

RESEARCH HIGHLIGHT



No pain, no gain — how nociceptors orchestrate tissue repair

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Cell Research (2024) 0:1–2; <https://doi.org/10.1038/s41422-024-00979-4>

Pain-sensing peripheral neurons, nociceptors, exert control over many aspects of the immune response through various means, including the secretion of immunomodulatory molecules. Adding to the growing list of such interactions, a recent article by Lu et al. reported that a nociceptive neuropeptide, calcitonin gene-related peptide, induces thrombospondin-1 expression in macrophages and neutrophils, limiting their pro-inflammatory functions and promoting tissue repair after injury.

Nociceptors, afferent somatosensory neurons of the peripheral nervous system that elicit the sensation of pain or itch in response to noxious stimuli, have risen to prominence as controllers of immune responses in barrier tissues. In particular, calcitonin gene-related peptide (CGRP), a prominent neuropeptide released by activated nociceptors, has received considerable attention owing to its pleiotropic, context-dependent effects. While CGRP has shown pro-inflammatory activities in some situations,^{1,2} in most cases, its effects appear anti-inflammatory.^{3–5} For example, CGRP-mediated immunosuppression has been shown to weaken the host response to certain bacterial infections^{4,5} and cancer.³ In light of this apparent fitness cost, it has been a conundrum why the sensation of pain should unleash CGRP-dependent immunosuppression. To be preserved throughout evolution, the potentially detrimental consequences of CGRP release should be outweighed by beneficial effects in other contexts.

A recent report by Lu et al.⁶ now provides compelling evidence for such a beneficial role of CGRP in the context of tissue repair after injury. The authors observed that wound healing in the skin and skeletal muscle of nociceptor-depleted mice was markedly delayed when compared to nociceptor-sufficient controls. This effect was due to the loss of nociceptor-derived CGRP which acted on neutrophils and macrophages infiltrating the site of an injury. These myeloid leukocytes responded to CGRP by upregulating thrombospondin-1 (TSP-1), an extracellular matrix protein involved in tissue regeneration. The auto- or paracrine secretion of TSP-1 then inhibited further pro-inflammatory leukocyte recruitment to the damaged tissue, boosted the clearance of apoptotic neutrophils by macrophages, and reprogrammed local macrophages to assume an anti-inflammatory state. As a result, CGRP release switched the wounded tissue from a pro-inflammatory histotoxic milieu to an environment that favored tissue repair (Fig. 1).

These findings implied that topical application of CGRP to an area of tissue injury could be useful to treat pathologic conditions such as type 2 diabetes where tissue healing is impaired. However, native CGRP has a short in vivo half-life and diffuses rapidly within tissues, which limits its clinical usefulness. Thus, Lu et al. engineered a chimeric peptide (eCGRP) by combining CGRP with an N-terminal extracellular matrix-binding sequence and a plasmin-sensitive linker

allowing for its gradual release. Upon application to a wound, eCGRP exhibited prolonged retention at the application site resulting in overall improved potency.

A common long-term consequence of type 2 diabetes is peripheral neuropathy and the occurrence of chronic, non-healing wounds. Thus, Lu et al. tested their eCGRP construct in *Lepr^{db/db}* mice, a model of type 2 diabetes. These mice exhibited a reduced density of CGRP⁺ fibers, recapitulating the overall decrease in CGRP expression observed in diabetic patients and suggesting that the CGRP-TSP-1 axis might be impaired. Indeed, local application of eCGRP after acute injury rescued TSP-1 expression in injured tissues, inhibited the accumulation of pro-inflammatory mediators, and significantly improved healing.⁶ In this context, we note that CGRP inhibitors are in clinical use to manage patients with migraine,⁷ and one such patient was found in a recent case report to have experienced severely impaired wound healing.⁸ Thus, a systematic clinical and epidemiological evaluation of the impact of CGRP inhibitors on tissue regeneration appears to be warranted.

Tissue repair represents a complex biological process, during which the immune system must strike a balance between pro-inflammatory functions to combat infections of open wounds, and anti-inflammatory tissue repair processes. Two separate nociceptor activities had previously been implicated in this process: first, nociceptors potentiate the ability of dendritic cells (DCs) to induce a tissue regeneration-promoting Th17-type T cell response,⁹ second, activated nociceptors release the neurokinine TAF4A, which induces macrophage production of IL-10, an anti-inflammatory cytokine.¹⁰ The CGRP-TSP-1 axis described by Lu et al. thus represents a third neuroimmune pathway through which nociceptors fine-tune the healing process. Future research will need to untangle the relative contribution of these different modalities and the response of individual nociceptor subsets (e.g., CGRP⁺ and TAF4A⁺) to different types of tissue damage.

To date, the immunosuppressive actions of CGRP have mostly been considered to be a direct, cell-intrinsic effect of CGRP receptor signaling.⁴ By contrast, the inflammation-promoting effects of nociceptor-derived CGRP are largely indirect, e.g., by driving a transcriptional program in DCs which favors the upregulation of genes involved in DC sentinel functions.¹ In vitro experiments by Lu et al. using siRNA to knock down TSP-1 in macrophages now indicate that at least some of the anti-inflammatory effects of CGRP are also indirect as they depend on the autocrine actions of TSP-1. In addition, TSP-1 has been shown to convert latent transforming growth factor β (TGF- β) to its biologically active form, which possesses potent anti-inflammatory activity.¹¹ More work will be necessary to fully unravel the relative contributions of autocrine TSP-1 effects on immune cells, TSP-1-induced TGF- β activation, and direct

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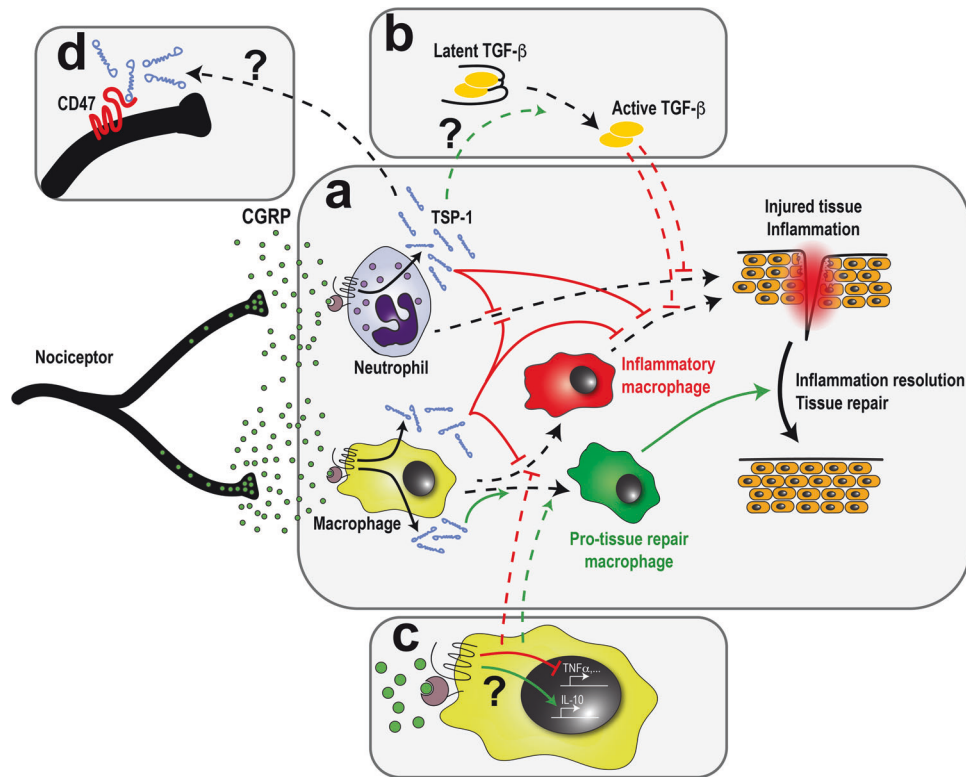


Fig. 1 Nociceptor-derived CGRP inhibits local inflammation and promotes tissue repair. **a** Lu et al. have shown that CGRP induces the expression of TSP-1 in neutrophils and macrophages. TSP-1, in turn, inhibits inflammatory functions of both cell types, thus dampening inflammation (red, blunt-ended arrows), while promoting the acquisition of a pro-tissue repair phenotype in macrophages and facilitating tissue repair (green arrows). **b–d** It remains to be established to what extent TSP-1-mediated TGF- β activation (**b**) and immunosuppressive cell-intrinsic CGRP signaling (**c**) play a role in the process, and whether immune cell-derived TSP-1 feeds back onto nociceptors to modify their activity (**d**).

CGRP receptor signaling to nociceptor-mediated immunosuppression and tissue regeneration. Intriguingly, TSP-1 has also been implicated in the maintenance of nociceptive fibers in the cornea.¹² Indeed, single-cell RNA sequencing data indicate that many nociceptors express the TSP-1 receptor CD47, suggesting a potential positive feedback loop between CGRP⁺ nociceptors and TSP-1-expressing immune cells (Fig. 1).

While many important questions remain, the work by Lu et al. provides compelling evidence that painful stimuli associated with tissue injury trigger nociceptor-mediated activation of the CGRP-TSP-1 axis to facilitate tissue repair. This novel pathway represents a potential target that may be pharmacologically tractable to accelerate wound healing, particularly in type 2 diabetes and other diseases associated with a loss of peripheral innervation.

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ADDITIONAL INFORMATION

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