Beyond Neurons: Evidence That Immune and Glial Cells Contribute to Pathological Pain States

Extracts from the above:

Based on such insights into neuronal changes in response to traumatic nerve injury, a variety of drugs have been tested in hopes of controlling chronic neuropathic pain. None ends the pain. Some work partially in some patients. Even when combinations of drugs are given that target different putative causes of the pain, they fail.

So, why do the therapies fail? Are conclusions drawn from the animal models wrong? Alternatively, could another critical factor influence the creation and maintenance of chronic pain?

One potentially critical factor that has been lacking until very recently has been an appreciation for the role of the immune system in pathological pain. With neuropathy as an example, it has been estimated that approximately one-half of the clinical cases are associated with infection/inflammation of peripheral nerves rather than nerve trauma.

Within the past few years, an explosion of research has delineated the dynamic and powerful effects of immune activation on pain.

From this work, it is now clear that each of these sites is powerfully modulated by the activation of peripheral immune cells and/or immune-like glial cells and that immune activation may indeed be a critical factor in the creation and maintenance of pathological pain. The general argument will be that although immune processes are highly adaptive when directed against pathogens or cancer cells, they can also come to be directed against peripheral nerves, dorsal root ganglia, and dorsal roots, with pathological pain as a result.

Peripheral nerves are the origin of almost all forms of neuropathic pain. The argument to be developed is that an immune attack of peripheral nerves, or even simply immune activation near peripheral nerves, is sufficient to increase peripheral nerve hyperexcitability and/or damage to be considered a significant contributor to the neuropathic pain observed.

This review has approached immune interactions with pain systems at multiple levels. It described how immune cells are a natural and inextricable part of *1*) skin, where nerves form their terminal receptive fields and express receptors for immune products;*2*) peripheral nerves, where multiple types of immune cells are in constant intimate contact with the nerve fibres and can midaxonally alter nerve anatomy and physiology; *3*) dorsal root ganglia, where they ensheath and modulate every neuronal cell body; and *4*) spinal cord, where they form dynamic networks well suited for maintaining and spreading excitation. This review has also attempted to define how immune activation can damage peripheral nerves and enhance their excitability. Finally, it illustrated how such immune-derived changes might participate in the etiology and symptomatology of various pathological pain states.

potentially has profound implications for the understanding of how such pain states occur. Equally profound are the implications that immune involvement poses for the future development of drug therapies aimed at controlling neuropathic pain. Given that all available pain therapies exclusively target neurons, the recognition of peripheral and central immune cell involvement in neuropathic pain of diverse etiologies offers hope for whole new approaches to pain control.

The last major point is that investigation of immune involvement in neuropathic pain is in its infancy. Many more immune cells and immune-derived substances are implicated in the etiology of pathological pain syndromes that have been studied for their potential involvement in the ensuing long-lasting neuropathic pains. Furthermore, precious little is understood about the immune-like glial cells within the pain-modulatory laminae of the spinal cord dorsal horn. This is because it has only very recently been recognised that glia residing in various sites in the central nervous system are not all the same; rather, their receptor expression and function reflect their microenvironment and so must be understood in this context. Given that studies of glial function have almost exclusively used glia isolated from supraspinal sites, much remains to be learned about the dynamics of dorsal spinal cord glial function as regards pain modulation and neural function more generally.

- Gianna Descalzi, Icahn School of Medicine, Mount Sinai, found that chronic pain led to changes in the expression levels of more than 17,000 genes in multiple brain regions, including some associated with stress and depression, and in different cell types, including astrocytes, which are thought to play a substantial role in chronic pain.