Neuronal alarmin IL-1α evokes astrocyte-mediated protective signals against oxaliplatin neurotoxicity. Effectiveness in chemotherapy-induced neuropathic pain

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Neuropathic pain is associated with glia activation, and glial inhibitors has been proposed as pain reliever. On the other hand, glial cells promote neuroprotective mechanisms leading to recovery following nervous injury. The distinction between glia painful and protective pathways is unclear and the possibility to finely modulate the system is lacking. Focusing on the initial phases of CNS alterations we studied the role of interleukin 1α (IL-1α), an alarmin belonging to the larger family of damage-associated molecular patterns (DAMPs) endogenously secreted to restore homeostasis.

Primary rat neuron and astrocyte cell cultures were obtained and treated with the anticancer agent oxaliplatin able to induce in vivo a peripheral neuropathy. Oxaliplatin induced apoptosis (caspase 3 activation) and cell viability decrease in neurons and, with less potency, in astrocytes. One μM oxaliplatin (48h) was chosen as treatment able to damage neurons but to maintain astrocytes alive. In this condition both neurons and glia released IL-1α in the culture medium. Neuronal damage was unmodified when a neuron-glia transwell co-culture was exposed to increasing concentration of oxaliplatin for 48h, whereas IL-1αrelease increased in a concentration-dependent manner. To evaluate the role of the cytokine we silenced IL-1αin neurons by specific small interfering RNA. IL-1α-knock down neurons co-cultured with astrocytes were more prone to neurotoxicity since 1 μM oxaliplatin increased cell mortality by about 50% in comparison to wild type neurons. On the other hand, the extracellular levels of ATP, a key neurotransmitter in neuropathic processes, strongly increased in IL-1α-deficient neuron/astrocyte co-culture treated with oxaliplatin. Moreover, in the absence of neuronal IL-1α the protective cytokine TGFβ1 was significantly decreased in the co-culture medium. TGFβ1 release was higher from astrocytes than neurons and was reduced by the astrocyte inhibitor fluorocitrate, suggesting astroglia as target of the alarm raised by neurons. Starting from these *in vitro* evidence, IL-1α was intrathecally (i.t.) injected by a spinal catheter in oxaliplatin-treated rats (2.4 mg kg^{-1} intraperitoneally, daily for 14 days). IL-1α (100 and 300 ng i.t.) relieved oxaliplatin-induced hypersensitivity to mechanical noxious and thermal non noxious stimuli. The effect was dose-dependent and lasted 48h.

Summarizing, oxaliplatin induces neuronal damage provoking IL-1α release. IL-1α-stimulated astrocytes are able to protect neurons by releasing TGFβ1 and limiting ATP levels in the extracellular environment. IL-1α i.t. induces a long-lasting relief of oxaliplatin-evoked neuropathic pain in the rat.