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PERSPECTIVE

Interactions of primary insult biomechanics and secondary cascades in spinal cord injury: implications for therapy

The complex and variable nature of traumatic spinal cord injury (SCI) presents a unique challenge for translational research. SCI is not bound by any demographic nor is it limited to specific injury biomechanics. Clinically, traumatic SCI results from any combination of mechanical trauma. This heterogeneity is at odds with the efforts of researchers who strive to minimize extraneous variables and create consistent injuries to derive reproducible results. Researchers primarily utilize animal models with specific injury modalities that inflict targeted spinal cord damage. Regardless of the intention or particular injury biomechanics, each model is ultimately classified under the umbrella of "SCI". Here we share perspectives on how different SCI biomechanics can affect injury progression and the implications of these differences both in the laboratory and in the clinic.

SCI can occur abruptly due to motor vehicle accidents, falls, and sport injuries, or it can occur gradually as a result of spinal stenosis, osteoarthritis, abscess, and tumors. Acute traumatic SCI encompasses a variety of biomechanical injuries (*e.g.*, contusion, compression, laceration) and a wide range of injury severities. Despite heterogeneity, the primary mechanical insult creates acute damage at the injury epicenter and triggers a cascade of secondary injury events including inflammation, apoptosis, oxidative stress/lipid peroxidation, and demyelination. These primary and secondary injury events lead to progressive tissue loss and dysfunction.

It is well documented that primary insult biomechanics influence the overall pathophysiology of SCI. For example, the impact severity of contusive injury to the spinal cord correlates with anatomical and functional recovery. Graded increases in contusion impact force, or contusion-induced tissue displacement, result in graded decreases in tissue sparing and functional recovery (Basso et al., 1996; Ghasemlou et al., 2005). The degree of spinal cord compression at the time of injury similarly determines outcomes, but compression depth causes unique stepwise decreases in tissue sparing and function (Gruner et al., 1996). Thus, the severity of contusion and compression injuries plays a key role in determining overall anatomical and functional outcomes in SCI.

The actual mode of injury is also a key regulator of secondary cascades. Chen et al. (2016) demonstrated that other clinically relevant injuries differentially affect histological and behavioral outcomes. They observed distinct patterns with regards to cavity shape and anatomical location of myelin and neural damage associated with contusion, distraction, or displacement SCI (Chen et al., 2016). Similarly, by altering compression after contusion injury, we found that regardless of the contusion impact force, compression decreases functional and anatomical recovery (Orr et al., 2017). Interestingly, our investigation also revealed a compression-dependent premature cessation of functional recovery, thereby identifying a unique feature of the residual compression injury modality regardless of overall contusion or injury severity (Orr et al., 2017). These studies highlight the importance the mode of injury plays in pathophysiological outcomes from SCI. The field has come to understand that distinct primary insult biomechanics lead to distinct functional and anatomical outcomes, but ongoing research is still uncovering highly specific relationships among biomechanical modalities.

The overall outcomes of SCI are not solely dependent on primary insult biomechanics. The body reacts to SCI with complex cellular and extracellular cascades that serve protective and reparative roles but also exacerbate damage and contribute to secondary injury. The mediators of this secondary injury after SCI have been reviewed extensively (for a recent and comprehensive review see Oyinbo, 2011). Briefly, resident glial cells and non-resident immune cells and fibroblasts activate, proliferate, and migrate to the injury site. A glial scar surrounds the lesion epicenter, which contains a fibrous scar filled with fibroblasts, immune cells, and extracellular matrix proteins. The scars form a barrier that prevents axonal regrowth through the lesion but also helps sequester toxic substances and salvage penumbral tissues. Additionally, cells within the scars influence the microenvironment through the production of chemorepellants, chemoattractants, and trophic factors. Meanwhile, activated immune cells, including endogenous microglia and peripherally derived neutrophils and macrophages, adopt a spectrum of phenotypes, which serve a variety of roles. This includes debris clearance and toxic and trophic factor release that further influence the cellular and extracellular microenvironment (Gensel and Zhang, 2015). Collectively, secondary injury depends on a multifaceted balance of cellular responses and contributions to a dynamic SCI microenvironment, which profoundly impacts the overall pathophysiology of SCI.

We consider the primary insult unavoidable due to its silent or accidental development. However, each aspect of the secondary injury provides a potential therapeutic target either as a lynchpin in damage progression or as a tool to promote regeneration. While it is necessary to understand the cause and effect relationship between the primary insult and the secondary cascades to fully realize the benefit of translational therapies, we are only beginning to understand these relationships. Here we consider one example, residual compression following a contusion injury, to provide insight into the extent to which primary insult biomechanics influence secondary cascades and the final SCI outcomes.

Residual compression alters the acute SCI microenvironment. For example, compression increases hemorrhage, thus, altering the fluid dynamics of the contused spinal cord (Sjovold et al., 2013). Additionally, residual compression alters acute hypoxia and cellular bioenergetics with significantly higher lactate:pyruvate ratios compared to contusion alone, likely due to hemorrhage-induced ischemia (Okon et al., 2013). We observed that residual compression drives a potentially destructive inflammatory response. As late as two weeks after the initial insult, acute residual compression (for 20 seconds) at the time of contusion SCI increased the relative ratio of pathological/pro-inflammatory *vs.* purportedly reparative microglia and macrophages compared to contusion alone (Orr et al., 2017). Together, these findings indicate that the addition of compression to the contusion SCI results in different microenvironments and downstream secondary cascades including, but not limited to, fluid dynamics, cellular bioenergetics, and inflammation (**Figure 1**). Further, we observed that acute residual compression increases anatomical and functional deficits and causes premature cessation of functional recovery (Orr et al., 2017). Collectively, these findings support the notion that primary SCI biomechanics have distinct effects on downstream, secondary events that significantly impact SCI recovery (**Figure 1**). Interestingly, similar injury mode-specific effects have been

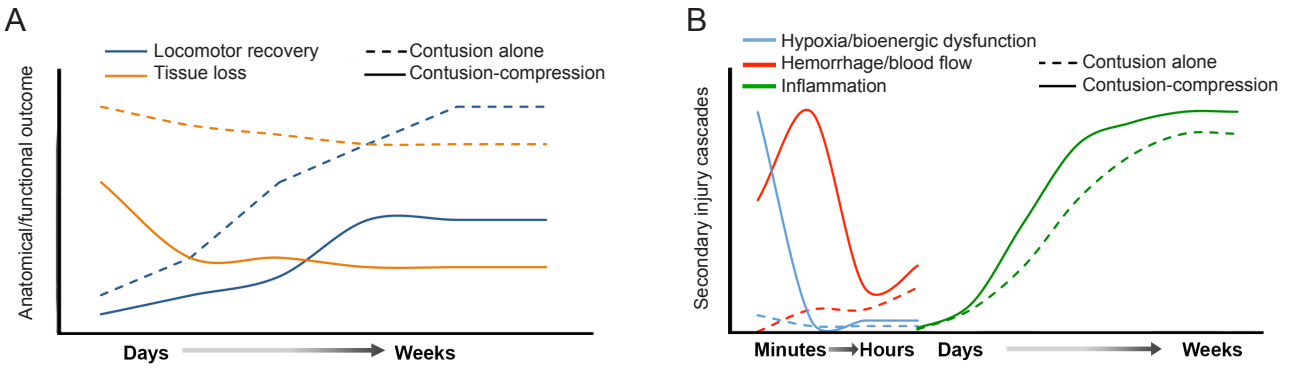

Figure 1 Primary spinal cord injury (SCI) biomechanics influence anatomical and functional recovery coincident with altered secondary injury cascades that serve as therapeutic targets.
Temporal associations of (A) anatomical/functional outcomes and (B) mediators of secondary injury after contusion SCI with or without residual compression illustrate the effect primary injury has on downstream events. Therapies may be differentially efficacious based on spinal cord injury modality. Values on the vertical axis represent relative changes and are not to scale. Curves were generated using data from Orr et al., (2017); Okon et al., (2013); Sjovold et al., (2013).

observed after contusion, dislocation, and distraction primary spinal cord injuries (Choo et al., 2008). Therefore, the primary mode of SCI may determine the efficacy of treatments targeting fluid dynamics, cellular bioenergetics, inflammation, or other secondary cascades.

Several lines of evidence support an intimate link between the primary insult biomechanics and secondary cascades that impact overall outcomes of SCI. The implications of these relationships should be considered both in the lab and in the clinic. Strengthening our understanding of how injury biomechanics affect secondary cascades will enable researchers to draw more accurate conclusions between studies that utilize different injury modalities and will improve future research designs by properly pairing injuries to research questions. Clinicians will likewise benefit by improving their ability to assess and predict SCI progression, potentially enabling personalized treatment based on the type of SCI suffered. Ultimately, understanding how primary insult biomechanics affect secondary cascades and overall outcomes of SCI is achievable by probing past literature and consciously designing future studies. Such pursuits may surmount the challenge of SCI heterogeneity thereby improving the efficacy of translational research and future therapies for the SCI community.

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