Glia emerge as pain therapy targets

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Glial cells have long been cast in a role secondary to neurons, providing merely support, insulation and 'glue', as their name indicates. These neuronal counterparts, however, are emerging as co-stars in many CNS signaling systems. Glial cells show independent calcium oscillations and complex intercellular communication, releasing a legion of molecular signals. Now, work presented at the Spring Pain Research Conference in Grand Cayman (http://www.caymanconferences.com/pain/pain_meeting_info.htm) indicates that they are shaping up as important drug targets for chronic pain [1].

Glia become activated and contribute to pain

With nerve injury often comes chronic pain that includes tactile hypersensitivity (allodynia), which spreads beyond the area of injury and does not respond to analgesic drugs – perhaps because sensory neurons alone no longer mediate the pain signals. Instead, an increasing body of evidence suggests that glial cells in the spinal cord become activated and contribute to pain.

P2X receptors are ionotropic channels activated by ATP, now a recognized pain-signaling molecule. Michael Salter of the Toronto Hospital for Sick Children (http://www.sickkids.ca/research/) presented work showing that the P2X4 receptor mediates the mechanical allodynia seen in a rat model of chronic pain after nerve injury [1]. But they did not find the molecule where they expected to: on sensory neurons. 'The shock for us came when we tried to figure out what cell type expressed the molecule. I was a dyed-in-the-wool neuronist,' said Salter, but he found P2X4 receptors expressed on microglia. A closer look at the glia in the spinal cord revealed glia that were 'swollen up, angry, on their way to being bad microglia'.

Glial transformation

The glia exhibited the phenotype of activation, a triggered genetic program that entails a host of changes in protein expression, morphology and phagocytic ability. This transformation from a resting to a hyper-excited state has been studied for over 20 years, says Salter, but the events that spark activation remain unclear.

Also still a mystery are the downstream actions of activated glia that produce pain. Presumably, in the case of mechanical allodynia, ATP contributes to the upregulation of P2X4 that Salter saw in spinal microglia. Beyond that, Salter describes two broad possibilities: either that glia release diffusible pro-nociceptive substances (like prostaglandin or nitric oxide) that increase neuronal excitability, or that glia act through direct physical contacts with neurons. Although they are 'still in the early days of sorting out' those questions, he said, 'we've got some good leads'.

Understanding the biology

Joyce DeLeo, a professor at Dartmouth University (http://cobweb.dartmouth.edu) also present at the meeting, provided an overview of some of the nociceptive substances released from glia [2,3]. Tumor necrosis factor alpha (TNFα), and interleukins (IL) 1 and 6 have received the greatest attention thus far, but DeLeo said researchers 'may have been using too narrow a focus'.

DeLeo said she is 'very excited that pharmaceutical companies…see the promise' of Salter's and others' work, but warns that 'it's important to realize that we can't turn off' glial activation; 'rather, we need to modulate it.' Glia provide critical support for neurons and maintain their homeostasis, and 'obviously that biology is there for a reason'. Both DeLeo and Salter are hopeful that understanding that biology can lead to better targets for pain.

References

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3 Raghavendra, V. *et al.* (2003) Anti-hyperalgesic and morphine-sparing actions of propentofylline following peripheral nerve injury in rats: mechanistic implications of spinal glia and proinflammatory cytokines. *Pain* 104, 655–664

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