weeks when IFN-β was combined with an anti-TNF-α antibody. The prolonged relief provided by IFN-β is likely mediated by its upregulation of IL-10 expression in the spinal cord [56] (Table 1). Similarly, Song and colleagues reported that the intrathecal administration of IFN-β significantly attenuated nerve injury-induced mechanical allodynia in mice for several days without affecting motor activity [57]. These sustained analgesic effects are attributed primarily to the inhibition of MAPK activation, a key pathway in nociceptive response pathogenesis [47], and the induction of ISG15 secretion following spared nerve injury [57]. The activation of ISG15 further inhibits MAPK signaling, specifically through phosphorylated extracellular signal-regulated kinase (pERK), phosphorylated c-Jun N-terminal kinase (pJNK), and pP38, by targeting regulators such as ERK1, leading to their degradation via ISGylation—a process in which ISG15 conjugates with cellular substrate proteins. Notably, ISG15 is localized mainly within neurons and astrocytes, with some presence in microglia in the dorsal horn's superficial layers [57]. These findings emphasize the immunomodulatory potential of IFN-β, ISG15, and

Table 1. Effects of IFN-α, IFN-β, and STING on pain and its underlying mechanisms.

Agent	Actions	IFN doses, STING treatment agent	Routes	Species	Conditions	Mechanisms	References
IFN-α	Antinociception	500 U	Intracerebral	Mouse	Naïve	Opioid receptor dependent	Blalock *et al*., 1980 [51]
		4, 8, 16 pmole	Intracranial ventricle	Rat	Naïve	Mu-opioid receptor dependent	Jiang *et al*., 2000 [52]
		100 ng	Intrathecal	Rat	Naïve, CFA	Opioid receptor dependent	Tan *et al*., 2012 [9]
		100 ng	Intrathecal	Rat	Naïve, CFA	Inhibits EPSC and capsaicin-induced p-ERK	Liu *et al*., 2016 [53]
		100 U	Intrathecal	Mouse	Naïve	IFNAR-mediated actions; inhibition of $\mathrm{Na_V}$1.7 and calcium channel activities	Donnelly *et al*., 2021 [8]
	Hyperalgesia	300 U	Intraplantar	Mouse	Naïve	Activation of MAPK and MNK-elF4e translation	Barragán-Iglesias *et al*., 2020 [55]
IFN-β	Antinociception	100 ng	Intrathecal	Mouse	LPS	IFNAR1-mediated and TLR-mediated actions	Stokes *et al*., 2013 [56]
		3600 U	Intrathecal, coinjection with TNF antibody	Mouse	Arthritis	Induction of IL-10 expression	Woller *et al*., 2019 [57]
		1000, 5000, 10,000 U	Intrathecal	Mouse	Spared nerve injury (SNI)	Induction of ISG-15 and inhibition of MAPK	Liu *et al*., 2020 [54]
		100 U	Intrathecal	Mouse	Naïve	IFNAR-mediated actions; inhibition of $\mathrm{Na_V}$1.7 and calcium channel activities	Donnelly *et al*., 2021 [8]
	Hyperalgesia	300 U	Intraplantar	Mouse	Naïve	Activation of MAPK and MNK-elF4e translation	Barragán-Iglesias *et al*., 2020 [55]
STING	Antinociception	STING agonist (ADU-S100)	Intrathecal (Spinal cord)	Mouse	SNI, CCI	Microglia STING-IFN-I activation	Silveira Prudente *et al*., 2024 [58]
		STING agonist (ADU-S100)	Intrathecal (DRG)	Mouse	Inflammatory pain	KChIP1-Kv4.3 regulation	Defaye *et al*., 2024 [59]
		STING agonist (ADU-S100)	Intrathecal (DRG)	Rat	Incision pain	Activation of the STING-IFN-I pathway	Ma *et al*., 2023 [60]
		STING agonists (DMXAA, ADU-S100)	Intrathecal (Spinal cord, DRG)	Mouse, Macaca mulatta	CIPN, CCI	Activation of the STING-IFN-I pathway	Donnelly *et al*., 2021 [8]
		STING agonists (DMXAA, ADU-S100)	Intrathecal (Spinal cord, DRG)	Mouse	Bone cancer pain	Activation of the STING-IFN-I pathway	Wang *et al*., 2021 [61]
		PTPRD inhibitor (7-BIA)	DRG injection	Mouse	CCI	Upregulation of STING and IFN-α	Sun *et al*. 2022 [62]
		Electroacupuncture (EA)	Bilateral ST36 (Zusanli) and SP6 (Sanyinjiao) acupoints	Rat	Acute postoperative pain (APP)	STING/IFN-1 pathway activation, mitigation of neuroinflammatory response	Ding *et al*., 2023 [63]
	Hyperalgesia	STING antagonist (C-176)	Intrathecal (Spinal cord)	Mouse	SNI	Activation of the STING/NF-κB/IL-6	Sun *et al*., 2022 [64]
		STING antagonist (C-176)	Spinal dorsal nerve (Spinal cord)	Rat	SNI, CCI	Suppression of the microglial M1-polarization	Wu *et al*., 2022 [65]
		Dexmedetomidine, ketamine	Intraperitoneal (Spinal cord)	Rat	Spinal nerve ligation	Inhibition of the STING/TBK1 pathway to increase ER-phagy	Liu *et al*., 2022 [66]
		STING antagonist (C-176)	Intrathecal (DRG)	Rat	Bone cancer pain	Activation of the STING-TBK1-NF-κB pathway	Zhang *et al*., 2023 [67]

IFN, Interferon; SNI, Spared nerve injury; CCI, Chronic constriction injury; CIPN, chemotherapy-induced peripheral neuropathy; DRG, dorsal root ganglion; RTPRD, Protein tyrosine phosphatase receptor type D; elF4e, eukaryotic initiation factor 4E; CFA, complete freund's adjuvant; EPSC, excitatory postsynaptic current; ERK, extracellular signal-regulated kinase; IFNAR, interferon-α receptor; TLR, toll-like receptor; LPS, lipopolysaccharide; IL-10, interleukin-10; ISG-15, interferon-stimulated gene-15; MAPK, mitogen-activated protein kinase; ADU, aducanumab; KChIP1-Kv4.3, Kv channel interacting protein 1-K^+ (Potassium) voltage-gated channel, subfamily 4, member 3; DMXAA, 5,6-dimethylxanthenone-4-acetic acid; 7-BIA, 7-butoxy-3-hydroxy-6-methoxy-1-oxo-3,4-dihydro-1H-2-benzopyran-5-carbaldehyde; EA, electroacupuncture; APP, acute postoperative pain; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cell; $\mathrm{Na_V}$1.7, sodium voltage-gated channel alpha subunit 7; MNK, MAPK-interacting serine/threonine-protein kinase; eIF4E, eukaryotic translation initiation factor 4E.

MAPK signaling in the treatment of the neuropathic nociceptive response, with intrathecal IFN-β effectively attenuating the arthritic nociceptive response.

Emerging evidence suggests that TLRs modulate the nociceptive response by regulating IFN-Is. TLR3, which detects dsRNA and activates IFN-I responses through TRIF signaling, plays a role in managing nociceptive and itch responses and is expressed primarily in immune and glial cells [13,70,74]. Interestingly, in addition to being expressed by immune and glial cells, TLR3 is also expressed in nociceptive sensory neurons, where it influences nociceptive synaptic transmission within the spinal cord [11,75,76]. However, whether TLR3 contributes to the antinociceptive effects of double-stranded RNAs remains unexplored. Von Frey testing has shown that intrathecal IFN-α (100 and 300 U) increases paw withdrawal thresholds in naïve mice, suggesting its potential analgesic effect [8]. Similarly, Stokes and colleagues demonstrated that intrathecal IFN-β (100 ng) relieves tactile allodynia induced by TLR2 and TLR4 ligands [55]. Compared with the TLR4 ligand LPS, intrathecal administration of the TLR3 ligand poly(I:C) induced prolonged allodynia in Ifnar1 knockout mice, suggesting that the rapid resolution of allodynia is dependent on IFN-I signaling [55] (Table 1).

Pronociceptive Effects Induced by IFN-Is

Recent reports indicate that IFN-Is can exert pronociceptive effects [66–68] (Table 1). Intraplantar injection of IFN-α or IFN-β (300 U in 25 µL) induced persistent mechanical hypersensitivity in mice lasting several days, as reported by Barragán-Iglesias *et al.* [55]. This prolonged hyperalgesia was attributed to IFN-I-induced MAPK activation and MAPK-interacting serine/threonine-protein kinase (MNK)-eukaryotic translation initiation factor 4E (eIF4E)-mediated translation in DRG neurons (Table 1). Patch-clamp electrophysiology further demonstrated that exposure of DRG neurons to IFN-α (300 U/mL) increased neuronal excitability [66]. While the role of IFNARs in these pronociceptive effects remains unclear, high-dose intraplantar IFN-α-induced mechanical hypersensitivity was shown to be blocked by intrathecal IFN-α, suggesting that differential effects depend on peripheral versus central administration [8]. IFNAR1 and IFNAR2 are highly expressed in vagal sensory neurons, including 70% of transient receptor potential vanilloid 1 (TRPV1)-positive neurons, which are likely nociceptors [77]. Calcium imaging revealed that high concentrations of IFN-α and IFN-β (1000 and 10,000 U/mL) acutely activate bronchopulmonary vagal nociceptors. Additionally, in mice treated with IFN-α for 8 d (8000 IU/g/d), formalin-induced nociceptive behavior was intensified; this dose was much greater than those producing analgesic effects [78]. Notably, peripheral IFN-β cannot easily cross the CNS directly [79], indicating that its pronociceptive effects may stem from local, peripheral actions. It is possible that the effects of IFN-α and IFN-β differ at central versus peripheral nociceptor terminals or that different doses yield opposite effects, with lower doses producing analgesia and higher doses causing nociceptive response sensitization. The antinociceptive effects of IFN-Is may also involve TYK2, as intrathecal TYK2 inhibition blocks STING agonist-induced analgesia and can induce hyperalgesia in naïve mice [8]. Distinct downstream signaling—TYK2 in antinociceptive pathways versus PI3K/MAPK in pronociceptive pathways—may account for differences in neuronal excitability, as PI3K/MAPK activation is known to sensitize nociceptors [80,81].

4. Therapeutic Potential of the STING-TBK1 IFN-I Pathway

Similar to host immunity, the nociceptive system serves as an alert mechanism to detect and respond to “danger signals”. Pathogens can exploit these signals to disrupt sensory responses such as smell and taste. Nociceptors recognize pathogen- and damage-associated molecular patterns (PAMPs and DAMPs) through PRRs, including TLRs, RIG-I-like receptors (RLRs), NOD-like receptors (NLRs), and cytosolic DNA sensors (CDSs). In DRG neurons, STING acts as a cytosolic DNA sensor, detecting self-DNA, viral DNA, and bacterial CDNs to trigger the production of type I interferons (IFN-α and IFN-β). Upon activation, STING dimerizes and activates TBK1, which phosphorylates IRF3, initiating interferon production (Fig. 1).

This process drives the expression of IFN-Is and other immune response genes, facilitating pathogen clearance and the removal of damaged cells during inflammation. By binding to the IFN-α/β receptor on nearby cells, IFN-Is stimulate a broad range of ISGs, providing cellular protection. Initially recognized for their antiviral properties, IFNs are now widely used for treating diseases such as hepatitis, multiple sclerosis, and melanoma.

STING has recently emerged as a key regulator of nociception. STING-deficient mice exhibit mechanical allodynia, while in neuropathic nociceptive response models, STING agonists have antinociceptive effects. IFN-Is have been shown to suppress nociceptor excitability in mice, monkeys, and humans [82]. In naïve, neuropathic, and cancer nociceptive response models, the intrathecal administration of STING agonists results in sustained antinociception lasting 24–48 hours without motor impairment [8,58] (Table 1). This effect is correlated with elevated IFN-α and IFN-β levels in DRG and spinal cord tissues and is absent in IFNAR1 knockout mice. Similarly, STING knockout mice or those with nociceptor-specific STING deletion exhibit nociceptive response sensitivity and neuronal hyperexcitability, similar to Ifnar1 knockout mice. STING messenger RNA (mRNA) is expressed in DRG nociceptors and spinal cord microglia, indicating that both neurons and glia contribute to IFN-I production [8]. In addition to providing acute relief of nociceptive responses through direct neuronal modulation, STING agonists have sustained analgesic effects on cancer-related pain by reducing the tumor burden and protecting against bone destruction via the modulation of osteoclast and immune cell functions [61] (Table 1). These effects are mediated by STING and IFN-I signaling within the host, suggesting a multifaceted approach to managing bone cancer pain by targeting nociceptors, immune cells, and osteoclasts. Wang *et al.* (2021) [61] demonstrated that repeated systemic administration of STING agonists alleviates bone cancer-induced pain and reduces local tumor burden and bone degradation, emphasizing the therapeutic potential of this pathway. However, contrasting findings by Zhang *et al.* (2023) [67] suggest a dual role for STING in bone cancer pain (Table 1). Their study revealed that the selective inhibition of STING with C-176, administered intrathecally or intraperitoneally, reduced hyperalgesia in a rat model of bone cancer pain. STING activation in this model was associated with elevated levels of the proinflammatory cytokines IL-1β, IL-6, and TNF-α in the DRG via the STING/TBK1/IKK/NF-κB signaling pathway (Fig. 1). STING signaling plays a dual role in cancer pain modulation, influencing both peripheral and central mechanisms. In peripheral tissues, STING activation can drive cytokine release, leading to nociceptor sensitization, as observed by Zhang *et al.* (2023) [67]. In contrast, central effects involve immune cell modulation, such as M1 microglial polarization in the medial prefrontal cortex, which exacerbates central sensitization and chronic pain [83]. These findings suggest that the role of STING in cancer pain is context dependent and influenced by factors such as disease stage and the tumor microenvironment. Understanding these nuances is critical for developing targeted therapies, as evidenced by studies showing both beneficial and deleterious effects of STING pathway modulation [58,59,83].

Defaye *et al.* [59] investigated the transcriptional changes in sensitized nociceptive neurons to identify genes involved in nociceptor plasticity during inflammation-induced sensitization and its resolution (Table 1). Their study revealed that the activation of STING in nociceptors plays a crucial role in resolving the inflammatory nociceptive response. Inflammation upregulated STING expression in DRG nociceptors, where its activation initiated TBK1-mediated signaling, leading to the production of IFN-I, predominantly IFN-β (Fig. 1), which facilitated nociceptive response resolution. Mice with a nociceptor-specific gain-of-function STING mutation presented reduced nociceptor excitability and inflammatory hyperalgesia. These effects were mediated by the upregulation of ISGs such as Kv channel interacting protein 1 (KChIP1) and the downregulation of TRPV1, an ion channel associated with thermal hyperalgesia. STING-mediated IFN-I production also modulated nociceptor properties by regulating potassium channels (K^+ (Potassium) voltage-gated channel, subfamily 4 (Kv4) via KChIP1) (Fig. 1), thereby increasing the activation threshold and reducing excitability. Notably, blocking the IFN-α/β receptor reversed these effects, confirming the pivotal role of neuronal IFN-α/β receptor signaling in mediating STING-induced antinociceptive responses. These findings establish STING as a marker of nociceptor sensitization and highlight the importance of the STING/IFN-I pathway in modulating ion channels to alleviate the inflammatory nociceptive response.

The neuropathic nociceptive response is a challenging condition to manage with currently available analgesics. Spinal microglia are central to the development and persistence of this response, largely through PRR signaling and the release of proinflammatory cytokines [49]. Silveira Prudente *et al.* [58] investigated the role of the STING pathway in spinal microglia and its modulation of the neuropathic nociceptive response, revealing significant sex-specific effects (Table 1). STING, which is expressed predominantly in spinal microglia, was upregulated following peripheral nerve injury. However, microglial STING expression was not required for the development of nerve injury-induced mechanical allodynia. Activation of STING with agonists such as 2′3′-c-di-AM (PS)2 (Rp,Rp) (ADU-S100) alleviated the neuropathic nociceptive response in male mice by reducing mechanical and cold allodynia as well as pinprick hyperalgesia. This analgesic effect was absent in female mice, likely due to increased production of proinflammatory cytokines in females, which counteracted the beneficial effects. In male mice, STING agonists reduced the neuropathic nociceptive response through the activation of TBK1 and IFN-β signaling. Blocking either TBK1 or IFN-β abolished the analgesic effects of STING activation. Notably, this study employed the STING-specific antagonist C-176, which was previously validated by Sun *et al.* [64] and Wu *et al.* [65] and significantly reversed mechanical allodynia ten days after spared nerve injury (SNI). Analgesia in male mice was attributed to reduced inflammation and increased IFN-β levels. In contrast, female mice presented elevated levels of proinflammatory cytokines such as IL-1β and TNF-α, negating the analgesic effects. This study is the first to demonstrate sex-specific differences in the alleviation of the neuropathic nociceptive response through STING activation, suggesting that targeting STING in spinal microglia could represent a promising therapeutic strategy for the neuropathic nociceptive response, particularly in males.

In the leukocyte common antigen-related receptor family, protein tyrosine phosphatase receptor type D (PTPRD) is located on human chromosome 9. It consists of extracellular immunoglobulin and fibronectin domains and plays an important role in adhesion and synaptic differentiation [84]. Inhibiting PTPRD activity reduces cocaine addiction [85], which suggests that PTPRD might be a potential therapeutic target for addiction disorders. Furthermore, chronic constriction injury (CCI) significantly increases PTPRD expression in the DRGs of rats [86,87].

Given its role in addiction treatment, findings by Sun *et al.* [62] suggest that targeting PTPRD may offer a safe, low-addiction-risk analgesic approach for managing the neuropathic nociceptive response. The CCI-induced neuropathic nociceptive response was alleviated through PTPRD knockdown and PTPRD inhibitor 7-butoxy-3-hydroxy-6-methoxy-1-oxoisochromane-5-carbaldehyde (7-BIA) treatment. Additionally, H-151, a STING inhibitor, reversed the analgesic effects of PTPRD knockdown (Table 1). Overall, the study by Sun *et al.* [62] indicated that elevated PTPRD levels in the DRG following CCI may contribute to the development of a neuropathic nociceptive response through the STING-IFN-I pathway (Fig. 1).

Electroacupuncture (EA) stimulation at 2/15 Hz has been shown to alleviate the postlaparotomy nociceptive response in rats [88], although the underlying mechanisms remain unclear. Ding *et al.* (2023) [63] investigated the analgesic effects of EA on the acute postoperative nociceptive response (APP) in rats, focusing on the role of the STING and IFN-1 signaling pathway (Table 1) (Fig. 1). APP was induced through abdominal surgery, and EA was applied at acupoints ST36 and SP6. This study revealed that APP caused mechanical and thermal hypersensitivities, reduced EEG rhythmic power, and increased neuroinflammation in the DRG and spinal dorsal horn. EA significantly mitigated these hypersensitivities, restored electroencephalography (EEG) rhythmic power, and reduced neuroinflammation. APP suppressed the STING/IFN-1 pathway, dampening anti-inflammatory signaling in the DRG and spinal cord dorsal horn (SDH), whereas EA reversed this suppression, activating the pathway and enhancing anti-inflammatory responses. Intrathecal administration of the STING inhibitor C-176 abolished the analgesic and anti-inflammatory effects of EA, confirming the pivotal role of this pathway in EA-mediated analgesia. The STING/IFN-1 pathway is expressed predominantly in C-type nociceptive DRG neurons (CGRP+ and IB4+), which are involved in mechanical and thermal nociceptive response detection. EA also shifted astrocytes and microglia toward an anti-inflammatory profile, further contributing to its analgesic effects. These findings highlight the STING/IFN-1 pathway as a promising therapeutic target and support the potential clinical application of EA as a nonpharmacological treatment for APP. Similarly, in an incision nociceptive response model, Ma *et al.* [60] demonstrated that activating the STING-IFN-I pathway alleviated the acute postoperative nociceptive response by inhibiting the activation of satellite glial cells and macrophages, thereby reducing neuroinflammation in the DRG. This pathway activation also downregulated the expression of IL-6, TNF-α, IL-1β, P-P65 and inducible nitric oxide synthase (iNOS) (Table 1).

Pronociceptive Effects Induced by STING Activation

Peripheral nerve injury in the neuropathic nociceptive response triggers M1 polarization of spinal microglia, contributing to neuronal hyperexcitability and central sensitization [49]. Suppressing M1 polarization has been shown to alleviate the neuropathic nociceptive response. In a mouse model of middle cerebral artery occlusion, cGAS knockdown shifted microglial polarization toward the M2 phenotype, suggesting that the cGAS-STING signaling cascade may modulate microglial polarization [89]. Wu *et al.* [65] demonstrated that spared nerve injury (SNI) promoted M1 polarization and activated the cGAS-STING signaling cascade in spinal microglia and neurons, as confirmed by double-label immunofluorescence (Table 1) (Fig. 1). *In vitro*, LPS-induced M1 polarization in BV-2 microglia activated the cGAS-STING signaling cascade, which was suppressed by cGAS-STING antagonists. *In vivo*, cGAS and STING antagonists reduced microglial M1 polarization and improved SNI-induced mechanical allodynia.

The cGAS-STING signaling pathway also plays a role in pain regulation in neurons, macrophages, and T cells, which is mediated by regulating the excitability of nociceptive neurons and neuroinflammatory responses. Recent studies [61,67,83] have provided compelling evidence that cGAS-STING signaling in nociceptive neurons has dual roles, contributing to both pronociceptive and antinociceptive processes. The activation of STING in sensory neurons has been shown to regulate nociceptor excitability via the modulation of ion channels, including $Na_V 1.7$, and to suppress synaptic transmission in spinal nociceptive circuits, as demonstrated by Donnelly *et al.* [8]. Zhang *et al.* [83] reported the activation of the downstream inflammatory pathway of STING in DRG neurons in a cancer-induced bone pain model, which was alleviated by administering a STING inhibitor during the middle to late stages of bone cancer. These findings highlight its biphasic function in pain modulation, suggesting potential therapeutic implications depending on the context of activation. Additionally, macrophages and T cells are central to neuroinflammatory processes, with the cGAS-STING pathway playing a critical role in their polarization and recruitment. For example, this pathway drives M1 macrophage polarization, exacerbating inflammation and pain, while also regulating T-cell differentiation, including proinflammatory Th1 and Th9 responses and anti-inflammatory Tregs [90,91]. These immune cell interactions emphasize the complexity of pain modulation by cGAS-STING signaling in different phases of pain progression. Emerging evidence also implicates astrocytes as significant contributors, with studies showing STING expression and activity in these glial cells. Astrocytic STING activation has been associated with inflammation in pathological states, and recent data suggest that STING agonists may attenuate astrogliosis and reduce pain signaling, although further investigation is needed to fully delineate these mechanisms [92,93]. Together, these findings underscore the multifaceted and cell type-specific roles of the cGAS-STING pathway in pain regulation.

The STING/TBK1 pathway plays a critical role in ER stress, where STING acts as an ER adaptor necessary under elevated ER stress conditions [94]. In a study by Liu *et al.* [66], dexmedetomidine and ketamine were shown to have analgesic and antianxiety effects in SNL rats, where the STING/TBK1 signaling pathway was found to be activated (Table 1) (Fig. 1). Dexmedetomidine and ketamine both appear to enhance ER-phagy by inhibiting the STING signaling cascade, thus reducing ER stress in spinal nerve ligation (SNL) rats. This antinociceptive mechanism differs from previous findings suggesting that STING/TBK1 signaling is a direct mechanism for nociceptive response relief. Variations in dosing and timing may impact STING modulation outcomes. Unlike Donnelly *et al.*'s study [8], which primarily collected behavioral data within hours post-injection, Liu's study [66] assessed nociceptive and anxiety-related behaviors over days and weeks following surgery.

STING is activated by endogenous and exogenous dsDNA, initiating immune and inflammatory responses [95]. Nerve injury induces the release of DNA from dying, dead, or injured cells into the extracellular environment through necrosis or apoptosis. Typically, this self-DNA is nonimmunogenic. However, emerging evidence indicates that extracellular self-dsDNA can enter the cytosol via Fc receptors. Additionally, the antimicrobial peptide LL37 facilitates the transfer of extracellular self-dsDNA into monocytes. Other cytoplasmic DNA receptors in macrophages may also contribute to DNA detection. mtDNA represents another significant source of cytosolic DNA for STING activation. Mechanisms for mtDNA release include B-cell lymphoma 2 (BCL-2)-like protein 4 (BAX)- and BCL-2 homologous killer (BAK)-mediated apoptosis, mitochondrial permeability transition pore (mPTP) activation, and deficiencies in transcription factor A mitochondrial (TFAM) or aberrant mtDNA packaging. These processes collectively contribute to increased cytosolic dsDNA levels in SNI models and underscore the role of the cGAS-STING pathway in driving inflammatory and nociceptive responses [64]. Sun *et al.* (2022) [64] reported that SNI significantly elevates dsDNA levels, activating the STING/TBK1/NF-κB pathway and promoting the release of proinflammatory cytokines such as IL-6 in both *in vivo* and *in vitro* models (Table 1) (Fig. 1). STING signaling peaks during the early post-SNI period (Days 3–7) in microglia, where it plays a pivotal role in initiating nociceptive response hypersensitivity, although its contribution to the later stages of the chronic nociceptive response appears limited. This study highlights that the effects of STING on the neuropathic nociceptive response are mediated by IL-6, which activates the JAK2/STAT3 pathway, further amplifying microglial activation and nociceptive response hypersensitivity. Administration of the STING inhibitor C-176 effectively reduces early microglial activation, dampens proinflammatory responses, and alleviates nociceptive response hypersensitivity. However, these effects are reversed when IL-6 is coadministered, underscoring the critical role of IL-6 in STING-mediated pathways. Experiments using microglia-like BV-2 cells further demonstrated that STING activation enhances NF-κB and STAT3 signaling, leading to increased cytokine production. Despite its contributions, the study has limitations, including the exclusive use of male mice, reliance on BV-2 cells instead of primary microglia, and the absence of STING knockout models to confirm its specificity. Additionally, comparisons of the roles of STING in the early versus late nociceptive response stages with the existing literature on other nociceptive response pathways remain underexplored. However, these findings advance the understanding of STING-mediated neuroinflammation in the nociceptive response in neuropathy and provide a strong basis for the development of early-stage therapeutic interventions.

There are ongoing clinical trials investigating STING agonists, which activate the production of IFN-I, primarily in the context of cancer immunotherapy. These trials aim to harness the ability of the STING pathway to stimulate innate immunity and enhance antitumor responses [96]. For example, several phase I and phase II trials are evaluating the safety and efficacy of STING agonists in patients with various cancers. These studies are exploring the use of STING agonists alone or in combination with other treatments, such as immune checkpoint inhibitors, to enhance antitumor immunity [96]. While these trials focus primarily on oncology, the role of the cGAS-STING pathway in the production of IFN-Is suggests potential therapeutic applications beyond cancer, including in the treatment of conditions involving immune dysregulation. However, clinical trials specifically targeting the STING-IFN-I pathway for pain management are currently lacking, and their analgesic effects could be assessed as secondary endpoints, particularly in cancer-related pain conditions. This highlights a gap in translational research that could explore the analgesic potential of this pathway, given its demonstrated effects on nociception in preclinical studies [4]. Importantly, therapeutic modulation of the STING pathway must be approached with caution, as inappropriate activation can lead to excessive IFN-I responses and associated immunopathology [97]. STING agonists are being actively investigated in clinical trials for cancer treatment, and their application in pain management remains an area for future exploration.

5. Concluding Remarks and Future Perspectives

IFNs are well-known cytokines involved in antiviral defense, with emerging evidence highlighting IFN-I regulation by the STING signaling cascade, which influences nociceptive response modulation and is active in the DRG under normal conditions. The role of IFN-Is in the nociceptive response remains controversial, as studies have reported both pronociceptive [58] and antinociceptive

[8,9,51–57,71] actions of IFN-α and IFN-β, which vary by dose, location, and physiological or pathological context (see Table 1).

In the CNS, IFN-Is generally exhibit antinociceptive effects. The cGAS-STING signaling cascade, a primary driver of IFN-I production in immune cells following infection or injury, has been shown to mediate analgesic outcomes. Donnelly *et al*. (2021) [8] demonstrated that STING activation confers significant nociceptive response relief, independent of opioid pathways, across models of chemotherapy-induced nociceptive responses, nerve injuries, and bone cancer nociceptive responses. These findings suggest the potential of STING-based therapies in refractory nociceptive response conditions, as evidenced by the small molecule 7-BIA, which reduces the neuropathic nociceptive response through STING activation and subsequent IFN-α production in the DRG [58].

Nevertheless, the influence of the cGAS-STING signaling cascade on the chronic nociceptive response is complex. While some studies link STING activation to proinflammatory cytokine release and worsened neuroinflammation, others highlight the nociceptive response-relieving effects of enhanced IFN-I signaling in sensory neurons. Consecutive and repeated administration of STING agonists likely caused central sensitization and nociception [84]. The STING–IFN-I pathway may have different effects on different parts of the peripheral nervous system (PNS) and CNS. These opposing roles underscore the need for further research to delineate the mechanisms underlying the dual influence of STING on the nociceptive response, including potential interactions with TLRs and the NF-κB/NOD-like receptor protein 3 (NLRP3) axis.

To advance the understanding of the role of the cGAS-STING pathway in pain processing, several critical areas warrant further exploration. While this pathway is activated in various central nervous system diseases [64,98], its specific contributions to pain modulation in distinct brain regions, such as the anterior cingulate cortex and amygdala, remain largely unexplored. These regions are central to pain perception and pain-related mood disorders, underscoring the need for focused research on the cGAS-STING pathway at the brain level. Another key area involves investigating the mechanisms underlying pain-induced aberrant DNA accumulation, which activates the cGAS-STING pathway. Elucidating how these DNA changes contribute to pain phenotypes could reveal novel targets for intervention. Furthermore, the pathway regulating pain through immune cells, particularly astrocytes, macrophages, and T cells, requires detailed investigation, as these cells play pivotal roles in pain modulation. Additionally, understanding the relationship between the cGAS-STING pathway's downstream regulatory mechanisms (e.g., TBK1, STATs, and NF-κB) and pain outcomes across different phases of nociception (acute vs. chronic) is essential. This includes exploring how patient-specific variables, such as age, sex, and genetic background, influence the pathway's effects. Finally, future studies should investigate how the analgesic potential of the cGAS-STING pathway can be harnessed while mitigating its pronociceptive effects. Such research could refine phase-specific, immune cell-targeted therapies for chronic and neuropathic pain, paving the way for more effective and personalized pain management strategies.

Author Contributions

PHT and TCC contributed to the sections of Type 1 interferon, STING, nociceptive response modulation, and conclusions as well as Fig. 1. TCC, KCH and PHF wrote the draft manuscript and Table 1 of this review. YYL and CHY edited the manuscript and Table 1. CCC contributed the conception and design of the article. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

References

[1] Pestka S, Langer JA, Zoon KC, Samuel CE. Interferons and their actions. Annual Review of Biochemistry. 1987; 56: 727–777. https://doi.org/10.1146/annurev.bi.56.070187.003455.

[2] Schoggins JW. Interferon-stimulated genes: what do they all do? Annual Review of Virology. 2019; 6: 567–584. https://doi.org/10.1146/annurev-virology-092818-015756.

[3] Jhuti D, Rawat A, Guo CM, Wilson LA, Mills EJ, Forrest JI. Interferon treatments for SARS-CoV-2: challenges and opportunities. Infectious Diseases and Therapy. 2022; 11: 953–972. https://doi.org/10.1007/s40121-022-00633-9.

[4] Park A, Iwasaki A. Type I and Type III interferons - induction, signaling, evasion, and application to combat COVID-19. Cell Host & Microbe. 2020; 27: 870–878. https://doi.org/10.1016/j.chom.2020.05.008.

[5] Calabrese LH, Lenfant T, Calabrese C. Interferon therapy for COVID-19 and emerging infections: Prospects and concerns. Cleveland Clinic Journal of Medicine. 2020; 1–6. https://doi.org/10.3949/ccjm.87a.ccc066.

[6] Ivashkiv LB, Donlin LT. Regulation of type I interferon re-

sponses. Nature Reviews. Immunology. 2014; 14: 36–49. https://doi.org/10.1038/nri3581.

[7] Seif F, Khoshmirsafa M, Aazami H, Mohsenzadegan M, Sedighi G, Bahar M. The role of JAK-STAT signaling pathway and its regulators in the fate of T helper cells. Cell Communication and Signaling: CCS. 2017; 15: 23. https://doi.org/10.1186/s12964-017-0177-y.

[8] Donnelly CR, Jiang C, Andriessen AS, Wang K, Wang Z, Ding H, *et al*. STING controls nociception via type I interferon signalling in sensory neurons. Nature. 2021; 591: 275–280. https://doi.org/10.1038/s41586-020-03151-1.

[9] Tan PH, Gao YJ, Berta T, Xu ZZ, Ji RR. Short small-interfering RNAs produce interferon-α-mediated analgesia. British Journal of Anaesthesia. 2012; 108: 662–669. https://doi.org/10.1093/bja/aer492.

[10] Akira S, Uematsu S, Takeuchi O. Pathogen recognition and innate immunity. Cell. 2006; 124: 783–801. https://doi.org/10.1016/j.cell.2006.02.015.

[11] Donnelly CR, Chen O, Ji RR. How do sensory neurons sense danger signals? Trends in Neurosciences. 2020; 43: 822–838. https://doi.org/10.1016/j.tins.2020.07.008.

[12] Fitzgerald KA, Kagan JC. Toll-like receptors and the control of immunity. Cell. 2020; 180: 1044–1066. https://doi.org/10.1016/j.cell.2020.02.041.

[13] Liu T, Gao YJ, Ji RR. Emerging role of Toll-like receptors in the control of pain and itch. Neuroscience Bulletin. 2012; 28: 131–144. https://doi.org/10.1007/s12264-012-1219-5.

[14] Makris S, Paulsen M, Johansson C. Type I interferons as regulators of lung inflammation. Frontiers in Immunology. 2017; 8: 259. https://doi.org/10.3389/fimmu.2017.00259.

[15] Goubau D, Deddouche S, Reis e Sousa C. Cytosolic sensing of viruses. Immunity. 2013; 38: 855–869. https://doi.org/10.1016/j.immuni.2013.05.007.

[16] Decout A, Katz JD, Venkatraman S, Ablasser A. The cGAS-STING pathway as a therapeutic target in inflammatory diseases. Nature Reviews. Immunology. 2021; 21: 548–569. https://doi.org/10.1038/s41577-021-00524-z.

[17] Ishikawa H, Barber GN. STING is an endoplasmic reticulum adaptor that facilitates innate immune signalling. Nature. 2008; 455: 674–678. https://doi.org/10.1038/nature07317.

[18] Ishikawa H, Ma Z, Barber GN. STING regulates intracellular DNA-mediated, type I interferon-dependent innate immunity. Nature. 2009; 461: 788–792. https://doi.org/10.1038/nature08476.

[19] McNab F, Mayer-Barber K, Sher A, Wack A, O'Garra A. Type I interferons in infectious disease. Nature Reviews. Immunology. 2015; 15: 87–103. https://doi.org/10.1038/nri3787.

[20] Asselin-Paturel C, Boonstra A, Dalod M, Durand I, Yessaad N, Dezutter-Dambuyant C, *et al*. Mouse type I IFN-producing cells are immature APCs with plasmacytoid morphology. Nature Immunology. 2001; 2: 1144–1150. https://doi.org/10.1038/ni736.

[21] Biron CA. Interferons alpha and beta as immune regulators–a new look. Immunity. 2001; 14: 661–664. https://doi.org/10.1016/s1074-7613(01)00154-6.

[22] Barchet W, Cella M, Odermatt B, Asselin-Paturel C, Colonna M, Kalinke U. Virus-induced interferon alpha production by a dendritic cell subset in the absence of feedback signaling in vivo. The Journal of Experimental Medicine. 2002; 195: 507–516. https://doi.org/10.1084/jem.20011666.

[23] Yum S, Li M, Fang Y, Chen ZJ. TBK1 recruitment to STING activates both IRF3 and NF-κB that mediate immune defense against tumors and viral infections. Proceedings of the National Academy of Sciences of the United States of America. 2021; 118: e2100225118. https://doi.org/10.1073/pnas.2100225118.

[24] Li N, Zhou H, Wu H, Wu Q, Duan M, Deng W, *et al*. STING-IRF3 contributes to lipopolysaccharide-induced cardiac dysfunction, inflammation, apoptosis and pyroptosis by activating NLRP3. Redox Biology. 2019; 24: 101215. https://doi.org/10.1016/j.redox.2019.101215.

[25] Zhang W, Li G, Luo R, Lei J, Song Y , Wang B, *et al*. Cytosolic escape of mitochondrial DNA triggers cGAS-STINGNLRP3 axis-dependent nucleus pulposus cell pyroptosis. Experimental & Molecular Medicine. 2022; 54: 129–142. https://doi.org/10.1038/s12276-022-00729-9.

[26] Chen J, Baig E, Fish EN. Diversity and relatedness among the type I interferons. Journal of Interferon & Cytokine Research: the Official Journal of the International Society for Interferon and Cytokine Research. 2004; 24: 687–698. https://doi.org/10.1089/jir.2004.24.687.

[27] Darnell JE, Jr, Kerr IM, Stark GR. Jak-STAT pathways and transcriptional activation in response to IFNs and other extracellular signaling proteins. Science (New York, N.Y.). 1994; 264: 1415–1421. https://doi.org/10.1126/science.8197455.

[28] Pestka S, Krause CD, Walter MR. Interferons, interferon-like cytokines, and their receptors. Immunological Reviews. 2004; 202: 8–32. https://doi.org/10.1111/j.0105-2896.2004.00204.x.

[29] Pestka S. The human interferon-alpha species and hybrid proteins. Seminars in Oncology. 1997; 24: S9–4–S9–17.

[30] Levin D, Schneider WM, Hoffmann HH, Yarden G, Busetto AG, Manor O, *et al*. Multifaceted activities of type I interferon are revealed by a receptor antagonist. Science Signaling. 2014; 7: ra50. https://doi.org/10.1126/scisignal.2004998.

[31] Dumitrescu L, Constantinescu CS, Tanasescu R. Recent developments in interferon-based therapies for multiple sclerosis. Expert Opinion on Biological Therapy. 2018; 18: 665–680. https://doi.org/10.1080/14712598.2018.1462793.

[32] Weise AM, Flaherty LE. New options for the adjuvant treatment of cutaneous melanoma? Current Oncology Reports. 2014; 16: 409. https://doi.org/10.1007/s11912-014-0409-x.

[33] Snell LM, McGaha TL, Brooks DG. Type I interferon in chronic virus infection and cancer. Trends in Immunology. 2017; 38: 542–557. https://doi.org/10.1016/j.it.2017.05.005.

[34] Benveniste EN, Qin H. Type I interferons as anti-inflammatory mediators. Science's STKE: Signal Transduction Knowledge Environment. 2007; 2007: pe70. https://doi.org/10.1126/stke.4162007pe70.

[35] Wang H, Wang J, Xia Y. Defective suppressor of cytokine signaling 1 signaling contributes to the pathogenesis of systemic lupus erythematosus. Frontiers in Immunology. 2017; 8: 1292. https://doi.org/10.3389/fimmu.2017.01292.

[36] Biernacki K, Antel JP, Blain M, Narayanan S, Arnold DL, Prat A. Interferon beta promotes nerve growth factor secretion early in the course of multiple sclerosis. Archives of Neurology. 2005; 62: 563–568. https://doi.org/10.1001/archneur.62.4.563.

[37] Ejlerskov P, Hultberg JG, Wang J, Carlsson R, Ambjørn M, Kuss M, *et al*. Lack of Neuronal IFN-β-IFNAR causes lewy body- and Parkinson's disease-like dementia. Cell. 2015; 163: 324–339. https://doi.org/10.1016/j.cell.2015.08.069.

[38] Kieseier BC. The mechanism of action of interferon-β in relapsing multiple sclerosis. CNS Drugs. 2011; 25: 491–502. https://doi.org/10.2165/11591110-000000000-00000.

[39] Delhaye S, Paul S, Blakqori G, Minet M, Weber F, Staeheli P, *et al*. Neurons produce type I interferon during viral encephalitis. Proceedings of the National Academy of Sciences of the United States of America. 2006; 103: 7835–7840. https://doi.org/10.1073/pnas.0602460103.

[40] Ji RR, Donnelly CR, Nedergaard M. Astrocytes in chronic pain and itch. Nature Reviews. Neuroscience. 2019; 20: 667–685. https://doi.org/10.1038/s41583-019-0218-1.

[41] Ransohoff RM. How neuroinflammation contributes to neurodegeneration. Science (New York, N.Y.). 2016; 353: 777–783. https://doi.org/10.1126/science.aag2590.

[42] Roy ER, Wang B, Wan YW, Chiu G, Cole A, Yin Z, *et al*. Type I interferon response drives neuroinflammation and synapse loss in Alzheimer disease. The Journal of Clinical Investigation. 2020; 130: 1912–1930. https://doi.org/10.1172/JCI133737.

[43] Matsuda M, Huh Y, Ji RR. Roles of inflammation, neurogenic inflammation, and neuroinflammation in pain. Journal of Anesthesia. 2019; 33: 131–139. https://doi.org/10.1007/s00540-018-2579-4.

[44] Rosenberg GA. Matrix metalloproteinases in neuroinflammation [published erratum in Glia. 2002; 40: 130]. Glia. 2002; 39: 279–291. https://doi.org/10.1002/glia.10108.

[45] Ashina H, Porreca F, Anderson T, Amin FM, Ashina M, Schytz HW, *et al*. Post-traumatic headache: epidemiology and pathophysiological insights. Nature Reviews. Neurology. 2019; 15: 607–617. https://doi.org/10.1038/s41582-019-0243-8.

[46] Ji RR, Xu ZZ, Gao YJ. Emerging targets in neuroinflammation-driven chronic pain. Nature Reviews. Drug Discovery. 2014; 13: 533–548. https://doi.org/10.1038/nrd4334.

[47] Ji RR, Gereau RW, 4th, Malcangio M, Strichartz GR. MAP kinase and pain. Brain Research Reviews. 2009; 60: 135–148. https://doi.org/10.1016/j.brainresrev.2008.12.011.

[48] Malcangio M. Role of the immune system in neuropathic pain. Scandinavian Journal of Pain. 2019; 20: 33–37. https://doi.org/10.1515/sjpain-2019-0138.

[49] Inoue K, Tsuda M. Microglia in neuropathic pain: cellular and molecular mechanisms and therapeutic potential. Nature Reviews. Neuroscience. 2018; 19: 138–152. https://doi.org/10.1038/nrn.2018.2.

[50] McMahon SB, La Russa F, Bennett DLH. Crosstalk between the nociceptive and immune systems in host defence and disease. Nature Reviews. Neuroscience. 2015; 16: 389–402. https://doi.org/10.1038/nrn3946.

[51] Blalock JE, Smith EM. Human leukocyte interferon: structural and biological relatedness to adrenocorticotropic hormone and endorphins. Proceedings of the National Academy of Sciences of the United States of America. 1980; 77: 5972–5974. https://doi.org/10.1073/pnas.77.10.5972.

[52] Jiang CL, Son LX, Lu CL, You ZD, Wang YX, Sun LY, *et al*. Analgesic effect of interferon-alpha via mu opioid receptor in the rat. Neurochemistry International. 2000; 36: 193–196. https://doi.org/10.1016/s0197-0186(99)00124-2.

[53] Liu CC, Gao YJ, Luo H, Berta T, Xu ZZ, Ji RR, *et al*. Interferon alpha inhibits spinal cord synaptic and nociceptive transmission via neuronal-glial interactions. Scientific Reports. 2016; 6: 34356. https://doi.org/10.1038/srep34356.

[54] Liu S, Karaganis S, Mo RF, Li XX, Wen RX, Song XJ. IFNβ treatment inhibits nerve injury-induced mechanical allodynia and MAPK signaling by activating ISG15 in mouse spinal cord. The Journal of Pain. 2020; 21: 836–847. https://doi.org/10.1016/j.jpain.2019.11.010.

[55] Barragán-Iglesias P, Franco-Enzástiga Ú, Jeevakumar V, Shiers S, Wangzhou A, Granados-Soto V, *et al*. Type I interferons act directly on nociceptors to produce pain sensitization: implications for viral infection-induced pain. The Journal of Neuroscience: the Official Journal of the Society for Neuroscience. 2020; 40: 3517–3532. https://doi.org/10.1523/JNEUROSCI.3055-19.2020.

[56] Stokes JA, Corr M, Yaksh TL. Spinal toll-like receptor signaling and nociceptive processing: regulatory balance between TIRAP and TRIF cascades mediated by TNF and IFNβ. Pain. 2013; 154: 733–742. https://doi.org/10.1016/j.pain.2013.01.012.

[57] Woller SA, Ocheltree C, Wong SY, Bui A, Fujita Y, Gonçalves Dos Santos G, *et al*. Neuraxial TNF and IFN-beta co-modulate persistent allodynia in arthritic mice. Brain, Behavior, and Immunity. 2019; 76: 151–158. https://doi.org/10.1016/j.bbi.2018.11.014.

[58] Silveira Prudente A, Hoon Lee S, Roh J, Luckemeyer DD, Cohen CF, Pertin M, *et al*. Microglial STING activation alleviates nerve injury-induced neuropathic pain in male but not female mice. Brain, Behavior, and Immunity. 2024; 117: 51–65. https://doi.org/10.1016/j.bbi.2024.01.003.

[59] Defaye M, Bradaia A, Abdullah NS, Agosti F, Iftinca M, Delanne-Cuménal M, *et al*. Induction of antiviral interferon-stimulated genes by neuronal STING promotes the resolution of pain in mice. The Journal of Clinical Investigation. 2024; 134: e176474. https://doi.org/10.1172/JCI176474.

[60] Ma L, Deng D, Zhang T, Zhao W, Liu C, Huang S, *et al*. STING-IFN-I pathway relieves incision induced acute postoperative pain via inhibiting the neuroinflammation in dorsal root ganglion of rats. Inflammation Research. 2023; 72: 1551–1565. https://doi.org/10.1007/s00011-023-01764-6.

[61] Wang K, Donnelly CR, Jiang C, Liao Y, Luo X, Tao X, *et al*. STING suppresses bone cancer pain via immune and neuronal modulation. Nature Communications. 2021; 12: 4558. https://doi.org/10.1038/s41467-021-24867-2.

[62] Sun C, Wu G, Zhang Z, Cao R, Cui S. Protein tyrosine phosphatase receptor type d regulates neuropathic pain after nerve injury *via* the STING-IFN-I pathway. Frontiers in Molecular Neuroscience. 2022; 15: 859166. https://doi.org/10.3389/fnmol.2022.859166.

[63] Ding YY, Xu F, Wang YF, Han LL, Huang SQ, Zhao S, *et al*. Electroacupuncture alleviates postoperative pain through inhibiting neuroinflammation via stimulator of interferon genes/type-1 interferon pathway. Journal of Integrative Medicine. 2023; 21: 496–508. https://doi.org/10.1016/j.joim.2023.07.001.

[64] Sun J, Zhou YQ, Xu BY, Li JY, Zhang LQ, Li DY, *et al*. STING/NF-κB/IL-6-mediated inflammation in microglia contributes to spared nerve injury (SNI)-induced pain initiation. Journal of Neuroimmune Pharmacology: the Official Journal of the Society on NeuroImmune Pharmacology. 2022; 17: 453–469. https://doi.org/10.1007/s11481-021-10031-6.

[65] Wu W, Zhang X, Wang S, Li T, Hao Q, Li S, *et al*. Pharmacological inhibition of the cGAS-STING signaling pathway suppresses microglial M1-polarization in the spinal cord and attenuates neuropathic pain. Neuropharmacology. 2022; 217: 109206. https://doi.org/10.1016/j.neuropharm.2022.109206.

[66] Liu Y, Kuai S, Ding M, Wang Z, Zhao L, Zhao P. Dexmedetomidine and ketamine attenuated neuropathic pain related behaviors *via* STING pathway to induce ER-phagy. Frontiers in Synaptic Neuroscience. 2022; 14: 891803. https://doi.org/10.3389/fnsyn.2022.891803.

[67] Zhang Y, Wang W, Gong Z, Peng Y, Li X, Zhang Z, *et al*. Activation of the STING pathway induces peripheral sensitization via neuroinflammation in a rat model of bone cancer pain. Inflammation Research. 2023; 72: 117–132. https://doi.org/10.1007/s00011-022-01663-2.

[68] Menzies RA, Patel R, Hall NR, O'Grady MP, Rier SE. Human recombinant interferon alpha inhibits naloxone binding to rat brain membranes. Life Sciences. 1992; 50: 227–232. https://doi.org/10.1016/0024-3205(92)90555-4.

[69] Wang JY, Zeng XY, Fan GX, Yuan YK, Tang JS. mu- but not delta- and kappa-opioid receptor mediates the nucleus submedius interferon-alpha-evoked antinociception in the rat. Neuroscience Letters. 2006; 397: 254–258. https://doi.org/10.1016/j.neulet.2005.12.046.

[70] Bridge AJ, Pebernard S, Ducraux A, Nicoulaz AL, Iggo R. Induction of an interferon response by RNAi vectors in mammalian cells. Nature Genetics. 2003; 34: 263–264. https://doi.org/10.1038/ng1173.

[71] Liu CC, Lu IC, Wang LK, Chen JY, Li YY, Yang CP, *et al*. Interferon-β suppresses inflam-

matory pain through activating μ-opioid receptor. Molecular Pain. 2021; 17: 17448069211045211. https://doi.org/10.1177/17448069211045211.

[72] Usoskin D, Furlan A, Islam S, Abdo H, Lönnerberg P, Lou D, *et al*. Unbiased classification of sensory neuron types by large-scale single-cell RNA sequencing. Nature Neuroscience. 2015; 18: 145–153. https://doi.org/10.1038/nn.3881.

[73] Yang JL, Chen KB, Shen ML, Hsu WT, Lai YW, Hsu CM. Sugammadex for reversing neuromuscular blockages after lung surgery: A systematic review and meta-analysis. Medicine. 2022; 101: e30876. https://doi.org/10.1097/MD.0000000000030876.

[74] Szöllősi AG, McDonald I, Szabó IL, Meng J, van den Bogaard E, Steinhoff M. TLR3 in Chronic Human Itch: A keratinocyte-associated mechanism of peripheral itch sensitization. The Journal of Investigative Dermatology. 2019; 139: 2393–2396.e6. https://doi.org/10.1016/j.jid.2019.04.018.

[75] Liu T, Berta T, Xu ZZ, Park CK, Zhang L, Lü N, *et al*. TLR3 deficiency impairs spinal cord synaptic transmission, central sensitization, and pruritus in mice. The Journal of Clinical Investigation. 2012; 122: 2195–2207. https://doi.org/10.1172/JCI45414.

[76] Zheng Y, Liu P, Bai L, Trimmer JS, Bean BP, Ginty DD. Deep sequencing of somatosensory neurons reveals molecular determinants of intrinsic physiological properties. Neuron. 2019; 103: 598–616.e7. https://doi.org/10.1016/j.neuron.2019.05.039.

[77] Patil MJ, Ru F, Sun H, Wang J, Kolbeck RR, Dong X, *et al*. Acute activation of bronchopulmonary vagal nociceptors by type I interferons. The Journal of Physiology. 2020; 598: 5541–5554. https://doi.org/10.1113/JP280276.

[78] Fitzgibbon M, Kerr DM, Henry RJ, Finn DP, Roche M. Endocannabinoid modulation of inflammatory hyperalgesia in the IFN-α mouse model of depression. Brain, Behavior, and Immunity. 2019; 82: 372–381. https://doi.org/10.1016/j.bbi.2019.09.006.

[79] Blank T, Prinz M. Type I interferon pathway in CNS homeostasis and neurological disorders. Glia. 2017; 65: 1397–1406. https://doi.org/10.1002/glia.23154.

[80] Khoutorsky A, Price TJ. Translational control mechanisms in persistent pain. Trends in Neurosciences. 2018; 41: 100–114. https://doi.org/10.1016/j.tins.2017.11.006.

[81] Zhuang ZY, Xu H, Clapham DE, Ji RR. Phosphatidylinositol 3-kinase activates ERK in primary sensory neurons and mediates inflammatory heat hyperalgesia through TRPV1 sensitization. The Journal of Neuroscience: the Official Journal of the Society for Neuroscience. 2004; 24: 8300–8309. https://doi.org/10.1523/JNEUROSCI.2893-04.2004.

[82] Delorey TM, Ziegler CGK, Heimberg G, Normand R, Yang Y, Segerstolpe Å, *et al*. COVID-19 tissue atlases reveal SARS-CoV-2 pathology and cellular targets. Nature. 2021; 595: 107–113. https://doi.org/10.1038/s41586-021-03570-8.

[83] Zhang X, Li X, Wang W, Zhang Y, Gong Z, Peng Y, *et al*. STING contributes to cancer-induced bone pain by promoting M1 polarization of microglia in the medial prefrontal cortex. Cancers. 2022; 14: 5188. https://doi.org/10.3390/cancers14215188.

[84] Song L, Jiang W, Liu W, Ji JH, Shi TF, Zhang J, *et al*. Protein tyrosine phosphatases receptor type D is a potential tumour suppressor gene inactivated by deoxyribonucleic acid methylation in paediatric acute myeloid leukaemia. Acta Paediatrica (Oslo, Norway: 1992). 2016; 105: e132–e141. https://doi.org/10.1111/apa.13284.

[85] Uhl GR, Martinez MJ, Paik P, Sulima A, Bi GH, Iyer MR, *et al*. Cocaine reward is reduced by decreased expression of receptor-type protein tyrosine phosphatase D (PTPRD) and by a novel PTPRD antagonist. Proceedings of the National Academy of Sciences of the United States of America. 2018; 115: 11597–11602. https://doi.org/10.1073/pnas.1720446115.

[86] Cao S, Yuan J, Zhang D, Wen S, Wang J, Li Y, *et al*. Transcriptome changes in dorsal spinal cord of rats with neuropathic pain. Journal of Pain Research. 2019; 12: 3013–3023. https://doi.org/10.2147/JPR.S219084.

[87] Sun W, Kou D, Yu Z, Yang S, Jiang C, Xiong D, *et al*. A transcriptomic analysis of neuropathic pain in rat dorsal root ganglia following peripheral nerve injury. Neuromolecular Medicine. 2020; 22: 250–263. https://doi.org/10.1007/s12017-019-08581-3.

[88] Feng XM, Mi WL, Xia F, Mao-Ying QL, Jiang JW, Xiao S, *et al*. Involvement of spinal orexin A in the electroacupuncture analgesia in a rat model of post-laparotomy pain. BMC Complementary and Alternative Medicine. 2012; 12: 225. https://doi.org/10.1186/1472-6882-12-225.

[89] Jiang GL, Yang XL, Zhou HJ, Long J, Liu B, Zhang LM, *et al*. cGAS knockdown promotes microglial M2 polarization to alleviate neuroinflammation by inhibiting cGAS-STING signaling pathway in cerebral ischemic stroke. Brain Research Bulletin. 2021; 171: 183–195. https://doi.org/10.1016/j.brainresbull.2021.03.010.

[90] Laumet G, Ma J, Robison AJ, Kumari S, Heijnen CJ, Kavelaars A. T cells as an emerging target for chronic pain therapy. Frontiers in Molecular Neuroscience. 2019; 12: 216. https://doi.org/10.3389/fnmol.2019.00216.

[91] Benoit-Lizon I, Jacquin E, Rivera Vargas T, Richard C, Roussey A, Dal Zuffo L, *et al*. CD4 T cell-intrinsic STING signaling controls the differentiation and effector functions of T_H1 and T_H9 cells. Journal for Immunotherapy of Cancer. 2022; 10: e003459. https://doi.org/10.1136/jitc-2021-003459.

[92] Jeffries AM, Marriott I. Human microglia and astrocytes express cGAS-STING viral sensing components. Neuroscience Letters. 2017; 658: 53–56. https://doi.org/10.1016/j.neulet.2017.08.039.

[93] Inoue Y, Ayaki T, Ishimoto T, Yamakado H, Maki T, Matsuzawa S, *et al*. The stimulator of interferon genes (STING) pathway is upregulated in striatal astrocytes of patients with multiple system atrophy. Neuroscience Letters. 2021; 757: 135972. https://doi.org/10.1016/j.neulet.2021.135972.

[94] Moretti J, Roy S, Bozec D, Martinez J, Chapman JR, Ueberheide B, *et al*. STING senses microbial viability to orchestrate stress-mediated autophagy of the endoplasmic reticulum. Cell. 2017; 171: 809–823.e13. https://doi.org/10.1016/j.cell.2017.09.034.

[95] Luo W, Wang Y, Zhang L, Ren P, Zhang C, Li Y, *et al*. Critical Role of Cytosolic DNA and Its Sensing Adaptor STING in aortic degeneration, dissection, and rupture. Circulation. 2020; 141: 42–66. https://doi.org/10.1161/CIRCULATIONAHA.119.041460.

[96] Le Naour J, Zitvogel L, Galluzzi L, Vacchelli E, Kroemer G. Trial watch: STING agonists in cancer therapy. Oncoimmunology. 2020; 9: 1777624. https://doi.org/10.1080/2162402X.2020.1777624.

[97] Domizio JD, Gulen MF, Saidoune F, Thacker VV, Yatim A, Sharma K, *et al*. The cGAS-STING pathway drives type I IFN immunopathology in COVID-19. Nature. 2022; 603: 145–151. https://doi.org/10.1038/s41586-022-04421-w.

[98] Hu X, Zhang H, Zhang Q, Yao X, Ni W, Zhou K. Emerging role of STING signalling in CNS injury: inflammation, autophagy, necroptosis, ferroptosis and pyroptosis. Journal of Neuroinflammation. 2022; 19: 242. https://doi.org/10.1186/s12974-022-02602-y.