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Review

NLRP3 Inflammasome Activation as a Potential Mechanism of Local Anesthetic-Associated Skin Desquamation After Brachial Plexus Block: A Hypothesis-Generating Review

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Abstract

Brachial plexus block (BPB) is widely used for perioperative analgesia in upper limb surgery. However, delayed, localized, non-infectious skin desquamation has anecdotally been described after upper-limb procedures, although its frequency, causal relationship with BPB, and underlying mechanisms remain uncertain. This review therefore considers NLR family pyrin domain containing 3 (NLRP3) signaling as a working hypothesis rather than an established mechanism. Local anesthetic (LA)-induced cellular stress can activate NLRP3-related pathways in experimental neural and immune models, with caspase-1-dependent maturation of interleukin (IL)-1β and IL-18 and gasdermin D (GSDMD)-mediated pyroptosis providing a plausible source of sterile inflammatory amplification. Whether perineural inflammation is transmitted to a distal cutaneous region through sensory-neural, humoral, cellular, or microvascular routes has not been demonstrated following BPB. Such signaling could, in principle, alter keratinocyte homeostasis and epidermal barrier integrity, but competing explanations including contact reactions, pressure or ischemic injury, thermal injury, infection, and local irritation must first be excluded. This review synthesizes evidence on LA-induced cellular stress, inflammasome biology, pyroptosis, neuroimmune signaling, and skin barrier dysfunction and defines a staged validation roadmap. The proposed NLRP3-centered model is hypothesis-generating and should not be interpreted as proof of causation or as a basis for preventive treatment before direct validation.

Keywords: brachial plexus block; local anesthetic; dermatitis; inflammasome; pyroptosis; neurogenic inflammation

1. Introduction

Brachial plexus block (BPB) is an important technique for perioperative analgesia in upper limb surgery, and randomized studies support its analgesic role [1,2]. Contemporary reviews also describe its use across upper-limb procedures [3]. With widespread ultrasound guidance, local and neurologic complications have received increasing attention [4,5]. Interscalene-block literature provides additional context for peripheral nerve injury [6]. Neurogenic inflammation and human barrier-tissue studies establish that neural signals can influence skin biology [7,8]. Recent work further supports a neuro-cutaneous axis in tissue repair [9]. Upper-extremity nerve symptoms have been reported after BPB [10,11], but these reports do not establish that delayed desquamation is caused by BPB. Older risk estimates and registry data characterize neurologic or systemic toxicity after regional anesthesia [12,13], not a BPB-specific desquamation phenotype. Accordingly, published evidence does not establish the incidence, typical timing, or causal relationship of postoperative desquamation with BPB. A molecular explanation should be considered only after the clinical phenotype is documented and competing perioperative exposures are excluded. Establishing whether a lesion maps to a peripheral-nerve cutaneous territory rather than to antiseptic, ultrasound gel, adhesive, dressing, positioning, pressure, tourniquet, or thermal exposure is a prerequisite for causal inference.

Clinical Phenotype and Differential Diagnosis

Because the available literature does not provide case-level datasets, incidence, recurrence, and typical onset timing cannot be determined. A clinically useful phenotype needs to include the number of cases and denominator data, block approach, local anesthetic (LA) type and dose, catheter status, lesion morphology and photographic records, exact anatomic distribution, onset timing, dermatologic assessment, infection exclusion criteria, treatment details, and clinical outcomes. The distribution should be compared directly with antiseptic preparation, ultrasound gel, adhesives, dressings, surgical positioning, pressure points, tourniquet location, and warming or thermal exposure. Only lesions that remain unexplained after these assessments should be considered for investigation of a BPB-associated neurocutaneous mechanism. Proposed risk modifiers such as diabetes, peripheral neuropathy, LA concentration, or block technique remain candidate variables until supported by comparative data. The differential diagnosis should compare morphology, distribution, neurologic findings, onset, and course rather than rely on desquamation alone. Contact or irritant injury commonly follows the

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Table 1. Practical differential features of postoperative upper-limb skin lesions after BPB.

Feature	Contact dermatitis/irritant injury	Pressure or ischemic injury	Candidate neurogenic pattern
Typical exposure	Antiseptic, ultrasound gel, adhesive, dressing	Positioning, focal pressure, tourniquet, warming or thermal exposure	LA exposure or operative nerve irritation; causal role unproven
Distribution	Matches preparation, adhesive, gel, or dressing footprint; may have sharp geometric borders	Matches pressure point, tourniquet field, dependent area, or vascular territory	Would need to map to a peripheral-nerve cutaneous territory rather than an exposure footprint
Inflammatory appearance	Erythema, pruritus, edema, vesiculation, or sharply demarcated desquamation may occur	Pain, pallor or dusky discoloration, edema, blistering, and later desquamation may occur	Desquamation may be accompanied by sensory symptoms, but a characteristic inflammatory morphology is not established
Neurologic findings	Usually absent unless swelling or pain limits examination	May coexist with pain, weakness, or numbness if nerve compression or ischemia occurs	Numbness, dysesthesia, itch, weakness, or neuropathic pain would support—but not prove—neural involvement
Timing	Often begins within hours to several days, depending on irritant versus allergic mechanism	May be immediate or early after sustained pressure/ischemia, with delayed blistering or peeling	A delayed pattern after block resolution is hypothesized; incidence and timing are not established
Course	Often improves after exposure removal and skin-directed care; recurrence may follow re-exposure	Depends on injury severity and relief of pressure or ischemia; not uniformly self-limited	Self-limited recovery would be compatible but is not diagnostic; persistent deficits require neurologic assessment

BPB, brachial plexus block; LA, local anesthetic.

footprint of antiseptic, ultrasound gel, adhesive, or dressing and may show sharply demarcated erythema, pruritus, edema, or vesiculation. Pressure, tourniquet, or thermal injury is more likely to match a pressure point or exposure field and may include pain, pallor or dusky discoloration, blistering, weakness, or numbness. A candidate neurogenic pattern would require concordance with a peripheral-nerve cutaneous territory, separation from exposure footprints, and documentation of dysesthesia, itch, weakness, or neuropathic pain; delayed onset and spontaneous resolution would remain supportive but non-specific features. The practical differential features are summarized in Table 1.

Experimental studies of LA neurotoxicity have focused on direct injury to neurons and Schwann cells [14,15]. Experimental work also documents LA-related injury in developing motor neurons [16]. Bupivacaine-associated oxidative stress and TXNIP-related signaling have been demonstrated in neural models [17]. Calcium-homeostasis disturbance provides another cytotoxic mechanism [18,19]. Endoplasmic reticulum (ER) stress has been implicated in bupivacaine-related cellular damage [20,21]. Lysosomal injury provides an additional stress pathway [22]. Potassium efflux and lysosomal proteases are well-characterized signals associated with NLR family pyrin domain containing 3 (NLRP3) activation [23,24]. Mitochondrial stress provides an additional mechanistic link to NLRP3 biology [25]. Priming, including transcriptional upregulation of NLRP3 and pro-interleukin (IL)-1β, should be distinguished from activation [26,27]. Spatial and cellular context further determines whether canonical activation occurs [28]. Thus, LA-related cellular stress provides biological plausibility for NLRP3 involvement, but it does not establish that this pathway is activated after clinical BPB or that it causes a distal skin lesion.

The NLRP3 inflammasome integrates cellular danger signals and, when canonically activated, recruits the adaptor protein apoptosis-associated speck-like protein containing a CARD (ASC) and activates caspase-1 [28,29]. A canonical activation framework distinguishes priming from assembly and downstream effector processing [30]. Activated caspase-1 processes pro-IL-1β and pro-IL-18 and cleaves gasdermin D (GSDMD), enabling mature cytokine release and pyroptotic membrane permeabilization [31]. Therefore, evidence of elevated NLRP3 mRNA expression or total protein abundance can only indicate inflammatory priming. More robust evidence for inflammasome activation requires detecting indicators such as ASC oligomerization or speck formation, caspase-1 cleavage, release of mature IL-1β/IL-18, and GSDMD cleavage. Damage-associated molecular patterns (DAMPs) released from injured or pyroptotic cells can then amplify sterile inflamma-

tion. Such feed-forward signaling offers a plausible way in which a short-lived pharmacologic exposure could be followed by a longer inflammatory phase, but the temporal link to postoperative desquamation remains unproven.

The skin epidermis maintains dynamic homeostasis through orderly proliferation, differentiation, and desquamation of keratinocytes. Inflammatory cytokines and neuropeptides can alter keratinocyte differentiation, survival, and intercellular adhesion, but their effects are context-dependent [32,33,34]. A lag can occur between inflammatory signaling and visible barrier disruption. Sensory nerves also participate in cutaneous immune regulation, creating a physiologic basis for nerve-immune-skin crosstalk [7,9]. These findings substantiate the biological plausibility of cross-tissue crosstalk, yet fail to identify a BPB-specific signaling pathway or confirm the predictable distribution of desquamation along peripheral nerves.

Based on the above evidence, this review proposes a working, testable hypothesis rather than an established mechanism. LA exposure around the brachial plexus may create cellular stress in perineural Schwann cells, macrophages, or other local cells and may, under some conditions, engage NLRP3-related signaling. If canonical inflammasome activation occurs, caspase-1-dependent IL-1β/IL-18 processing, GSDMD cleavage, and DAMPs release could sustain a local sterile inflammatory response. Whether that local response can influence a distal cutaneous territory through sensory-neural signaling, humoral or cellular dissemination, or limited microvascular exposure remains unknown. In particular, neither NLRP3 itself nor an 'NLRP3 signal' is known to undergo retrograde axonal transport from a BPB site to the skin. The central purpose of this review is therefore to separate established within-cell inflammasome biology from unverified inter-compartmental links and to define experiments that could test or refute the proposed model.

2. LA Toxicity as a Potential Trigger for NLRP3 Inflammasome Activation

The key question is not whether LA can injure cells, but whether clinically relevant perineural exposures create the activation-specific conditions required for canonical NLRP3 signaling. The following synthesis therefore separates evidence of cellular stress and priming from activation-specific readouts and emphasizes drug, concentration, route, exposure time, and cell type.

Cellular Stress and Evidence Linking LA Exposure to NLRP3 Signaling

LA-induced cellular stress provides a potential basis for immunomodulation. The literature on neurogenic inflammation and neuronal survival also indicates that neural responses to local injury are not reducible to a single inflammasome pathway [35,36]. Mitochondria are important targets of LA toxicity: bupivacaine can inhibit respiratory chain function, reduce adenosine triphosphate (ATP) generation, and increase reactive oxygen species (ROS) production [37]. Mitochondrial ROS has long been linked to NLRP3 activation, while priming-associated mitochondrial assembly adds further mechanistic context [38,39]. Oxidative stress can promote dissociation of thioredoxin-interacting protein (TXNIP) from thioredoxin (TRX), after which TXNIP may interact with NLRP3; free TRX is not considered the activating species [40]. LA-related ion-homeostasis disturbance can also contribute to cellular injury, and calcium signaling can modulate NLRP3 activity [41]. Lysosomal membrane permeabilization and cathepsin release provide another potential link between cell injury and inflammasome signaling [42]. ER stress can increase inflammatory priming and intensify ROS or calcium disturbances [43,44]. Related ROS-dependent NLRP3 activation has also been shown in other stress models [45]. Other cellular models also demonstrate that NLRP3-linked pyroptotic stress is highly context-dependent [46]. These pathways establish mechanistic overlap between LA toxicity and NLRP3 biology, but their relative contribution depends on drug, concentration, exposure time, and cell type.

Available experimental studies may support a relationship between LA exposure, cellular injury, and inflammasome-related signaling, although the evidence is heterogeneous. Schwann cell toxicity is time- and concentration-dependent, with LDH release used as a major indicator of cell death [47]. However, this study did not assess NLRP3 activation, caspase-1 cleavage, GSDMD cleavage, or pyroptosis. In human neuronal cells, bupivacaine and lidocaine reduced cell viability and induced caspase-3/7 activation under selected exposure conditions, whereas the acute cell death was interpreted predominantly as necrotic rather than caspase-1-dependent pyroptotic death [48]. General studies have established that inflammatory caspases can cleave GSDMD and induce pyroptosis [49,50]. An *in vivo* study reported increased NLRP3, ASC, cleaved caspase-1, N-terminal fragment of GSDMD, and mature IL-1β/IL-18 after intrathecal lidocaine administration, supporting inflammasome-associated pyroptotic signaling in that specific model after local anesthetic exposure [51]. However, these findings cannot be interpreted as direct evidence that the same mechanism operates after BPB. Although they are consistent with the presence of sterile inflammatory signaling, studies that only assess NLRP3-related protein expression are not sufficient on their own to confirm canonical inflammasome activation.

NLRP3 deficiency can reduce neuroinflammatory outcomes in non-BPB models [52,53]. Additional knockout and neuropathy studies support pathway involvement in other neural injuries [54,55]. MCC950 has also reduced pyroptotic or neuroinflammatory outcomes in perioperative central-nervous-system models [56,57]. However, these models differ from clinical BPB in route, anatomy, tissue exposure, and outcome, and they do not establish a causal

chain from peribrachial plexus NLRP3 activation to distal skin desquamation. Global knockout or systemic inhibition also cannot identify whether the critical compartment is perineural immune cells, neurons, dorsal-root-ganglion cells, or skin.

Several gaps are therefore central to this hypothesis. Much of the LA toxicity literature emphasizes bupivacaine, whereas ropivacaine and levobupivacaine are widely used for contemporary BPB. Their physicochemical properties, including relative lipophilicity, may alter membrane partitioning, intracellular exposure, mitochondrial stress, and cytotoxic thresholds, but direct head-to-head evidence for differential NLRP3-activating potency is lacking. Bupivacaine-related mechanistic findings should not be extrapolated automatically to ropivacaine or levobupivacaine. Existing sciatic-nerve and intrathecal models also differ from the complex fascial, vascular, and adipose environment of the brachial plexus. Most importantly, no direct study has demonstrated the proposed sequence of perineural LA exposure, compartment-specific inflammasome activation, neural or systemic signal transfer, and regionally restricted cutaneous injury after BPB.

3. Downstream Events of NLRP3 Inflammasome Activation: The Molecular Path to Skin Injury

If LA-related cellular stress engages canonical NLRP3 inflammasome activation in tissues surrounding the brachial plexus, downstream cytokine processing and pyroptosis could generate a local sterile inflammatory microenvironment [27,31]. This within-tissue sequence is biologically plausible, but extension from the perineural compartment to distant skin remains hypothetical. The following sections therefore distinguish established molecular events from proposed routes of cross-compartmental communication.

3.1 Formation of a Local Inflammatory Microenvironment

Canonical NLRP3 activation can produce caspase-1-dependent mature IL-1β and IL-18 and GSDMD-mediated pyroptosis [27,31]. Pyroptotic membrane disruption releases intracellular DAMPs such as high-mobility group box 1 (HMGB1) and ATP, which can activate neighboring immune and stromal cells [58,59]. This creates a potential feed-forward loop in which secondary inflammatory signaling persists after the initiating LA concentration has declined. Such persistence provides temporal plausibility for a delayed tissue response, but it does not establish that the response reaches distal skin or causes desquamation. The duration, magnitude, and cellular source of any post-BPB inflammatory response therefore need direct time-series measurement.

3.2 Signal Transmission via the Nerve-Immune-Skin Axis

How might a perineural inflammatory response influence a distant cutaneous territory? At present, no study demonstrates retrograde transport of IL-1β, NLRP3, or an 'NLRP3 signal' from a BPB site to distal skin. Local inflammatory mediators can affect sensory neurons and their excitability [60]. NGF signaling provides a well-established model of long-distance neuronal communication and dorsal root ganglion (DRG) responses [61,62]. Classical retrograde signaling is mediated by internalized neurotrophin receptor signaling endosomes that move from peripheral axons toward neuronal cell bodies [63]. Because a successful BPB suppresses voltage-gated sodium channel conduction, any neuropeptide-mediated distal effect would more plausibly need to emerge after block resolution or in the setting of injury-related ectopic activity; this has not been shown in BPB. If altered sensory activity occurs, substance P (SP) or calcitonin gene-related peptide (CGRP) release could modulate cutaneous immunity, but the direction of that effect is context-dependent. Nociceptive sensory neurons can amplify IL-23-mediated psoriasiform inflammation [64]. In contrast, CGRP-positive sensory neurons can promote tissue repair through neutrophil and macrophage regulation [65], while an itch-neuron subset can shape cutaneous immunity through myeloid cell cytokine control [66]. Humoral or cellular dissemination and direct microvascular exposure remain additional possibilities, but their ability to produce regionally restricted delayed desquamation is also unproven. These routes are therefore presented as competing, testable hypotheses rather than components of a completed pathway. NGF-TrkA signaling is used here only as a model of established neurotrophin-endosome transport; no evidence currently links perineural NLRP3 activation to altered NGF production, TrkA internalization, or NGF-dependent signaling after BPB. A valid test would therefore quantify NGF-TrkA separately from inflammasome readouts and determine whether route-specific blockade changes the distal phenotype without assuming that the two pathways are connected.

3.3 Disruption of Skin Epidermal Homeostasis

Regardless of the route, any cutaneous mechanism would ultimately need to explain a reproducible change in epidermal homeostasis. Keratinocyte proliferation and differentiation can be altered by inflammatory signaling [67,68]. Junctional and barrier integrity can also deteriorate under cytokine stress [69,70]. SP and other neuropeptides can alter keratinocyte cytokine signaling [71,72]. Neuropeptide effects should not be assumed to be uniformly injurious because sensory-neural signaling can also support repair [65]. Under defined inflammatory conditions, GSDMD-mediated keratinocyte pyroptosis and NLRP3-related signaling have been demonstrated in skin-disease models [73,74]. Skin lipid-barrier and sebaceous-gland bi-

ology can further influence barrier homeostasis and desquamation susceptibility [75,76]. At the same time, NLRP1 is a major keratinocyte inflammasome and should be considered as an alternative or parallel pathway rather than assuming epidermal NLRP3 dominance [32,33]. Thus, barrier dysfunction and desquamation are plausible downstream phenotypes of inflammation, but neither the responsible inflammasome nor a BPB-specific upstream trigger has been established. NLRP1 and NLRP3 are distinct cytosolic sensors rather than sequential components of one inflammasome. In keratinocytes, NLRP1 can respond to ultraviolet injury, ribotoxic or proteotoxic stress, and disruption of cellular homeostasis, whereas NLRP3 evidence is more context- and model-dependent. Either pathway may converge on ASC-caspase-1 signaling, mature IL-1 family cytokine release, and GSDMD cleavage, but activation of one does not demonstrate activation of the other. Future skin studies should therefore measure NLRP1 and NLRP3 activation-specific readouts in parallel and include non-inflammasome stress pathways, including Mitogen-Activated Protein Kinase/Nuclear Factor kappa-light-chain-enhancer of activated B cells (MAPK/NF-κB) signaling, apoptosis, and junctional or lipid-barrier dysfunction.

In summary, the evidence supports a set of competing, testable hypotheses rather than a complete pathological pathway (Fig. 1). LA-induced perineural cellular stress could be followed by local inflammasome-related signaling, while any subsequent effect on a distal cutaneous territory could involve sensory-neural, humoral/cellular, or microvascular mechanisms. Each cross-compartmental step remains unverified in the BPB setting, and common perioperative causes of postoperative skin injury must be evaluated in parallel. Fig. 1 therefore distinguishes established within-cell biology from proposed inter-compartmental links and alternative explanations.

4. Translational Orientation: From Theory to Validation and Intervention

The framework presented here is intended to generate testable questions rather than to direct prevention or treatment. Its scientific validity and clinical relevance require staged empirical validation, beginning with reproducible clinical phenotyping and exclusion of more common perioperative skin injuries. Only after a BPB-associated phenotype is established should mechanistic studies attempt to localize inflammasome activation, identify the relevant cellular compartment, and test candidate routes of communication to the skin.

4.1 Clinical Observation and Sample Collection Strategies

The first priority is rigorous clinical phenotype definition. Prospective observation should record all postoperative skin abnormalities with precise photographs, lesion morphology, onset and duration, associated symptoms, treatment, and outcome. Case-level data should include BPB approach, LA agent, concentration and dose, additives, catheter use, co-medications, and neurologic symptoms. Equally important, lesion boundaries should be mapped against antiseptic preparation, ultrasound gel, adhesives, dressings, surgical positioning, pressure points, tourniquet location, warming devices, and the cutaneous territory of the relevant peripheral nerves. Infection and dermatologic differential diagnoses should be assessed before attributing a lesion to BPB. Candidate factors such as diabetes, peripheral neuropathy, drug concentration, or block technique should be recorded as variables rather than labeled as risk factors until an association is demonstrated. If a reproducible phenotype is identified, ethically appropriate biopsies of affected and control skin could then assess histology and markers of inflammasome activation, differentiation, and barrier injury.

4.2 Construction of Experimental Models

Controlled *in vitro* and *in vivo* models can address different portions of the hypothesis, but their inferential limits should be explicit. A Transwell co-culture system can test whether Schwann cells or macrophages release soluble mediators that alter keratinocyte viability, differentiation, or inflammatory signaling [77]. Such a model cannot demonstrate retrograde neuronal signaling, axon reflexes, dorsal-root-ganglion involvement, or regional skin specificity. It should therefore be used only to test a soluble-mediator route and should include LA-only keratinocyte controls to distinguish direct drug exposure from mediator-dependent effects.

An *in vivo* BPB model should first establish whether a reproducible cutaneous phenotype occurs after anatomically appropriate perineural LA exposure [78]. Evaluation should proceed in stages: document sensory block and any post-block dysesthesia or ectopic activity; map skin findings against nerve territory and local contact or pressure exposures; then measure canonical inflammasome activation in perineural tissue, dorsal-root ganglia, and skin over time. Only after those steps should route-specific tracing and compartment-specific interventions be introduced (Table 2). This sequence avoids interpreting a global molecular change as proof of a perineural-to-skin causal pathway.

4.3 Key Techniques for Mechanism Validation

Mechanistic validation should follow a staged causal design. First, a reproducible BPB-associated phenotype must be established. Second, canonical inflammasome activation should be confirmed using activation-specific readouts and its cellular source localized in perineural tissue, neural tissue, or skin. Third, neural, local inflammatory, systemic, and contact mechanisms should be separated with route-specific experiments. Classical retrograde-signaling tracers or labeled neurotrophin-receptor cargo can test neuronal transport, whereas cytokine measurements alone can-

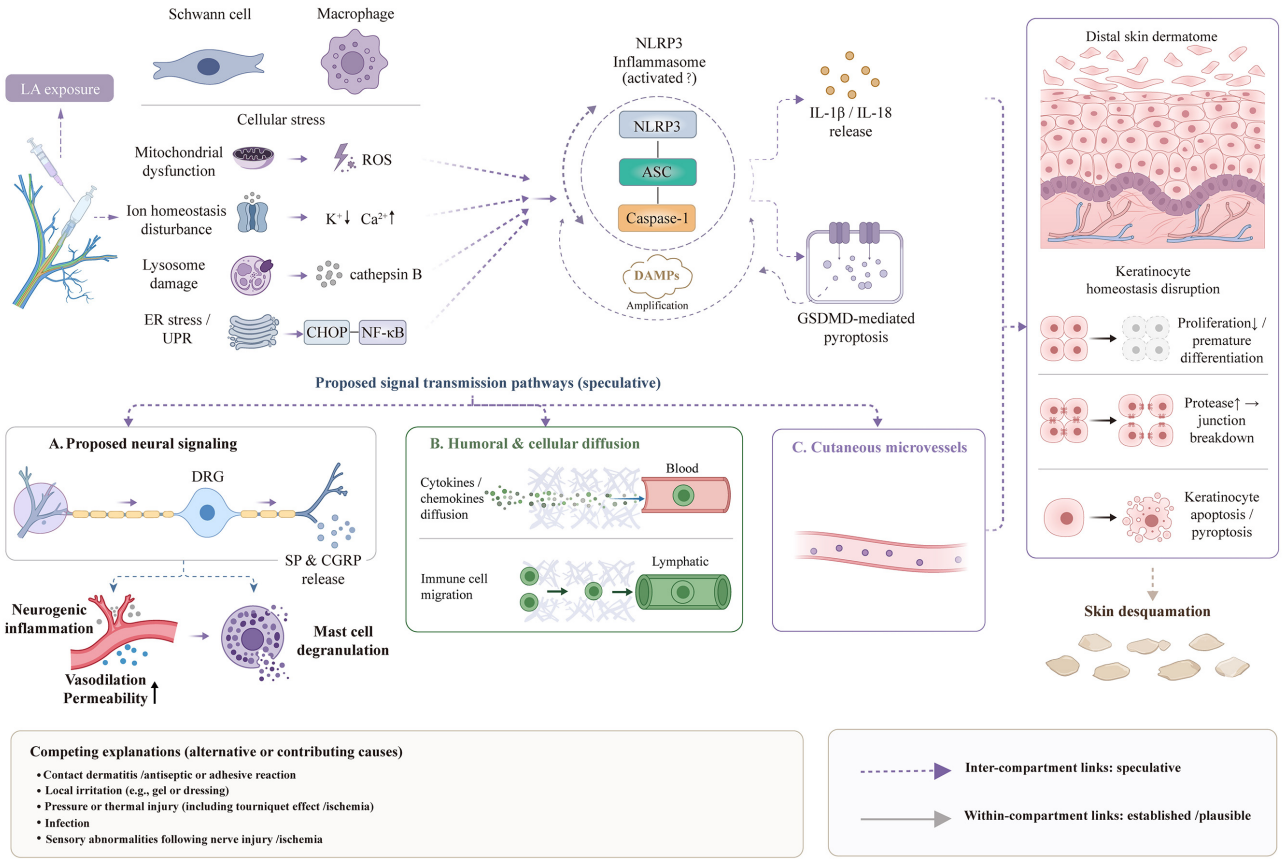


Fig. 1. Hypothesized mechanisms linking perineural local-anesthetic exposure to neuroimmune and cutaneous responses. Solid arrows denote relatively well-supported within-compartment cellular relationships, whereas dashed arrows denote unverified inter-compartmental links in the BPB setting. Perineural LA exposure may produce mitochondrial, ionic, lysosomal, or ER stress and may under some conditions lead to NLRP3 priming or canonical activation. Candidate routes to a distal cutaneous response include sensory-neural signaling after block resolution or nerve irritation, humoral or cellular dissemination, and limited microvascular exposure. Neuroimmune effects are context-dependent and may be inflammatory or reparative. Competing perioperative explanations include contact dermatitis from antiseptic, ultrasound gel, adhesive, or dressings; pressure or tourniquet-related ischemic injury; thermal injury; infection; local irritation; and sensory abnormalities after peripheral nerve injury. The proposed validation sequence is to establish a reproducible phenotype, map lesion distribution against exposure areas and peripheral-nerve cutaneous territory, demonstrate inflammasome activation and its cellular source, distinguish candidate routes, and only then test compartment-specific causal interventions. LA, local anesthetic; ROS, reactive oxygen species; ER, endoplasmic reticulum; IL, interleukin; GSDMD, gasdermin D; DAMPs, damage-associated molecular patterns; DRG, dorsal root ganglion; NLRP3, NLR family pyrin domain containing 3; ASC, apoptosis-associated speck-like protein containing a CARD; NF-κB, Nuclear Factor kappa-light-chain-enhancer of activated B cells; CHOP, CCAAT-enhancer-binding protein homologous protein; UPR, unfolded protein response.

not demonstrate axonal transport [63]. Global NLRP3 knockout or systemic MCC950 can indicate pathway contribution but cannot identify the critical cellular compartment. Stronger causal inference would require local delivery or cell-type-restricted perturbation, combined with temporal sampling. Only after these steps should downstream interventions such as caspase-1 inhibition, IL-1 blockade, or neuropeptide-receptor modulation be tested as mechanistic probes rather than proposed therapies.

4.4 Exploration of Potential Preventive and Therapeutic Strategies

Potential intervention should remain a preclinical research question until the mechanism and phenotype are validated. MCC950 and related NLRP3-directed compounds are useful experimental probes, but adding an inflammasome inhibitor to a clinical LA formulation would require evidence that the compound itself is not neurotoxic, does not alter block onset or efficacy, has predictable perineural pharmacokinetics, and is compatible with formulation, sterility, and regulatory requirements. Similar

Table 2. Evaluation index system for animal models of BPB.

Assessment dimension	Specific indicators	Detection methods	Scientific questions
Behavioral	Frequency of spontaneous scratching or biting of ipsilateral forelimb; mechanical hyperalgesia threshold	Video recording analysis; Von Frey filaments	Is there evidence of nerve irritation/sensory abnormality? What is its time course?
Macroscopic skin	Erythema, edema, blistering, crusting, hair loss, or peeling; map lesion boundaries against peripheral-nerve cutaneous territory and antiseptic, gel, adhesive, dressing, pressure, tourniquet, and thermal exposure areas	Visual inspection, high-resolution photography	Is a reproducible skin phenotype present, and does its distribution favor a neural territory over competing perioperative exposures?
Histopathology	Neural tissue: nerve fiber edema, myelin sheath structure, inflammatory cell infiltration; Skin tissue: epidermal thickness, stratum corneum integrity, dermal inflammation, appendage status	H&E staining, Luxol Fast Blue staining, immunohistochemistry, and immunofluorescence	Is there structural damage and inflammation in nerves and skin?
Molecular biology	Perineural tissue, dorsal root ganglia, and skin: NLRP3 expression/priming plus ASC oligomerization or specks, cleaved caspase-1 p20, mature IL-1β/IL-18, GSDMD-N; skin differentiation markers such as keratin 10 and Loricrin	Western blot, qRT-PCR, ELISA, immunofluorescence	Is canonical inflammasome activation demonstrated, and in which cellular compartment? Is skin differentiation impaired?

BPB, brachial plexus block; ASC, apoptosis-associated speck-like protein containing a CARD; GSDMD-N, N-terminal fragment of gasdermin D; IL, interleukin.

caution applies to IL-1 or neuropeptide-directed strategies. At present, management of postoperative desquamation should be guided by clinical diagnosis and standard skincare principles after infection, contact reactions, pressure or ischemic injury, and other causes have been assessed; this review does not establish a targeted NLRP3-based treatment.

5. Discussion

This review develops a hypothesis-generating framework in which LA-related perineural stress could engage inflammasome signaling and, through one or more unverified routes, contribute to a distal cutaneous response. The strongest evidence supports the intracellular biology of cellular stress, inflammasome priming or activation, cytokine processing, and pyroptosis in experimental systems [27,31]. The weakest part of the chain is cross-compartmental: no study has shown that clinical BPB activates perineural NLRP3 and then produces regionally restricted skin desquamation. The model should therefore be interpreted as a set of falsifiable links rather than a unified causal pathway.

Several considerations further constrain interpretation. First, perioperative skin lesions have common alternative explanations, including contact reactions, local irritants, pressure or tourniquet-related ischemia, thermal injury, infection, and local nerve injury; these should be assessed before a neuroimmune mechanism is invoked. Second, LA effects on inflammasome signaling are not uniformly pro-inflammatory. Ropivacaine has been reported to inhibit NLRP3 activation in a high-glucose endothelial model [79], illustrating that drug effects can depend on concentration, cell type, and inflammatory context. Third, sensory-neural regulation of skin immunity is bidirectional: nociceptive activity can amplify inflammatory skin responses [64], whereas CGRP-positive sensory neurons can support tissue repair [65]. These observations argue against treating SP or CGRP release as an inherently damaging endpoint.

A further issue is the relevance of different local anesthetics to contemporary BPB. Bupivacaine is relatively lipophilic and has a substantial mechanistic literature on mitochondrial stress and cytotoxicity, whereas ropivacaine and levobupivacaine are commonly selected for peripheral blocks because of their clinical safety profiles. Watanabe et al. [80] reported similar postoperative analgesia with levobupivacaine and ropivacaine in BPB; equivalent analgesic performance, however, does not establish equivalent intracellular exposure or inflammasome effects. A case report of high-dose ropivacaine toxicity after infraclavicular block shows that ropivacaine can still produce clinically relevant toxicity under high-exposure conditions [81], but it does not demonstrate NLRP3-mediated skin injury. Direct comparative studies are needed to measure cellular uptake, mitochondrial stress, ROS, and activation-specific inflammasome readouts at clinically relevant concentrations. More broadly, this review remains limited by the absence

of a formal clinical case series with complete exposure mapping, dermatologic assessment, and photographic documentation. Future work should therefore prioritize phenotype definition and validation over therapeutic extrapolation. Clinical duration is also an imperfect surrogate for intracellular inflammatory exposure. Lidocaine suppressed potassium efflux-dependent NLRP3 activation and IL-1β release in LPS/ATP-challenged macrophages [82]. In an axillary BPB trial, bupivacaine produced longer sensory and motor block than ropivacaine, whereas ropivacaine produced earlier onset and faster motor recovery [83]. Perineural dexmedetomidine prolonged ropivacaine block in a randomized supraclavicular BPB study [84], showing that adjuvants can alter exposure duration without identifying the direction of inflammasome signaling. These findings suggest that anti-inflammatory and injury-associated effects are determined jointly by molecular structure and lipophilicity, free concentration, dose and tissue retention, exposure duration, cell type, baseline inflammatory state, and co-administered drugs. Short, long, and extended duration formulations should therefore be compared at matched unbound tissue exposure, because nominal concentration or block duration alone cannot explain a positive skin phenotype.

6. Conclusion

In conclusion, this review presents an NLRP3-centered working hypothesis for a possible link between perineural LA exposure and delayed cutaneous responses after BPB. The hypothesis remains indirect: no study has demonstrated the complete sequence in patients or in a BPB-specific animal model. Three experiments should be prioritized. First, a prospective clinical phenotype study should document case-level BPB exposure, lesion photographs and distribution, competing skin exposures, dermatologic assessment, infection exclusion, neurologic symptoms, and outcome, with biopsy only when clinically and ethically appropriate. Second, an anatomically faithful BPB animal model should establish a reproducible skin phenotype and then localize canonical inflammasome activation with time-resolved, compartment-specific measurements and neural-tracing experiments. Third, only after phenotype and pathway localization are established should local or cell-specific NLRP3 inhibition, IL-1 blockade, or related mechanistic interventions be tested with dedicated neurotoxicity and block-function safety assessment. Until these steps are completed, NLRP3 should be regarded as a candidate mechanism for validation rather than a basis for prevention or therapy.

Abbreviations

NLRP3, NLR family pyrin domain containing 3; BPB, brachial plexus block; LA, local anesthetic; IL, interleukin; GSDMD, gasdermin D; ER, endoplasmic reticulum; ASC, apoptosis-associated speck-like protein containing a CARD; DAMPs, damage-associated molecular patterns; ATP, adenosine triphosphate; ROS, reactive oxygen species; TXNIP, thioredoxin-interacting protein; TRX, thioredoxin; LDH, lactate dehydrogenase; HMGB1, high-mobility group box 1; DRG, dorsal root ganglion; SP, substance P; CGRP, calcitonin gene-related peptide.

Author Contributions

SR contributed to conceptualization, literature review, and original draft preparation. HZ contributed to conceptualization and critical revision. XY contributed to manuscript editing, table preparation and visualization. All authors contributed to editorial changes in the manuscript. All authors reviewed 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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Conflicts of Interest

The authors declare no conflicts of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

The authors used an AI-assisted tool (ChatGPT) solely for text refinement and enhancement. No AI tool was used to generate scientific content. All authors take full responsibility for the integrity and accuracy of the manuscript. All scientific content, interpretations, and conclusions were developed and verified by the authors.

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