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Cutaneous Pain in Disorders Affecting Peripheral Nerves

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Abstract

Our ability to quickly detect and respond to harmful environmental stimuli is vital for our safety and survival. This inherent acute pain detection is a “gift” because it both protects our body from harm and allows healing of damaged tissues[1]. Damage to tissues from trauma or disease can result in distorted or amplified nociceptor signaling and sensitization of the spinal cord and brain (Central Nervous System; CNS) pathways to normal input from light touch mechanoreceptors. Together, these processes can result in nagging to unbearable chronic pain and extreme sensitivity to light skin touch (allodynia). Unlike acute protective pain, chronic pain and allodynia serve no useful purpose and can severely reduce the quality of life of an affected person. Chronic pain can arise from impairment to peripheral neurons, a phenomenon called “peripheral neuropathic pain.” Peripheral neuropathic pain can be caused by many insults that directly affect peripheral sensory neurons, including mechanical trauma, metabolic imbalance (e.g., diabetes), autoimmune diseases, chemotherapeutic agents, viral infections (e.g., shingles). These insults cause “acquired” neuropathies such as small-fiber neuropathies, diabetic neuropathy, chemotherapy-induced peripheral neuropathy, and post herpetic neuralgia. Peripheral neuropathic pain can also be caused by genetic factors and result in hereditary neuropathies that include Charcot-Marie-Tooth disease, rare channelopathies and Fabry disease. Many acquired and hereditary neuropathies affect the skin, our largest organ and protector of nearly our entire body. Here we review how cutaneous nociception (pain perceived from the skin) is altered following diseases that affect peripheral nerves that innervate the skin. We provide an overview of how noxious stimuli are detected and encoded by molecular transducers on subtypes of cutaneous afferent endings and conveyed to the CNS. Next, we discuss several acquired and hereditary diseases and disorders that cause painful or insensate (lack of sensation) cutaneous peripheral neuropathies, the symptoms and percepts patients experience, and how cutaneous afferents and other peripheral cell types are altered in function in these disorders. We highlight exciting new research areas that implicate non-neuronal skin cells, particularly keratinocytes, in cutaneous nociception and peripheral neuropathies. Finally, we conclude with ideas for innovative new directions, areas of unmet need, and potential opportunities for novel cutaneous therapeutics that may avoid CNS side effects, as well as ideas for improved translation of mechanisms identified in preclinical models to patients.

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Keywords

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I. Introduction: Landscape of our review

A living organism's ability to quickly detect and respond to harmful environmental stimuli is vital for their safety and survival. This reflexive process functions to protect our body from harm and allow healing of damaged tissues. The first step in the perception of pain is called nociception, the process of detecting and encoding noxious stimuli. Nociception is mediated by a network of peripheral sensory nerve endings (nociceptors) which innervate the skin, muscle, tendons, fascia and visceral organs[2,3] to enable the detection of potentially damaging environmental and endogenous stimuli. These nociceptors synapse onto central neurons (located in the dorsal spinal cord for the body or the brainstem for the head) which further process the nocifensive information and relay the signal to the brain. Here we will focus on cutaneous nociceptors and peripheral neuropathies that affect the skin.

Damage to tissues from trauma or disease can result in distorted or amplified nociceptor signaling. This amplified signaling is typically protective, preventing further damage and resolving once the underlying condition has healed. Sometimes however, pain can persist long after the initial tissue insult, serving no obvious beneficial purpose and severely reducing the quality of life of those affected. This is chronic pain, or pain that typically lasts longer than 6 months, sometimes for years. Chronic pain can be driven by the amplified nociceptor signaling itself, or by the secondary sensitization of CNS circuits that now in an amplified state, respond to light touch-sensitive afferents to signal pain (tactile allodynia). Chronic pain is especially common in states of injury and disease that directly affect the somatosensory nervous system, such as painful peripheral neuropathies. Neuropathic pain can result from a variety of common injury and disease states, including mechanical trauma, metabolic imbalance (e.g., diabetes), viral infections (e.g., shingles, AIDS), bacterial infections (e.g., leprosy which is caused by Mycobacterium leprae), alcoholism, and chemotherapy treatment (e.g., Taxol). Peripheral neuropathic pain involves multiple distressing sensory dysfunctions, including spontaneous pain (shooting, burning or stabbing pain; "pins and needles" feeling) and enhanced evoked pain responses to touch and cold stimuli. Despite the high prevalence of neuropathic pain (7–8% of the general population), treatment options are limited owing the diversity and complexity of the underlying biological mechanisms[4].

The focus of this review is on how cutaneous nociception (pain perceived from the skin) is altered following diseases that affect peripheral nerves. Whereas many types of common acute and chronic pain are associated with deeper target tissues such as muscle, bone, fascia and visceral organs, the mechanisms and processes underlying deep tissue pain are reviewed elsewhere[3,5–10]. Importantly, the spinal cord, brainstem, cortex and descending pain faciliatory and inhibitory pathways are extensively involved in central sensitization[11] and altered circuit signaling in painful peripheral neuropathies. For example, ectopic activity in sensitized sensory neurons drives enhanced input to the spinal cord; this ectopic activity

occurs not only in nociceptive Aδ and C fibers, but can also occur in Aβ fibers[12–19]. The enhanced input to the spinal cord can then amplify spinal cord circuits which subsequently respond to normal inputs from low threshold, light touch myelinated (Aβ) afferents that gain access to pain pathways and convey signals to the brain that are interpreted as tactile allodynia (extreme touch sensitivity)[20,21]. Further details of the complex CNS sensitization circuits and their sensitization mechanisms are beyond the scope of this review and are reviewed elsewhere by CNS experts[22–26]. Here, we will focus on peripheral mechanisms and review cutaneous nociception in peripheral nerve diseases. We will highlight common and rare diseases that cause painful peripheral neuropathies and exciting new research that implicate non-neuronal skin cells in cutaneous nociception and neuropathic pain.

II. Cutaneous nociception primer:

Anatomy, detection, encoding, conveying stimuli to CNS.

The process of cutaneous nociception is mediated by peripheral nociceptor endings in the skin. Both hairy skin (covers most of the body) and glabrous skin (covers the palms of the hands, feet and lips) are densely innervated by nociceptors as well as other somatosensory afferent endings[27–30]. Nociception begins when these terminals detect a noxious physical or chemical stimulus of sufficient intensity to induce action potential firing. These action potentials are propagated toward central terminals in the spinal cord or brainstem where this sensory information is encoded into CNS processing centers, ultimately mediating the perception of pain.

Anatomically, nociceptors that innervate the skin have their cell bodies contained within the dorsal root ganglia (DRG) which are located outside the spinal cord, within the bony vertebral foramen. One DRG contains the somata of nociceptors as well as other sensory afferent fibers (e.g., low threshold, light touch mechanoreceptors). Each nociceptor soma is pseudounipolar in that a single process projects and bifurcates, making a “T-junction” such that the peripheral axon innervates the periphery, whereas the central axon projects to and synapses in the spinal cord. In general, one entire DRG innervates one cutaneous dermatome on one side of the body and the central axons of the DRG nociceptors project to a given spinal cord level. Amazingly, a single DRG nociceptor peripheral axon that innervates the skin of a human foot can be 1.2 meters in length, while the central axon that innervates the spinal cord can measure 30 cm[31]. Furthermore, most of the nociceptor’s protein synthesis and energy metabolism occur in the soma, which comprises only ~0.2 % of the cell’s total cytoplasm, making the soma a tiny factory that must support the enormous peripheral and central processes[31]. The face and head’s counterpart to the DRG is the trigeminal ganglia, where one large trigeminal ganglia is located on either side of the head under the brain in Meckel’s cave of the dura matter; the trigeminal ganglia contain the somata of nociceptors (and other sensory afferents) that give rise to the trigeminal nerve which branches peripherally to innervate the skin of the face and head. The central process of trigeminal neurons project to the brainstem and enter the CNS at the level of the pons.

Many functional subtypes

Many cutaneous nociceptors that innervate the body and the head have unmyelinated axons (C fibers) or thinly myelinated axons (Aδ fibers); however, some thick myelinated (Aβ) cutaneous nociceptors, normally associated with non-painful touch sensation, also have been identified in species from rodents to primates[32,33] suggesting that the contributions of Aβ nociceptors to cutaneous pain should not be overlooked. The speed of action potential transmission is directly correlated with the amount of myelin and the diameter of the axon; C fibers conduct action potentials slowly and mediate slow-onset, persistent pain, whereas Aδ fibers conduct more rapidly and mediate fast-onset, protective, reflexive pain[32].

Myelinated and unmyelinated cutaneous nociceptors are extremely heterogeneous. In addition to being classified by their conduction velocities, they are categorized by their responsiveness to noxious thermal and mechanical stimuli. The most common type of C fibers are polymodal, meaning that they respond to many modes including heat, cold, mechanical and chemical stimuli[9]. Other C fibers respond to a smaller repertoire of stimuli such as C-mechano heat, C-mechano cold, C-mechano heat cold. Some C fibers sense warming stimuli[34], whereas other low threshold C fibers mediate gentle, pleasant skin touch[35]. A fiber nociceptors are not usually chemically sensitive but can be categorized into subtypes including A-mechano, A-mechano heat and A-heat; some of these A fibers are also cold sensitive[9]. Furthermore, a class of C fiber nociceptors that are normally insensitive to mechanical stimuli (“silent nociceptors”) can become responsive to mechanical stimuli following peripheral skin tissue injury. Whereas silent nociceptors are relatively rare in rodent skin[36], they are common in human and pig skin[37–39].

Transducers that detect and encode

Thermal heat: A variety of molecular transducers have been identified that convert thermal, chemical and mechanical stimuli into action potentials in the nerve terminal. The most is known about cutaneous heat transducers, in part because the pioneer molecular heat transducer was identified a quarter of a century ago in 1997. The discovery of the capsaicin (the spicy chemical in hot chili peppers) and heat-sensitive channel Transient Receptor Potential Vanilloid 1 (TRPV1[40]) launched the pain and somatosensory fields into the molecular transduction sphere. TRPV1 is a member of the Transient Receptor Potential (TRP) family, which in mammals encompasses around 30 members. All TRP channels are made of four subunits, where each subunit has six transmembrane domains and intracellular N- and C-termini. TRPV1 is expressed in C fiber and some Aδ fiber nociceptors and mediates all responsiveness to capsaicin[41,42]. When expressed in heterologous cells, TRPV1 confers responsiveness to noxious heat (42°C) to the cell[40,41]. However, *in vivo*, genetic deletion of TRPV1 in mice only modestly reduces the noxious behavioral and sensory neuron responses to heat[42], indicating that other noxious heat transducers exist. In line with this finding, the Transient Receptor Melastatin 3 (TRPM3) channel has recently been identified to be a noxious heat sensor in mammalian nociceptors and to function independent of TRPV1[43]. Subsequent studies have reported that noxious heat sensation in rodents is mediated by three channels (TRPV1, TRPM3 and TRPA1 (Transient Receptor Potential Ankyrin 1) [44]. Such functional redundancy in channels suggests that there may be a fail-safe mechanism to avoid acute burn injury. Mammals are also sensitive to non-noxious warm

temperatures (30–42°C), and as such three TRP channels, TRPV3, TRPV4 and TRPM2 are activated by warm temperatures in this range (25–42°C) [45–51] and likely encode our perception of warmth to the skin. Whereas TRPV3 and TRPV4 have been found in sensory neurons, they are far more highly expressed in skin keratinocytes[45,47,48,52–54]. Indeed, heat activates TRPV3 in keratinocytes which signal to sensory neurons via ATP[55]. Growing evidence (see section below on keratinocytes) indicates that keratinocytes are intimately involved in how we detect cutaneous temperature and touch, including in the noxious range.

Thermal cold: On the opposite side of physiological zero (temperature at which our skin feels neither warm nor cold) are transducers for cold temperature. Two TRP channels mediate cold transduction in mammals. First, Transient Receptor Potential Melastatin 8 (TRPM8) was identified by its responsiveness to the cold-mimetic chemical menthol[47,56]. TRPM8 can be activated by modest decreases in ambient temperature (~26°C) and mice that lack TRPM8 have severe deficits in behavioral detection of both cooling and noxious cold (10°C) temperatures[57–60]. That some responsiveness to noxious cold remains in these mice spurred the search for additional noxious cold sensors. Indeed, another TRP channel, Transient Receptor Potential Ankyrin 1 (TRPA1) channel (aka “the wasabi receptor), has been shown to respond to intensely cold temperatures (<18°C) when expressed in heterologous cells[61]. Some *in vivo* studies support this finding as mice lacking TRPA1 were reported to have decreased withdrawal responses to cold surfaces or acetone-mediated cooling[62] and decreased cold-induced nociceptive behaviors and trigeminal neuron responses[63]. However, other studies have reported normal cold-evoked behavioral and afferent responses in TRPA1 null mice[64,65]. It is possible that the disparate findings may be due to TRPA1 acting as a cellular sensor following cold-induced tissue damage[66,67]. Recently, the metabotropic G protein-coupled glutamate receptor GluK2 has been identified in mammalian sensory neurons and shown to be sensitive to noxious cold (~18 C[68]); although behavioral studies in rodents have not yet determined its contribution to cold detection *in vivo*. Alternatively, some two-pore potassium channel family members (KCNK4 or TRAAK) together with KCNK2 (TREK-1) have been shown to contribute to noxious cold-induced behaviors and neuronal activity[69].

Mechanical: Most cutaneous sensory neurons of all conduction velocities (Aβ, Aδ and C fibers) respond to mechanical stimuli. For cutaneous sensory neurons to respond to mechanical stimuli and initiate action potentials, they must express force-sensitive molecules that somehow convert physical energy into receptor potentials. Sophisticated studies in model organisms including bacteria, fruit flies (*Drosophila melanogaster)* and nematodes (*Caenorhabditis elegans*) have discovered a number of intrinsically mechanically-gated ion channels[70–72]. However, in mammals, the identification of bona fide mechanotransduction channels that transduce skin touch into action potentials remained elusive until 10 years ago. A major breakthrough in somatosensory mechanosensation occurred with the discovery of the novel, mechanically-gated ion channels Piezo1 and Piezo2[73]. Piezo channels are the largest identified ion channels and have the greatest number of transmembrane domains (24–36[74]). Piezo channels exist as a three-blade-propeller-like homotrimer in naïve cells[75–78]. Both Piezo1 and Piezo2 channels form an ion pore that is directly gated by membrane stretch[79–81]. Piezo channels are found in nearly every organ of the body including

bladder, colon, lung, bone, vasculature, skin and even red blood cells, reflecting on a molecular level the physiological fact that most organs rely on mechanical signaling[73,82]; as a result, Piezo channels are essential for survival[83,84]. Patients that have mutations in Piezo2 suffer from profound mechanosensory and proprioceptive deficits[85–87]. Interestingly, patients with Piezo2 mutations also fail to develop sensitization and painful reactions to touch after skin inflammation[88]. Complete deletion of Piezo2 from sensory neurons in mice reduces nociceptor responses to force and eliminates mechanical allodynia following skin inflammation and peripheral nerve injury[89]. Together these data suggest that Piezo2 may serve as a drug target for the cutaneous mechanical allodynia associated with skin inflammation and perhaps peripheral neuropathies in patients. The finding that cutaneous nociceptors retain some responsiveness to acute noxious mechanical stimuli suggests that there are other noxious mechanotransduction channels to discover. Other channels that have been validated to be inherently mechanically-activated include OSCA/TMEM63 and members of the K2P family including TREK-1, TREK-2 and TRAAK[90–92] and further studies will need to determine their relevance to noxious mechanosensation in skin. Another protein TACAN (Tmem120A) was recently identified and found expressed extensively in nociceptive sensory neurons[93]. Although recent studies have not supported the premise that TACAN is a bona fide mechanotransduction ion channel[94,95], it may serve a modulatory role in nociceptive mechanosensation after tissue injury[96]. Key questions are whether cutaneous nociceptors use a repertoire of mechanically-activated channels to transduce mechanical pain[97] and whether different subtypes of nociceptors utilize different combinations of these and yet undiscovered noxious mechanotransducers[97].

Transmission of nociceptor signals to CNS: Once transduction of a noxious stimulus occurs, the membrane of the sensory neuron depolarizes (known as a generator potential), and, if the membrane potential rises above threshold, an action potential is generated that transmits the signal to the spinal cord or brainstem. Voltage-gated sodium (Na^+; Na_V) channels are critical for the upstroke or rapid depolarization phase of the action potential. Voltage-gated Na^+ channels are comprised of one α-subunit and two β-subunits[98]. The α-subunit contains all components necessary for a functional voltage-gated channel, including the ion pore, voltage sensor and inactivation gate, whereas the β-subunits influence channel gating, inactivation and trafficking[99,100]. Voltage-gated Na^+ channels are key regulators of the excitability of sensory neurons in that they are critical for amplification of the generator potential following stimulus transduction, electrogenesis of the action potential and release of neurotransmitters from sensory neuron terminals. The subtypes Nav1.7, Nav1.8 and Nav1.9 are preferentially expressed in nociceptive afferent neurons and have been linked to pain disorders in humans, including small-fiber neuropathies[101–103], whereas nociceptors and non-nociceptive afferents both express Nav1.1 and Nav1.6[104]. On a functional level, the subunits Nav1.9 and Nav1.7 set the threshold and excitability of the nociceptor and amplify subthreshold stimuli, Nav1.7 and 1.6 contribute to the rising phase of the action potential, and Nav1.8 is the main contributor to the rising phase and mediates the shape and duration of the action potential in the nociceptor soma[104–110].

Other families of voltage-gated ion channels mediate the action potential downstroke in nociceptors. Once voltage-gated Na^+ channels inactivate at peak depolarization, delayed

rectifier voltage-gated K+ channels and Ca2+ modulated K+ channels activate and mediate membrane repolarization[111,112]. Action potentials in the soma of nociceptors are followed by a long-duration after hyperpolarization where the membrane potential falls below the resting potential for a period of time[113–115]. The after hyperpolarization can be mediated by multiple channel types including voltage-gated K+ channels, Ca2+-activated K+ channels, and HCN (Hyperpolarization-activated cyclic nucleotide–gated) channels; the physiological role of the afterhyperpolarization phase is thought to be in regulating inter-spike intervals and limiting input from fast-firing nociceptors[116]. The central terminals of C fiber and Aδ fiber nociceptors innervate the superficial layers of the dorsal spinal cord or brainstem. For example, C fibers innervate the most superficial lamina I and II, whereas Aδ nociceptors innervate lamina I and V[117]. Once the action potential reaches the central terminal of the nociceptor in the spinal cord or brainstem, voltage-gated Ca2+ channels are activated, allowing Ca2+ influx that elicits release of classic neurotransmitters including glutamate that activates AMPA and NMDA receptors on spinal cord or brainstem neurons, and peptide neurotransmitters such as Substance P and CGRP that activate and modulate CNS neurons to relay the signal to toward higher brain centers[117].

III. Cutaneous peripheral neuropathies from common to rare

Peripheral neuropathy:

Peripheral neuropathies encompass a broad class of heterogeneous disorders that stem from direct damage, disease or impairment of peripheral sensory neuron terminals, axons or even pathology that originates within the DRG, such as altered Na_V channel function, that drives the cutaneous pain[21,118,119]. The perceptions associated can range from painful to insensate where skin is numb. Their underlying causes are multifarious, ranging from metabolic, traumatic, toxic, infectious and hereditary. Over 100 types of peripheral neuropathies exist, with each type having its own symptoms and prognosis. As a group, peripheral neuropathies are common, affecting 1–12% of individuals of all age and up to 30% of those 65 and older[120]. Peripheral neuropathies have variable etiologies and are classified according to the deficits they cause and the mechanisms that cause the neuropathy. Peripheral neuropathies can be generally classified into either mononeuropathy if a single peripheral nerve is affected, or polyneuropathy if multiple peripheral nerves are affected. Mononeuropathies and polyneuropathies can affect cutaneous sensory, motor and autonomic nerve fibers or a combination of these nerve types, and thereby elicit symptoms in skin, motor control or autonomic nervous system function. For the purposes of this review, we will focus on peripheral neuropathies that elicit cutaneous symptoms and deficits. Cutaneous symptoms can include sensory loss, hypersensation, pain or a mixture of all of these.

Mononeuropathies:

Physical injury or trauma from an accident is the most common cause of mononeuropathies. Additionally, prolonged pressure on a nerve, caused by extended periods of being sedentary such as lying in bed or sitting in a wheelchair or continuous, repetitive motions, can trigger a mononeuropathy. The most common mononeuropathy is carpal tunnel syndrome, which results from overuse and strain injury of the wrist. Carpel tunnel affects 4–5% of the general population ages 40–60 years and is more common in women[121–123]. It frequently occurs

in assembly-line workers who perform repetitive wrist motions (fish and meat processing factories report incidences up to 73%[124]) and those who work with computer keyboards (repetitive data entry) for prolonged periods of time. The median nerve courses through the carpel tunnel passageway in the wrist to innervate the thumb and first three fingers of the hand. Pinching or compressing the median nerve often results in numbness or unpleasant tingling percepts ("paresthesias"), burning and pain in the hand, and the pain can radiate proximally to the arm and shoulder. The pathophysiological mechanisms that cause the pain in carpel tunnel syndrome are complex and multifactorial. Entrapment of the nerve causes compression and traction which results in malfunction in the intraneural microcirculation, ischemic vascular injury and breakdown of the blood nerve barrier. This results in edema, hypoxia, lesions in the myelin and damage to the nerve axons. In addition to spontaneous pain, some mononeuropathies can manifest as allodynia (pain due to a stimulus that does not normally provoke pain) and hyperalgesia (enhanced sensitivity to a normally painful stimulus) to cutaneous applied stimuli; mechanical and thermal allodynia have been reported in animal models of traumatic neuropathy, as well as in patients suffering traumatic nerve injuries[125–127].

Small-fiber neuropathies:

Small-fiber neuropathy (SFN) is a disorder that selectively affects thinly myelinated Aδ and unmyelinated C fibers where the endings of fibers are damaged and die back (Wallerian degeneration) into the peripheral nerve trunk, where they continue to fire aberrantly[128]. Clinically SFN is characterized by neuropathic pain, most frequently described as burning, stabbing, shooting or prickling, but can also include numbness or tingling. It typically involves length-dependent or stocking-glove decrease in sensation to light-touch or pinprick[129,130]. SFN is typically associated with autoimmune diseases, diabetes and vitamin B deficiencies and toxicity (e.g. alcohol), although in over 50% of patients, no underlying etiology can be identified (idiopathic)[131]. As autonomic nerves also contain small fibers, some patients also experience autonomic dysfunction including altered sweating or thermoregulation, bowel dysfunction, dizziness or dry eyes or mouth. SFN severely affects patients quality of life. It can be diagnosed by skin punch biopsy and is evident by reduced or disrupted intraepidermal nerve fiber density. Recently, gain-of-function variants in the genes that encode for the $Na_V1.7$, $Na_V1.8$ and $Na_V1.9$ sodium channel subunits have been identified in patients with SFN[131].

Diabetic Neuropathies:

The most common cause of peripheral polyneuropathy is diabetic neuropathy. A staggering 463 million individuals world-wide have diabetes[132], making diabetes the largest global epidemic of the 21st century[105,133]. Diabetic neuropathy affects nearly 30% of individuals with diabetes over their lifespan[134,135]. If the rate of diabetes continues unabated, estimates indicate that among the 9.5 billion people living across the world in 2045, 10.9% of the population (>700 million individuals) will have diabetes and approximately half of these individuals will experience diabetic neuropathy[136]. Diabetic neuropathy occurs in both patients with type 1 diabetes (when the body's immune system attacks pancreatic beta cells which stop producing insulin) and type 2 diabetes (insufficiency in response to insulin and decreased insulin production). Diabetic neuropathies are heterogeneous in etiology where

the most common type is distal sensory neuropathy which affects the distal ends of large myelinated Aβ fibers, more often sensory than motor axons, and the next most common form is distal small fiber neuropathy which largely affects the unmyelinated C fibers and is associated with burning feet syndrome[137]. However, recent evidence suggests that the selective involvement of large or small fibers is uncommon and most patients with pain have a mixed-fiber polyneuropathy that affects Aβ, Aδ and C fibers similarly[138]. Distal sensory neuropathy is a symmetric, primarily sensory neuropathy that affects the distal regions of the lower limbs and can spread proximally. It is caused by high circulating blood glucose and triglyceride levels that, if not well controlled, over time result in damage to the long-projecting peripheral nerves in the feet and hands.

Several systemic metabolic disturbances cause diabetic neuropathy. The prolonged hyperglycemia results in excess glucose moving into the polyol pathway where it is converted to sorbitol and fructose, the accumulation of which leads to structural breakdown of nerve axons[139]. Furthermore, the excess glucose reacts with proteins, nucleotides and lipids resulting in production of advanced glycation end products which disrupt peripheral nerve metabolism and result in peripheral neuropathy[140]. Additionally, oxidative stress and the production of free radicals damage blood vessels, leading to ischemia in tissue around peripheral nerves, produce advanced glycation end products and collectively, damage the peripheral nerve fibers[141]. Diabetic neuropathy targets peripheral sensory axons, autonomic axons and over time, motor axons. As it progresses, the sensory nerve terminals degenerate or die back into the nerve trunk but the somata remain relatively unaffected anatomically. It is a length-dependent neuropathy whereby the longest sensory axons that innervate the skin of the distal limbs (such as skin of the toes) die back first, followed by loss of cutaneous innervation of more proximal limbs. This process results in the glove and stocking pattern of sensory deficits. The increased serum glucose also causes damage to a range of cells beyond neurons, including Schwann cells, endothelial cells, fibroblasts and keratinocytes (see below for more on keratinocytes and cutaneous nociception). For example, the supportive Schwann cells, which are intimately involved in peripheral nerve function and myelination, can be damaged by severe chronic hyperglycemia, leading to demyelination of peripheral nerves and sensory deficits[142].

Approximately 30–50% of patients with diabetic neuropathy develop neuropathic pain or parasthesias[105,143–145]; the remainder have insensate diabetic neuropathy. The most common symptoms of painful diabetic neuropathy include paresthesias (unpleasant, abnormal sensations), tingling, numbness, burning and lancinating pain in the feet and hands (distal “stocking-and-glove” distribution of deficits). Cutaneous hypersensitivity or hyperesthesia that results from contact with clothing or sheets at night is particularly bothersome to these patients and can interrupt their sleep quality, which can further amplify the pain sequela. Patients often have a mixture of cutaneous pain but also regions of sensory loss. Paradoxically, spontaneous pain can often even be perceived in numb, denervated skin (anesthetic dolorosa). A likely mechanistic explanation for this paradox is that hyperexcitable cutaneous afferent endings die back into the nerve trunk (but not all the way to the DRG somata) where they continue to fire spontaneously, perhaps via activation of aberrantly-expressed ion channels in the nerve ending as an “ectopic pacemaker”[146]. This mechanisms also accounts for Tinel’s sign when a nerve trunk is tapped and elicits

a tingling, “pins and needles” sensation. Mechanistically, the spontaneous burning pain is correlated with spontaneous activity in sensory neurons. The spontaneous activity may result from increased expression of $Na_v1.8$ channels in sensory neurons which will result in increased action potential transmission to the CNS and neuropathic pain[147]. Furthermore, the chronic hyperglycemia in diabetes induces changes in cellular oxidative status, increase in free radicals and oxidative damage to tissues. The changes in cellular oxidative status has been shown to modulate the activities of a variety of redox-sensitive TRP channels including TRPA1, TRPC5, TRPM2, TRPM7 and TRPV1[148]. Therefore, targeting redox TRPs has potential in treating painful diabetic neuropathy.

Conversely, insensate diabetic neuropathy is even more common than painful diabetic neuropathy[149]. While not painful, it can have equally or worse negative effects on quality of life because the numbness or loss of mechanical sensation in the feet can lead to dangerous, even life-threatening falls. Patients also often lose their sensation of heat and cold in the feet. Since patients can’t feel physical stimuli, blisters and calluses in the skin of the toes, feet and legs develop. A common and serious complication of diabetic neuropathy is cutaneous ulcers of the foot resulting in major decreases in quality of life due to the prolonged immobilization required to heal the ulcers. If inadequately treated, the ulcers can become infected, worsen to gangrene, result in foot deformation and ultimately require amputation. As the distal axons are affected first and most severely, insensate diabetic neuropathy is more common in individuals who are taller than average[150]. The causes underlying insensate neuropathy include demyelination and slowed conduction velocities of large sensory and motor conduction velocities, demyelination and depletion of small sensory nerves in the skin (and cornea). Although there can be regeneration of fibers in clusters[151], this is not sufficient to overcome the distal degeneration of fibers[149].

Chemotherapy-induced peripheral neuropathy (CIPN):

Many modern first-line chemotherapy drugs used to treat cancer cause both acute and chronic peripheral polyneuropathy (incidence ranges from 19–85%; [152,153]). Multiple classes of chemotherapeutics used include long established compounds platinum agents (e.g., oxaliplatin), taxanes (e.g., paclitaxel) and vinca alkaloids (e.g., vincristine). Newer compounds include bortezomid, eribulin and ixabepilone[154,155]. While each chemotherapeutic combats cancer cell proliferation through different anti-mitotic mechanisms, they all can induce peripheral neuropathies by inadvertently damaging sensory neurons[156]. While CIPN often resolves after cessation of treatment, approximately 30% of patients suffer from persistent neuropathic pain that affects their function and quality of life[157]. Further, the severity of acute neuropathy during treatment may limit the dose of chemotherapeutic that can be administered, or even require termination of treatment. As many common cancers such as breast, ovarian and colorectal are prevalent and are treated with chemotherapeutics, CIPN affects several million patients globally each year. Chronic CIPN can persist for months or years after cessation of treatment. Treatment options are extremely limited and often ineffective; there are currently no FDA approved therapeutics for prevention or treatment of CIPN[157].

CIPN presents as a glove and stocking peripheral neuropathy where patients describe symptoms including numbness, paresthesia, spontaneous pain, and cutaneous hypersensitivity to mechanical and cold stimuli. Severe cases can also involve loss of vibration sensation. The long axons of toes and feet are typically affected first, followed by impairment in the fingers and hands. Quantitative sensory testing in patients with CIPN has demonstrate sensory deficits in thermal and touch sensation, suggesting that CIPN is associated with deficits in multiple sensory afferent subtypes[158–160]. Changes in epidermal nerve fiber density in the skin inversely correlate with pain severity; the lowest nerve counts are found in the most painful, distal areas, while higher densities are in more proximal regions where there is numbness or no sensory deficit[161]. Recently, it was demonstrated using *ex vivo* skin nerve recording that chemotherapeutic treatment can directly sensitize Aδ and C fiber afferents to mechanical stimulation in mice[162]. Thus, direct sensitization of primary afferents may contribute to the development of CIPN mechanical allodynia and hyperalgesia.

Chemotherapeutic treatment also appears to affect sensory neuron mitochondrial function; both myelinated A fiber and C fiber peripheral axons and the dorsal root ganglia somata exhibit swollen, vacuolated mitochondria in rodent models of CIPN[163–167]. Mitochondrial dysfunction can increase the production of reactive oxygen species (ROS), which can damage sensory neurons and lead to the development of CIPN pain[162,168,169]. Additionally, a variety of alterations to neuronally expressed ion channels have been associated with CIPN pain, including several members of the TRP family of ion channels (see[170] for an in-depth review). For example, both antagonism of TRPV4 and TRPA1 inhibited paclitaxel-induced mechanical allodynia, while TRPA1 antagonism attenuate paclitaxel-induced cold allodynia[171]. Thus, treatments utilizing drugs that can reduce oxidative stress, as well as drugs that can modulate CIPN associated ion channels, may be useful for alleviating CIPN pain.

Post herpetic neuralgia (PHN): Infection: Example:

The varicella-zoster virus (VZV) is a highly virulent neurotropic virus that causes varicella (chickenpox) upon initial infection and, upon later reactivation, herpes zoster (shingles). Following the initial infection, the virus is transported retrogradely along the axons of sensory neurons in the skin to establish a latent infection within the dorsal root or trigeminal ganglia[172–174]. Because senescence of cellular immunity occurs as individuals advance in age, the virus can be reactivated, particularly after a stressful life event, transported anterogradely down axons to the skin and present as the painful blistering rash characteristic of herpes zoster[172,175]. While the pain associated with herpes zoster typically resolves within 2–4 weeks, a common complication (10% of patients) is the development of post herpetic neuralgia (PHN), a condition characterized by excruciating chronic neuropathic pain that can last at least 3 months after healing of the acute skin lesions[176]. This neuropathic pain is characterized as ongoing spontaneous burning or stabbing pain, as well as touch and thermal allodynia, which persist in the same location of the herpetic rash. The mechanisms underlying the development PHN pain are not fully understood, although one likely locus for the ongoing (ectopic) activity is the dorsa root ganglion[146]. A second likely locus is the endings of peripheral sensory neurons that die back from

the epidermis[146]. Additionally, peripheral sensitization of nociceptors by inflammation and direct viral damage, as well as the central reorganization of normally innocuous touch Aβ afferent input to dorsal horn pain pathways, have been proposed[177,178]. Rat models of post herpetic neuralgia have been developed and have sensory deficits, including long-lasting cutaneous mechanical allodynia and hyperalgesia, that is similar to those observed in patients with post herpetic neuralgia. However, rodents are not fully permissive hosts to VZV infection, which complicates small animal model studies of post herpetic neuralgia[179]. Skin nerve recordings in rodents or microneurography recordings in humans could reveal important information about how sensory afferent subtypes are sensitized in postherpetic neuralgia.

Hereditary neuropathy:

Hereditary neuropathies are a group of inherited disorders that affect the peripheral nervous system. They can affect any combination of motor, sensory and autonomic nerves. The most common type is Charcot-Marie-Tooth disease, a motor and sensory neuropathy that includes weakness or paralysis of the foot and lower leg muscles, inability to sense heat, cold and touch, shortening of muscles or tendons that causes cramping and pain. Another category of hereditary sensory neuropathies include channelopathies, a heterogeneous group of disorders resulting from the dysfunction of ion channels, most often involving mutations in transient receptor potential family members involved in stimulus transduction, or in voltage-gated channels involved in action potential transmission[180,181]. For example, Na_V 1.7 channels set the excitability of nociceptors, and either gain- or loss of function mutations profoundly affect pain sensation. Gain of function mutations underlie inherited erythromelalgia or paroxysmal extreme pain disorder whereas in contrast, loss of function mutations result in congenital insensitivity to pain[182].

Specific example of hereditary neuropathy: Fabry disease:

Fabry disease is an X-linked recessive lysosomal storage disorder caused by mutations the gene encoding for α-Galactosidase A (α-Gal A), a lysosomal hydrolase that catalyzes the removal of the terminal α-galactose residue from glycosylated molecules in the lysosome. Dysfunction or absence of α-Gal A causes accumulation of glycosylated products such as globotriaosylceramide (Gb3), lyso-globotriaosylceramide (lyso-Gb3). The glycosphingolipid products build up and form aggregates in lysosomes of many cell types[183,184]. Whereas many tissue types and organs are affected including kidney, heart, eye and gut, peripheral neurons are particularly susceptible to the substrate buildup since neurons do not replicate. The dorsal root ganglia neurons and their peripheral axons are a particular site of substrate buildup as they do not turnover and cannot reduce the substrate on their own. This results in small fiber neuropathy where nerve fibers are lost or damaged, resulting in sensory abnormalities and severe pain[185]. Pain begins in childhood and persists throughout life, disrupting work, daily activities and social interactions. Patients have high rates of anxiety and depression, which also decrease their quality of life. Treatment of the underlying disease with enzyme replacement therapy is costly, complicated to receive, and does not adequately alleviate patient's pain[186,187]. While Fabry Disease is categorized as a rare hereditary neuropathy, with a historic estimated prevalence of 1:40,000–117,000[188,189], recent newborn genetic screening suggests that it may be far more prevalent and as frequent

as 1:1,400[190]. Fabry patients experience a plethora of pain symptoms that affect the skin and that severely impact daily function. These include hypersensitivity to mechanical stimuli, heat and cold intolerance, and intense episodic pain episodes that can be triggered by environmental heat, fever or stress[185]. Dorsal root ganglia and axons of peripheral nerves are an epicenter of Fabry disease and may be an example of the DRG being the key driver of the pain pathology since DRGs accumulate Gb3 and lyso-Gb3 and exhibit profound sensitization[185146,191–193]. Peripheral neuropathy affects over 25% of patients with Fabry disease and is characterized by loss of small myelinated and unmyelinated fibers particularly in the lower extremities and skin of the feet[194–196]. The fiber loss is significantly greater in the skin than in the peripheral nerve trunk[195] and although this has not been directly documented for Fabry disease, this may be due to length-dependent dying back of the peripheral nerves into the nerve trunk, as occurs with diabetic neuropathy. Mechanistically, it is not yet known whether the accumulation of Gb3 leads to metabolic changes through mitochondrial dysfunction, whether long-term high concentrations of Gb3 have neurotoxic effects, or whether Gb3 accumulation can lead to activation of inflammatory states within the neuron that cause distal axon degeneration at the molecular level. Several sensory neuron expressed ion channels have been implicated in the pathology of Fabry peripheral neuropathy, including $Na_V1.7$, TRPV1, and inward-rectifying potassium channels[197,198]. In particular, it was recently demonstrated that TRPA1 is sensitized in Fabry rat sensory neurons and that antagonism of TRPA1 reduces *in vivo* mechanical hypersensitivity in Fabry rats[193]. Future studies into how sensory neuron ion channel function is altered in Fabry disease could lead to the discovery of novel therapeutic targets for treating Fabry pain.

IV. Beyond sensory neurons: are non-neuronal cells involved in cutaneous peripheral neuropathic pain?

Where are the peripheral sites of the dysfunction in cutaneous neuropathic pain? First, nociceptive sensory neurons are critical for the transduction of noxious stimuli under normal conditions, and the cutaneous terminals and axons of nociceptors become sensitized after tissue or nerve injury through a plethora of molecular and cellular mechanisms of nociceptor sensitization (reviewed in [117,199–207]). Second, large myelinated Aβ fibers that normally transduce non-painful tactile stimuli can become sensitized[17,19]. Third, the DRG itself is a key site for ectopic activity and sensitization[146,185,193]. Exciting translational studies of DRGs excised from patients with either chemotherapy-induced neuropathy pain or radicular/neuropathic pain demonstrate that ectopic (spontaneous) activity and hyperexcitability occurs in DRGs that innervate dermatomes associated with pain[208,209]. Future studies on human DRGs and other human tissues in the pain pathway will be invaluable for translating preclinically-identified pain targets to the clinic.

Growing evidence indicates that a number of non-neuronal cell types that are beneficial and protective under normal, healthy conditions can be dysregulated in pathological conditions and contribute to persistent cutaneous neuropathic pain by releasing cytokines, chemokines, growth factors and other biologically active small molecules. These non-neuronal cells include monocytes, macrophages, Schwann cells, satellite glial cells, astrocytes, mast cells and T cell lymphocytes, microglia and their intricate roles in sensory neuron sensitization

are reviewed elsewhere[210–212]. Moreover, what is often underappreciated is that substances circulating in blood can access and thereby sensitize sensory neurons and glial cells at the level of the DRG because the DRGs are densely vascularized with capillaries protected by a permeable blood-nerve barrier. In some pathological conditions associated with neuropathic pain, this blood-nerve barrier can be further disrupted through impaired peripheral pericyte function[31,213–215].

Here we will focus attention on keratinocytes. Keratinocytes are the predominant epidermal cell type, comprising 95% of the epidermis and forming the key barrier to external pathogens; vice versa, they are the key barrier to loss of water and solutes from within the body[216]. All subclasses of cutaneous primary afferent neurons, including nociceptors, terminate within or in close proximity to keratinocytes and keratinocytes are often the first point of contact between the body and external stimuli[33,217–220]. Thus, keratinocytes are in a prime position to modify the firing of cutaneous afferents. However, this intimate association between keratinocytes and sensory neurons, as well as the fact that keratinocytes and sensory neurons express many of the same sensory relevant receptors, complicates research efforts to dissect the effects of individually stimulating keratinocytes or sensory neurons in awake behaving animals. This problem was solved in a landmark study by the Caterina group, who re-expressed the TRPV1 capsaicin receptor specifically in the keratinocytes of TRPV1 global knockout mice, allowing for the selective stimulation of keratinocytes with capsaicin. Remarkably, application of capsaicin to the skin of these animals resulted nocifensive paw-attending responses[221]. The sole way this behavioral response is elicited is via capsaicin activation of keratinocytes, which subsequently transmits the signal to nociceptive afferent endings to convey the signal to the spinal cord. Successive studies utilizing optogenetics to selectively activate keratinocytes demonstrated that keratinocytes can shape the responses of primary afferents to cutaneously-applied stimuli[222]. Moreover, optogenetic inhibition of keratinocytes *in vivo* dampens responses to noxious mechanical and thermal stimuli[223,224].

Mechanistically, keratinocytes depolarize in response to mechanical stimuli and signal to sensory nerve endings by releasing ATP, which activates sensory neuron P2X4 channels[225]. This release of ATP from keratinocytes appears to be voltage-dependent and may occur through vesicular mechanisms and/or connexin hemichannels[223,226,227]. Recent evidence shows that keratinocyte and sensory neurons are more intimately associated than previously thought. Structurally, sensory neurons have been shown to tunnel directly through the keratinocyte cytoplasm and be entirely encapsulated by keratinocytes[220]. Exciting new data from Talagas and colleagues shows that human keratinocytes make en-passant synapse-like contacts with fine sensory neuron fibers (C and Aδ type) as the fibers course through the epidermis. These keratinocytes contain synaptic vesicles that express synaptophysin and synaptotagmin 1 and communicate with sensory neurons through SNARE-mediated vesicle release[228]. These findings are intriguing since keratinocytes turn over from basal stem cells to superficial stratum corneum every 40–56 days in humans[229] (8–10 days in mice[230]). This suggests that keratinocyte to sensory neuron associations are transient, perhaps with the keratinocyte sliding up along or around the sensory fiber as they migrate from the basal epithelial layer superficially[228]. The en passant synapse like contacts may allow keratinocytes to concentrate signaling molecules and modulators at the nerve membrane

and tune sensory detection[228]. Therefore, the long-used textbook terminology of “free nerve endings” is not likely correct, as many cutaneous afferent fibers are connected to keratinocytes[228] or Schwann cells[231]. All together, these exciting data indicate that keratinocytes are essential peripheral participants in the transmission of acute noxious cutaneous mechanical, thermal and chemical stimuli to the CNS.

Keratinocytes are the first site of cutaneous injury and are anatomically well positioned at the cellular and tissue levels to modulate signaling in sensory neuron fibers. A key question is whether keratinocytes contribute to the cutaneous hypersensitivity, allodynia and pain following skin injuries. This exciting hypothesis remains to be tested but the potential for keratinocytes involvement in painful skin is high. Indeed, alterations in keratinocyte function and signaling are known to contribute to inflammatory skin disorders such as dermatitis and psoriasis[232,233]. Keratinocytes can function as primary transducers of itch through the ion channel TRPV4; TRPV4 expression in skin keratinocytes is required for histaminergic itch and cholestatic itch induced by the lipid lysophosphatidylcholine[234,235]Keratinocyte-expressed TRPV4 has also been implicated in inflammatory sunburn pain, as selective knockout of TRPV4 from keratinocytes protects against the development of UVB induced mechanical and thermal hyperalgesia[236]. Furthermore, keratinocytes from patients with fibromyalgia display increased expression of the pain mediators interleukin-10 (IL-10) and ephrin receptor-A4 (EPHA4)[237]. Keratinocytes may also contribute to persistent neuropathic pain, as human keratinocytes transplanted into a ligated and transected peripheral nerve in rodents lead to hyperexcitability of sensory neurons and chronic pain behavior *in vivo*[238]. Additionally, “sensitive skin syndrome” is a clinical condition that often occurs with small fiber neuropathies and is characterized by the occurrence of unpleasant sensations such as burning, stinging, tingling, pricking or itching in response to innocuous thermal, physical or chemical stimuli[239]. Paradoxically, in small fiber neuropathies, the density of fine nerve endings is decreased indicating that factors other than increased nerve ending density mediate the cutaneous pain. Intriguingly, in skin from patients with small fiber neuropathy, keratinocytes associated with fine nerve endings express a higher density of synaptic vesicles, suggesting that these en passant synapses between keratinocyte and nerve membranes might possibly contribute to hypersensitivity in cutaneous painful conditions by tuning or amplifying nerve ending responsiveness[228]. Additionally, Keratinocytes from patients with neuropathic pain have changes in gene expression profiles of signaling molecules and ion channels known to be involved in pain conditions. For example, keratinocytes from patients with complex regional pain syndrome and post-herpetic neuralgia exhibit increased expression of the pro-algesic factor CGRP[240] and a number of voltage-gated sodium channels including $Na_V1.1$, $Na_V1.2$, $Na_V1.6$, $Na_V1.7$, and $Na_V1.8$[241]. In patients with SFN, the density of synaptic vesicles in keratinocytes is increased[228], suggesting that despite the decreased density of nerve endings in SFN, the enhanced synaptic-like contacts may contribute to the cutaneous pain in this neuropathy. Furthermore, keratinocytes from patients with SFN display increased expression of interleukin-8, C-X-C motif chemokine 3, endothelin receptor type A, NTN1 and transforming growth factor-β1[237,242]. These data suggest that keratinocytes might be peripheral drivers of nociceptor signaling in injury states, potentially through increased keratinocyte transduction

of cutaneous stimuli and through the release of neuroactive factors that modulate nociceptor action potential firing (Figure 1).

Keratinocytes may not be the only cutaneous cell capable of modulating nociceptor firing. A recent study has shown that cutaneous nociceptive C fiber endings, long thought to be “free” unencapsulated nerve endings, are actually ensheathed by a novel type of glial cell called “nociceptive Schwann cells,” which form a mesh-like sensory organ that extends from the dermis into the epidermis. These Schwann cells appear to participate in detecting noxious stimuli applied to the skin and conveying nociceptive signals to the sensory terminals of nociceptors[231]. Like keratinocytes, nociceptive Schwann cells may be sensitized following tissue injury and release factors that modulate nociceptor firing, enhancing the perception of allodynia and hyperalgesia in cutaneous pain conditions.

V. The Horizon: What can we see and seek in the future?

For many neuropathic pain states, there are few effective treatments, leading to suffering and low quality of life in patients. Developing better therapeutics will require increased understanding of how peripheral and central pain circuits are altered in neuropathic injury. While current animal models of neuropathic pain are useful for studying evoked pain (allodynia and hyperalgesia), many patients primarily complain of spontaneous shooting or burning pains, as well as paresthesia like “pins and needles” sensations. The development of better “face-valid” and quantitative assays for measuring spontaneous pain in peripheral neuropathies would aid in investigating the mechanisms behind these devastating symptoms. Some assays that may be useful for studying spontaneous neuropathic pain include conditioned place preference, measurements of facial grimace, and automated behavior recognition software, such as HomeCageScan, that can monitor animals for ongoing pain behaviors[243–245]. The development of more clever behavioral assays that evaluate spontaneous pain in rodents would boost the field. Additionally, there are still relatively few studies that employ single nerve fiber recordings of identified afferent subtypes, either through *ex* or *in vivo* skin-nerve fiber recordings in animal models of cutaneous neuropathic pain, or microneurography studies in human patients suffering from peripheral neuropathies[17,110,246–251]. Future research utilizing these techniques could provide critical information regarding how specific fiber types are modulated in neuropathic injury in an *in vivo* or *ex vivo* setting.

Future directions must investigate the roles of keratinocytes, as well as nociceptive Schwann cells, in cutaneous pain and neuropathic disease states. This investigation could be done in a variety of animal models of inflammatory and neuropathic pain. Pairing these animal models with optogenetic, chemogenetic, and gene editing techniques that enable the selective activation and modulation of keratinocytes, nociceptive Schwann cells, or sensory neurons, could potentially reveal how these cutaneous cell types function together to encode noxious stimuli to the CNS in painful disease states. Research into bidirectional, or even tridirectional, signaling between keratinocytes, nocifensive Schwann cells, and sensory neurons, could reveal novel signaling pathways that drive cutaneous pain. The ability to garner human skin tissue samples provides an easy translational advantage to the field since human keratinocytes, Schwann cells, and other non-neuronal cell types can be

directly investigated[220,224]. Transcriptomics analyses of keratinocytes, Schwann cells and other skin cell types can be performed on skin samples from human patients, potentially patients with a variety of peripheral neuropathies. The development of iPSC nociceptors, keratinocytes and nociceptive Schwann cells from stem cells derived from patients with cutaneous neuropathies is an exciting reality[252–255]. *In vitro* co-cultures of animal and/or human skin cells and sensory neurons could reveal important signaling interactions between these cell types, perhaps even how these interactions are altered upon *in vitro* exposure to neuropathy-inducing agents like paclitaxel. An exciting therapeutic opportunity is the possibility to develop novel, topically-administered cutaneous therapeutics that affect skin cells and sensory endings only while avoiding CNS side effects. For example, lidocaine gels and patches target voltage-gated Na_V channels and block cutaneous nerves from firing action potentials; when applied to painful skin, these are routinely used to treat postherpetic cutaneous neuropathy. Additional topical patches, gels that rapidly penetrate skin and even injectable or micro dermal abrasion applied analgesics for painful skin could be developed that target novel keratinocyte pain targets. For example, Piezo1 and TRPV4 are extensively expressed in keratinocytes and involved in cutaneous sensitization. Perhaps these channels could be topically targeted to alleviate mechanical pain without anesthetizing the affected skin from all sensation.

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Highlights:

- Cutaneous nociceptors exist in a plethora of diverse subtypes based on their anatomy, sensitivity to external and internal stimuli, molecular transducers and receptors, and signaling molecules within.
- Many peripheral neuropathies have prominent cutaneous deficits including pain, sensory loss, hypersensation, or a mixture of deficits.
- The focus of this review is on how cutaneous nociception (pain perceived from the skin) is altered following diseases that affect peripheral nerves.
- We discuss mechanisms underlying acquired neuropathies (small-fiber neuropathies, diabetic neuropathy, chemotherapy-induced peripheral neuropathy, post herpetic neuralgia) and hereditary neuropathies (channelopathies, Fabry disease).
- Sensory neurons are not the sole transduction cell type in skin. Keratinocytes and nociceptive Schwann cells are critical players in somatosensation and pain transduction. Much remains to be discovered about the roles of these non-neuronal skin cells in painful and insensate peripheral neuropathies.

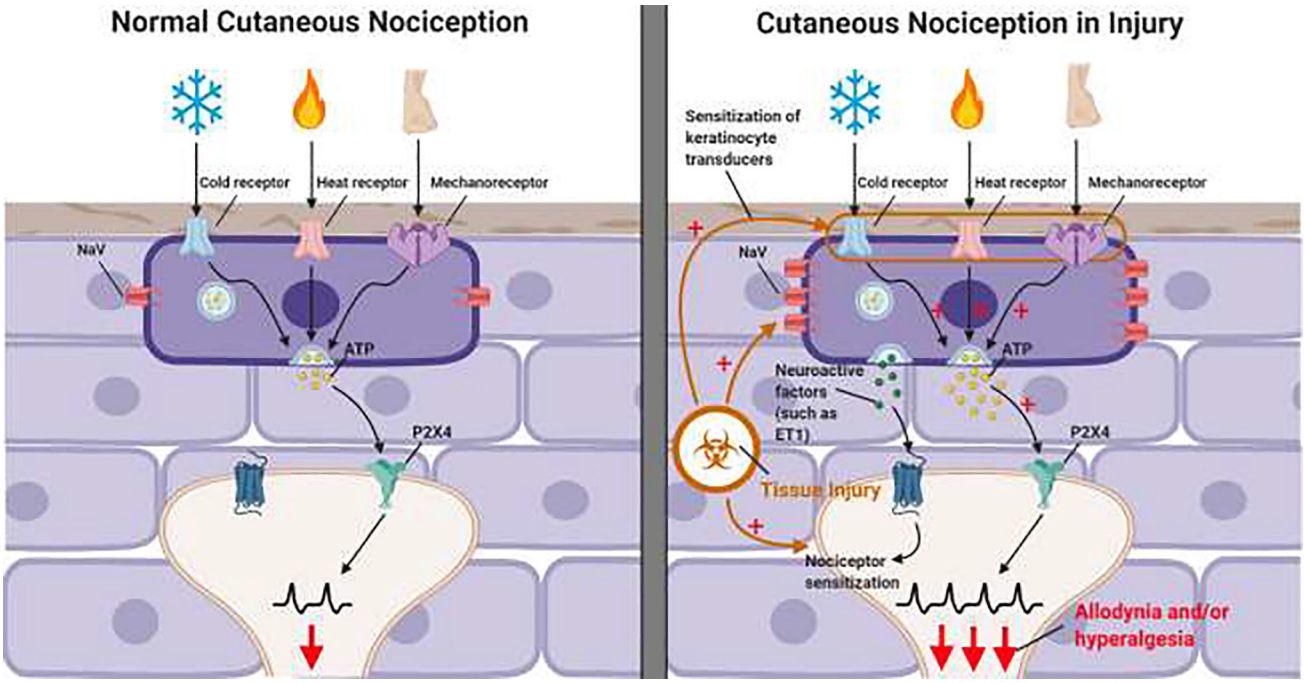

Figure 1.

Under normal healthy conditions, keratinocytes contribute to the detection of innocuous and noxious cutaneously applied cold, heat, and mechanical stimuli. This is mediated by keratinocyte to sensory neuron ATP-P2X4 signaling but also likely involves other unidentified signaling pathways[224,256]. The molecular machinery that enables keratinocytes to detect heat, cold and mechanical stimuli have not been definitively identified, though keratinocytes do express the cold receptor TRPM8, the warm and heat activated receptors TRPV1, TRPV3 and TRPV4, as well as the mechanoreceptor Piezo[145,47,257–259]. Keratinocyte to nociceptor signaling may be enhanced following injury, contributing to the sensitization of nociceptors and the development of allodynia and hyperalgesia following skin injury. A potential mechanism through which keratinocytes could enhance nociception is through the injury induced sensitization of keratinocyte expressed receptors. Keratinocyte also express a variety of voltage gated sodium channels (NaV) and the expression of many of these are upregulated in states of neuropathic injury[241]. Sensitization of keratinocyte expressed ion channels could lead to increased activation of keratinocytes in response to cutaneous applied stimuli and a subsequent increase in the release of ATP and other keratinocyte-expressed neuroactive factors onto nociceptor terminals. Figure 1 *was Created with* BioRender.com