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Commentary

The prickly, stressful business of burn pain

Kristofer K. Rau[a], R. Christopher Spears[b], Jeffrey C. Petruska[c,d,*]

[a] University of Louisville, Dept. of Anesthesiology, USA
[b] University of Louisville, School of Medicine, USA
[c] University of Louisville, Dept. of Anatomical Sciences and Neurobiology, USA
[d] University of Louisville, Kentucky Spinal Cord Injury Research Center, Dept. of Neurological Surgery, USA

For essentially all of the millions of people around the world who are treated for burns each year, pain and other sensory pathologies are an issue, often becoming an unwelcome partner in daily life. In spite of the pressing need and ongoing search, clinical options for treating these sensory pathologies are still quite limited and often ineffective. Tan and colleagues have broken new ground in this quest by identifying an important response to burn by neurons that are well-positioned to act as mediators of many of these sensory pathologies — a dramatic Rac1-mediated plasticity of dendritic spines of the spinal wide-dynamic-range (WDR) neurons. Intriguingly, this plasticity closely resembles the WDR neuron response to nerve injuries which result in pain. We consider their data within a potentially unifying theme: that damage of peripheral tissues, be it from burn or other causes, may induce a response in the nervous system akin to that induced by nerve injury and cellular stress, and that both burn-injured and non-injured primary afferents contribute to the overall outcome, though may do so differently. This proposition could impact how we approach the etiology, treatment, and mechanistic examination of pain induced by burn and other tissue damage.

Over 500,000 individuals present with burn injuries to Emergency Departments in the US each year, and approximately 40,000 of these are hospitalized. Children have the highest burn risk, and approximately 80% of burns in young children are scald-type burns, with flame-type burns gaining prevalence in children over 6 years old (Bessey and Board, 2012; Lloyd et al., 2012). This is a mere fraction of the incidence and severity of the issue world-wide. While the impact on quality of life is paramount, the impact economically is also significant. In Germany an estimated 270,000 EUR per burn-patient per year are spent on burn sequelae, including pain, exclusive of the cost of acute treatment (Mirastschijski et al., 2013). The prevalence of burn and its impact on individuals and society drives the many efforts to develop treatments for the burn wound and the many associated conditions.

Pain goes hand-in-hand with burn in the acute setting, and the prevalence of continuing pain and sensory pathologies is high, increasing with severity of the burn. An estimated 36% of extensively burned patients suffer from chronic pain and 71% of extensively-burned patients experience some form of notable abnormal sensation (Browne et al., 2011; Carrougher et al., 2013; Falder et al., 2009; Malenfant et al., 1996; Summer et al., 2007). These can take many forms (e.g., itching, burning, dysesthetic, dull, etc.) and be spontaneous and/or stimulus evoked. These are often resistant to much of the usual arsenal of analgesic treatments including anti-inflammatory agents. Part of the effort to develop new and more effective treatments is the necessary characterization of the responses of the many tissues and systems affected by burn and the identification of contributing mechanisms.

The effects of thermal injury to skin will vary with the extent of tissue destruction, which is a function of the intensity of the heat source, the duration of contact, and the thickness of the skin, regardless of the cause of the burn wound, and are what defines the different burn-degrees (Herndon, 2002). Superficial partial thickness burns involve damage to the epidermis and superficial portions of the dermis, causing minor skin alterations such as erythema and edema, which elevates the wound surface from the surrounding uninjured tissue. Deep partial thickness burns result in the loss of sensation, though deep pressure receptors remain intact, and there is necrosis in both the epidermal and dermal layers. Intercellular edema develops, resulting in the detachment of basal cells from the epidermal basement membrane and the formation of subepidermal bulla. Progressive eosinophilia and fusion of collagen fibers occur as a result of the dermal injury, and blood vessels become occluded due to the formation of thrombi. Full thickness burns render the wound insensate to all but deep pressure stimuli. Cells are initially still viable deep and peripheral to the central affected area, but platelet microthrombus formation, vasoconstriction, and the rigidity of heat-damaged erythrocytes result in ischemia. Coagulative necrosis eventually extends through the entire thickness of the epidermis and dermis, usually extending into the subcutaneous layer, leading to eschar (slough of dead tissue) (Herndon, 2002). There is also usually edema present at the junction between coagulated and viable tissue (Teplitz, 1979). Vasodilation occurs peripheral to the necrotic tissue as a result of the inflammatory response, and cells in this zone of hyperemia are minimally injured and usually show full recovery (Herndon, 2002; Jackson, 1953; Koenig, 1965). Burn eschar results in tissue which is essentially analogous to an open wound and lacks nearly all of the normal functions of healthy skin, especially the barrier function. Rather than protecting from infection, this devitalized tissue may actually provide a medium for bacterial growth (Pruitt and Moncrief, 1967).

* Corresponding author at: University of Louisville, Dept. of Anatomical Sciences and Neurobiology, 511 S. Floyd St., Louisville, KY 40205, USA. Fax: +1 502 852 5148.
E-mail address: j.petruska@louisville.edu (J.C. Petruska).

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Much of the adverse alterations to skin tissue as a result of thermal injury are facilitated by inflammation and edema. Burn injury byproducts stimulate phospholipase A activity which fuels the arachidonic acid cascade (Arturson, 1985). Various prostanoids and leukotrienes are produced, facilitating inflammation responses such as increased capillary permeability and chemotaxis of neutrophils and other inflammatory cells. Edema diminishes oxygen and nutrient delivery to the already ischemic tissue, while neutrophils further damage the tissue via the release of oxygen free radicals. Histamine, released due to mast cell damage, not only contributes to the massive amount of edema seen in burn wounds, but also stimulates the production of oxygen free radicals. These free radicals not only directly inflict damage on cell membranes, but also stimulate the activity of phospholipase A, further exacerbating the subsequent inflammatory response (Herndon, 2002). Therefore, burn wound damage is mediated both by direct thermal injury and the inflammatory response, both of which sensitize the surviving sensory axons innervating the peri-eschar tissue, and certainly must impact the neurons with axons resident in the burned tissue, though the nature of this impact is unclear.

Burns affect more than just the skin, however. Significant pathologies and derangements occur in the acute- and long-term after burns, particularly the more severe burns which degrade barrier functions. These are well documented across organs and essentially every system and are similar to the fallout from traumatic injuries (e.g., Brandfellner et al., 2013). For example, fluid loss resulting from disruption of the fluid barrier results in a decreased bloodflow to and from the gastric mucosa. This flow, which normally helps remove gastric acids but is decreased after burn, can result in sloughing of the gastric mucosa or an ulcer in the proximal duodenum due to excessive levels of acid in the stomach (Curling ulcer). This in turn, if not treated properly, may lead to even further complications (e.g., iron-deficiency anemia). Excessive heat loss due to skin breakdown may increase the basal metabolic rate, in turn increasing caloric demand (hypermetabolic syndrome). Further, there is a post-burn insulin resistance (e.g., Cree and Wolfe, 2008), a significant hepatic response to thermal injury (e.g., Jeschke, 2009), and even altered intestinal permeability leading to a variety of sequelae (e.g., Othman et al., 2008).

Many different cell types present in the different systems are affected by a skin burn, but the nervous system is unique in that single neurons contact multiple tissues simultaneously. Thus, any influence the skin exerts on the sensory neurons innervating it can be reflected in other tissues, particularly the sensory ganglion and the spinal cord, and vice-versa — the peripheral neurons can be affected by events in numerous other tissues. Nervous system-related post-burn issues are not limited to the peripheral nervous system, but are numerous and include blood–nerve-barrier vascular issues (Chen et al., 2011), late-emerging widespread nerve compression from compartment syndrome (Ferguson et al., 2010), and with sufficiently-severe burns there is blood–brain-barrier breakdown and CNS inflammation (Flierl et al., 2009).

As the nervous system is integrated throughout all of the various tissues which are directly and indirectly affected by burns, and can be influenced by the status of these tissues, the number of sites where the effects of burns can influence the nervous system is vast. There are likely indirect humeral routes of influence, such as changes in metabolism, kidney and liver function, cardiovascular and respiratory issues, to name a few (cited throughout). This concept is schematized in Fig. 1. This leads to the broad question of where and how burn affects the nervous system and ultimately leads to the pathological pain conditions. The difficult and detailed work by Tan et al. (2013) to reveal significant changes to spinal neurons offers some insight into potential sites of interaction.

Tan et al. used a second-degree burn model which produces well-characterized pain in rat (Chang and Waxman, 2010; Chang et al., 2010). Spinal wide-dynamic range (WDR) neurons showed hyperexcitability in response to peripheral stimuli. WDR neurons also showed

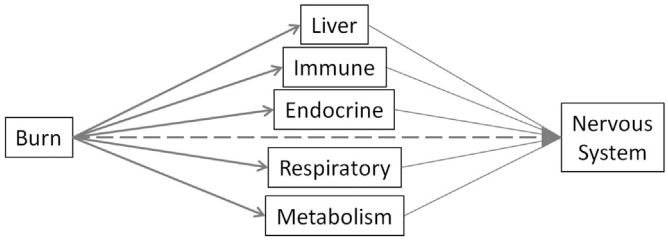

Fig. 1. Schematic of a variety of tissues affected by burn. Burn-induced tissue damage can affect the nervous system through a wide variety of routes.

changes in dendritic spine shape, density, and distribution. Burn-induced pain-behaviors and dendritic spine changes were largely prevented by administration of NSC23766 (used as an inhibitor of Rac-1). The work breaks new ground by identifying novel cellular changes induced by burn and which are well-positioned to underlie aspects of burn-induced pain, and by identifying Rac-1-mediated mechanisms as a major contributor to these changes.

Although the possible sites through which burn sequelae can influence the CNS are many, damage to the skin directly affects the sensory and sympathetic axons innervating that skin, as well as in the neighboring non-burned skin, even if the underlying peripheral nerve itself is undamaged by the burn (e.g., Coert, 2010). Typically with more severe burns axonal profiles are absent from the directly-burned skin. One day after thermal injury, no innervation is seen within the burn. Although neither burned skin nor its innervation may ever return to the pre-injury condition (Altun et al., 2001), evidence suggests that about 4 weeks after thermal injuries similar to those used by Tan et al. the skin and its innervation (assessed anatomically) resembles the pre-injury condition. Four weeks after thermal injury, nerve trunks run perpendicularly to the surface of the scar with a “characteristically varicose appearance”, and at 4 months after burn there was no significant difference in axon counts between burned and control skin, though in some cases there may have been an increase in the density of axons in the burned skin (Ward et al., 1998). No studies conducted thus far have determined whether the axonal ingrowth is from regenerating axons that had been injured by the burn or from intact axons innervating neighboring skin which reinnervated the recovered skin by collateral sprouting (Blais et al., 2013; Diamond et al., 1987; Diamond et al., 1992a, 1992b; Gloster and Diamond, 1992), though it is most likely both. This concept is schematized in Fig. 2.

It is important to note that in recent articles by Tan et al. (2011, 2012, 2013) and others (Gao et al., 2010; Shields et al., 2012; Summer et al., 2008; Xu C et al., 2009, Xu J et al., 2009), the models used are likely to induce a mixed population of dorsal root ganglion (DRG) sensory neurons projecting to similar spinal cord locations — those DRG neurons that are directly injured by the nerve constriction, diabetes model, or burn, and those that are not overtly injured yet can still be affected by the injury to neighboring axons/tissue (Fig. 2). This assumes that burn indeed injures or stresses some sensory neurons, presumably those innervating at least the superficial levels of the burned skin. This important assumption has yet to be empirically-demonstrated, but is likely the case. Evidence for this comes from other skin injury models (Hill et al., 2010) and what has been shown for diabetic neuropathic pain. In that model the temporal profile of dendritic spine remodeling occurred in accord with the development of allodynia (Tan et al., 2012) and appears also to occur in accord with the induction of the injury/stress marker ATF3 in sensory neurons in this model (Wright et al., 2004).

It is currently not clear if the effects on the spinal WDR neurons come about (directly or indirectly) through the DRG neurons innervating the burned skin (i.e., presumably injured) or those innervating the peri-burn skin (i.e., presumably non-injured), or some other route. Indeed, if burn induces axonal injury that sufficiently mimics nerve injury then burn may affect both — direct injury induces changes