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Close encounters of the third kind: Evidence for contact with TNF-alpha

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If you have not heard that glial cells are involved in pain processing then you have missed some significant advances in our understanding of the generation and maintenance of pain [3]. It is well established that spinal astrocytes and microglial cells become activated after peripheral nerve injury. The stream of incoming primary afferent activity that accompanies such injury bombards the spinal cord with a variety of neurotransmitters, including substance P (Sub-P) (Fig. 1). Microglial cells exposed to Sub-P increase their expression of OX-42 as well as their expression of inflammatory mediators, such as tumor necrosis factor alpha (TNF-alpha) and chemokine ligand 2 (CCL2) [1,4]. That this process is involved in the generation of pain is borne out by the finding that preventing or reversing the activation of microglial cells with minocycline reduces nerve injury-associated pain behavior [5]. Consistent with these observations, intrathecal administration of the TNF-alpha inhibitor, etanercept, is antinociceptive.

Despite the effects of inhibiting TNF-alpha, surprisingly intrathecal administration of TNF-alpha, itself, has no effect on nociceptive thresholds [8]. What could account for these somewhat paradoxical effects on nociceptive processing? In this issue of PAIN, Zhou and colleagues enlighten us with a new explanation as to how TNF-alpha produced by activated microglia contributes to the development of neuropathic pain. The take home message is that the TNF-alpha that plays a role in nociception is not released. Rather, it is membrane bound.

Prior to explaining how the authors came to this conclusion, a little background is in required. TNF-alpha is first produced as a long, membrane bound molecule, called mTNF-alpha (Fig. 1). To be released into the extracellular environment, mTNF-alpha is cleaved to the soluble form of TNF-alpha (sTNF-alpha) by the TNF-alpha converting enzyme (TACE). TACE is an inducible enzyme, which means that unless it is turned on, mTNF-alpha remains intact and there is no release of sTNF-alpha.

Zhou and colleagues [9] found that when cultured microglial cells are exposed to Sub-P (Fig. 1), these cells increase their expression of mTNF-alpha, but not of TACE or sTNF-alpha. Nevertheless, the increase in mTNF-alpha is sufficient to trigger the activation of neighboring microglial cells, through direct contact with TNF-alpha receptors (Fig. 1). Stimulation of the TNF-alpha receptors is followed by an increase of OX-42 and the release of pro-inflammatory compounds, such as CCL2. The authors substantiate their claim by transfecting COS cells with a cleavage resistant TNF-alpha gene, resulting in the expression of mTNF-alpha at the cell surface. What follows is the activation of neighboring, non-transfected, cells, in the absence of any sTNF-alpha. The authors propose that when a nerve injury occurs, there is a volley of

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Conflicts of interest

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primary afferent activity and release of Sub-P. This, in turn, leads to a transformation of the spinal cord involving local microglia and release of inflammatory mediators.

The key here is that microglia form a meshwork in the neuropil, so that activation of microglial cells through direct contact results in a spread of activation to microglia far from the site of initial activation (Fig. 1). In turn, because activated microglia release inflammatory mediators, this will affect adjacent neurons, many of which are also distant from the site of original activation. This spread of activation over a large area is likely critical to the initiation and maintenance of neuropathic pain.

As activation of microglia cells is implicated in several CNS disorders these data are not only thought provoking but, in our view, will also have a broad impact. Some details, however, need to be confirmed. For example, although the presence of the Sub-P receptor (NK1-R) on macroglial cells was reported 20 years ago [7], there are surprisingly few reports about the expression of this receptor on microglial cells [2]. Anatomical studies (confocal and ultrastructural) are needed to establish that NK1-Rs are indeed at the surface of these cells and that, as for neurons, these receptors are internalized after binding Sub-P [6]. Another issue that needs further investigation is how to explain why clinical trials of NK1-R antagonists for pain relief have not been successful. The failure may have to do with patient selection or with timing of drug administration, but it is also possible that Sub-P is not the only or main player in activation of microglia. If this is the case, then giving a combination of drugs, such as an NK1 antagonist together with etanercept, assuming that it binds to both sTNF and mTNF, should be considered.

We predict that current discoveries in the arena of neuro-immune interaction will eventually find their way to clinical applications. Therapies that target TNF-alpha and other inflammatory mediators will likely influence nerve regeneration and repair and consequently pain. This should be good news for our patients.

Acknowledgments

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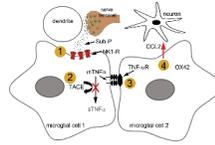


Fig. 1.

Diagram summarizing the findings of Zhou and colleagues. Step 1: substance P (Sub-P) is released by primary afferents and activates Sub-P receptors (NK1-R) on microglial cells. Step 2: Sub-P stimulated microglial cells increase their expression of membrane bound tumor necrosis factor (mTNF-alpha). Because NK1-R stimulation does not activate the TNF-alpha converting enzyme (TACE), mTNF-alpha is not converted to the soluble form of TNF-alpha (sTNF-alpha). Step 3: the activation of neighboring, unstimulated, microglial cells occurs through direct contact between mTNF-alpha and TNF-alpha receptors (TNF-alphaR). Step 4: TNF-alphaR stimulation induces an increase of OX-42 levels and evokes the release of chemokine ligand 2(CCL2). The latter, in turn, activates spinal neurons, which induces and maintains neuropathic pain.