Shifting to Translational Research on Postoperative Pain and Its Chronification

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IN this issue of Anesthesiology, Liu *et al.* report on the relevance of a serine protease, cathepsin G, for postoperative pain.[1] With their work, these authors place cathepsin G in a long list of proteins that have been identified as being with altered expression profiles in relation to pathological pain. Up to now, the clinical and, thus, translational value of most of these proteins has remained poor as bridges between animal and human research have been notably lacking.

In these days, translational research has become increasingly important, and Liu *et al.* have highlighted that promising data from laboratory animals may indeed have clinical relevance. A genome-wide screening approach showed that more than 150 genes were differently (> 1.5-fold) expressed in the dorsal horn of the spinal cord ipsilateral to a chronic inflammatory stimulus in the hind paw of rats. Among these genes, cathepsin G showed a particularly strong up-regulation. The relevance of this up-regulation for inflammatory pain was proven when a specific cathepsin G inhibitor reduced early heat hyperalgesia and reversed established heat hyperalgesia. What makes these findings from animal studies particularly meaningful is the additional data on postoperative pain patients. Two single-nucleotide polymorphisms in the intron regions of the human cathepsin G gene were associated with reduced risk of chronic postoperative pain. Here, surgical patients carrying homozygous alleles of the polymorphisms rs2070697 and particularly rs2236742 were less likely to report chronic postoperative pain (at 12-month follow-up) compared with patients not carrying these alleles.

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The transition from acute to chronic pain and the maintenance of chronic pain states have been attributed primarily to pathobiological modifications in the central nervous system (CNS), the most of which have been studied in the spinal cord dorsal horn.[2] Also, Liu *et al.* propose a *central mechanism* for their analgesic effects after cathepsin G inhibition. First, the expression of cathepsin G was unaltered in the peripherally located dorsal root ganglia making a central mechanism of action for the inhibitor likely. Second, reduced chemoattraction of blood-borne leukocytes and cytokine modulation were detected in the dorsal horn of the spinal cord after cathepsin G inhibition. Third, spinal astrocytic glial cell reactions, which have been repeatedly implicated in chronic pain states, were found to be aggravated after systemically delivered cathepsin G.

Cathepsin G is certainly not the first protease to be linked with chronic pain; proteases such as matrix metalloproteinases (MMPs) and cathepsin S have been particularly studied in relation to neuropathic pain models. In such models, protease-up-regulated expression and/or activity was spatiotemporally observed in a protease-specific manner.[3] Whereas MMP-9 was quickly induced in primary afferent neurons after nerve injury, MMP-2 was induced with a delay of more than 1 week in spinal cord astrocytes. Inhibitors of these MMPs could, also here, reduce early pain-like behaviors and reverse them once established. The spinal up-regulation in cathepsin G after hind paw inflammation, as reported by Liu *et al.*, was pronounced in the later stages, suggesting a role in the more chronic stages of inflammation. Together with the findings on cathepsin G's relevance for astrocytic glial cell reactivity in the dorsal horn, it is likely that this specific protease has a main role in the maintenance of pain.

The mechanisms can be several by which proteases drive chronic pain states. For one, cathepsin G is known to target protease-activated receptor-4. It is unlikely, however, that the prohyperalgesic effect after chronic hind paw inflammation

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reported by Liu *et al.* involves protease-activated receptor-4 because previous work indicated that activation of this receptor mediates inflammation and acts in an antinociceptive way.[4] Alternatively, proteases are known to cleave canonical cytokines, thereby activating them. The effects of the cathepsin G inhibitor on spinal interleukin-1β expression favor such a mechanism. It could then be proposed that chronically elevated levels of spinal interleukin-1β maintain astrocytic glial cells in an activated, pain-related state.

Although Liu *et al.* should be applauded for the translational character of their work, a few cautious notes need to be given. First, cathepsin G is only one of the many proteins showing a pathological alteration after chronic hind paw inflammation in the rat. Although its relevance for heat hyperalgesia was evidenced in this single animal model, a broader investigation could be envisioned, stretching out to further relevant animal models characterized by their own pain mechanisms (*e.g.*, ectopic firing of primary afferent neurons in neuropathic pain). Also, other measures of pain-like behaviors (*e.g.*, tactile allodynia) deserve testing. These considerations are particularly important in light of the predictive value of early tactile allodynia and iatrogenic nerve lesions for chronic postoperative pain.[2] Second, the human investigation was restricted to the identification of two single-nucleotide polymorphisms in intron regions of the human cathepsin G gene. As such, sequencing of the exons is the necessary next step to reveal the locus that may interfere with the functionality of the protease. Moreover, before considering cathepsin G inhibition as a therapeutic strategy, details on the expression and/or function of cathepsin G in human are undeniably needed as well as evidence that surgery induces, in human patients, an up-regulation of this protease.

There are so many differences between species, surgical injuries, psychosocial factors, and assessments of pain that promising new data, like the ones on cathepsin G, deserve and need further investigations to understand the true translational relevance for chronic pain. Reproducibility of the findings by independent laboratories is then also needed to strengthen the belief in results as these eventually leading us forward in our quest for effective treatments of chronic postoperative pain.

Within the confinements of the abovementioned considerations, we consider the findings by Liu *et al.* to have two major implications. First, translational research is duly needed for the progress in our understanding of both the processes by which acute pain transits into chronic pain and the processes that maintain chronic pain states. The study by Liu *et al.* shows that translational research has the potential to reveal genetic biomarkers with *predictive value* for the pain chronification process after surgery. Second, even though the mechanisms of pain chronification and chronic pain may be centered in the CNS, pharmacological approaches with systemic drug delivery can be considered for medical approaches to prevent chronic postoperative pain. This, under the prerequisites that the targeted molecule(s) show(s) a CNS-specific rather than a broad induction and that the compound can easily reach the site of interest, which lies beyond the blood–CNS barrier.

Translational research will permit tailored medical strategies. Liu *et al.* literally designed a trial-to-understand, complementary to laboratory research. Their approach will encourage us to constitute registries, as a part of a global strategy in pain research as in perioperative medicine, and could eventually motivate us to work with a recognition of patient subgroups through the identification of biomarkers. Subsequently, clinical trials can be better designed so that they suffer less from variability but may reveal a better therapeutic efficiency and effectiveness. The answer to our progress in the management of postoperative pain and its chronification may indeed lie in a new paradigm of translational pain research conjointly with database analyses.

Competing Interests

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

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