Interferon-gamma and neuropathy: balance between pain and neuroprotection

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Chronic pain is sustained by a phenomenon of hyper-activation of nociceptive neurons both at peripheral (peripheral sensitization) and central (central sensitization) levels. The onset and maintenance of pain, however, is to be found in the interaction among the various cell populations in the nervous tissue including neurons and glia (Nam et al., 2016). The pathogenesis of neuropathic pain is extremely complex depending on the primary cause of nerve damage, e.g. traumatic nerve injury is associated with a robust inflammatory response while chemotherapy-induced pain is characterized by a modest phlogistic component (Di Cesare Mannelli et al., 2013). Despite these differences, a powerful common concept to explain the cellular mechanisms underlying pain is the activation of glia. The existence of a causal relationship between glia response and pain has been amply demonstrated starting from the mid 1990s (Colburn RW et al., 1999). During the development of neuropathy, a pivotal role has been imputed to microglia, whereas astrocytes are involved in the chronicization of pain (Scholz et al., 2007).

Astrocytes are the main supportive cells in the brain with important functions including the supply of nutrients and the regulation of neuronal activities; so, their role in pain persistence does not seem to be separable from their neuroprotective role (Milligan et al., 2009). The study of the phenotypic changes of astrocyte populations in a pathology-dependent manner helps in clarifying their deleterious or conservative roles (Di Cesare Mannelli et al., 2021).

Recently, the transcriptome profile of astrocytes isolated from the parabrachial nucleus (a circumscribed pontine structure also responsible for nociceptive signaling in a context of pain) of neuropathic mice (oxaliplatin was used as a neurotoxic agent) was analyzed by RNA sequencing in comparison to naive animals (Toti et al., 2019). The study of the transcriptomic profile of astrocytes isolated from the parabrachial nucleus revealed the deregulation of a series of pathways. Among others, the interferon gamma (IFN-γ) pathway emerged for the strength of this alteration and for its physiopathological relevance. IFN-γ is a pleiotropic cytokine and a crucial modulator of the central and peripheral immune responses, it may inform astrocytes as well as it may be synthesized and released from activated astroglia (Abd-El-Basset et al., 2020). As shown in Table 1, IFN-γ is upregulated in the dorsal horn upon peripheral nerve injury (Tanga et al., 2005) increasing neuronal electrical activity (Vikman et al., 2001). IFN-γ directly activates microglia (Racz et al., 2008) and subsequently potentiates NMDA receptor signaling in the neurons (critical in chronic pain hypersensitivity) via microglia-neuron interactions (Sonekatsu et al., 2016). Further, IFN-γ facilitates the synaptic transmission between primary afferent C-fibers and lamina I neurons in the rat spinal dorsal horn (Reischer et al., 2020). IFN-γ decreases the astrocyte-specific connexin 43 (Cx43) expression in cultured astrocytes through activation of the C-Jun terminal kinase (JNK) signaling pathway so altering glial connectivity (Zhang et al., 2013), a feature of painful neuropathic conditions (Di Cesare Mannelli et al., 2015). The activation of JNK also induces C-C Motif Chemokine Ligand 2 (CCL2), a cytokine known to increase the sensitivity of dorsal horn neurons (Gao et al., 2010). In astrocytes, IFN-γ evokes persistent phosphorylation of STAT1 (pSTAT1), an important transcriptional factor that supports the involvement of the cytokine in glial activation mechanisms (Barcia et al., 2011). A decrease of IFN-γ response is related to the cannabinoid CB2 receptor-mediated control of neuropathic pain. In a double knock-out mouse strain deficient in CB2 receptors and IFN-γ the enhanced hypersensitivity observed in CB2 knock-out was no longer shown (Racz et al., 2008). Clinically, IFN-γ has been suggested to correlate with pain intensity in patients after lumbar microdiscectomy (Kamieniak et al., 2020).

Next to this preeminent pro-algic role, IFN-γ is pivotal in the restorative and protective mechanisms on the base of neuropathy healing. IFN-γ enhances the secretion of the Brain-Derived Neurotrophic Factor (BDNF), one of the many neurotrophic (but painful) factors after brain injury, promoting the survival of cortical neurons (Abd-El-Basset et al., 2020) and influencing the mechanisms of neural cell genesis and synaptic plasticity (Monteiro et al., 2017). During acute neuroinflammation, IFN-γ, via induction of astrocyte-secreted interleukin 6 (IL-6), reduces neuronal apoptosis and intercellular Ca2+ influx (Sun et al., 2017). The IFN-γ-dependent secretion of interleukin 10 (IL-10) from type-1 helper T-conditioned (Th1) cells, as well as from native microglia and macrophages is described as pivotal for promoting functional recovery with enhanced axonal remodeling after spinal cord injury (Ishi et al., 2013).

IFN-γ signaling promotes the protection of the central nervous system during chronic autoimmune by inducing immune-proteasome in regional astrocytes, it reduces reactive oxygen species burden and decreases oxidatively damaged and polyubiquitinated protein accumulation in human spinal cord astrocytes (Smith et al., 2020). All information is summarized in Table 2.

Table 1 | An overview of pro-algic effects of IFN-γ on various cell populations in nervous tissue

| IFN-γ activity | Pro-algic effects |
|----------------|------------------|
| In astrocytes  | ▮Cx43 expression with alteration of glial connectivity |
|               | ▮pSTAT1 which enhanced astrogliosis |
| In microglia   | ▮INOS and CCR2 activity |
| In spinal dorsal horn neurons | ▮NMDA receptor signaling |
|                | ▮Synaptic transmission between C-fibers and lamina I neurons |

Table 2 | Biological functions of IFN-γ: an overview of neuroprotective effects

| IFN-γ functions | Neuroprotective effects |
|-----------------|------------------------|
| BDNF secretion  | ▮Survival of cortical neurons |
| IL-6            | ▮Neuronal apoptosis and intercellular Ca2+ influx |
| Activated | ▮Accumulation of unfunctional proteins |
| Immunoproteasome activation | ▮ROS burden |
| Microglia-secretion of IL-10 | ▮Axonal remodeling |

In conclusion, the solely hyperalgesic role of IFN-γ should be revised in light of its protective properties, a two-faced effect of IFN-γ depending on concentration, disease, cell type (Ottum et al., 2015). It is therefore interesting to learn more about the physiopathological changes of IFN-γ signaling during neuropathies as well as about the effects of its modulation in the attempt to dissect the different underlying pathways.
Perspective

Insights into the distinction between the painful and protective mechanisms may open the route to novel, strategically selective, pharmacological approaches.

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