Editorial

Pain in chronic pancreatitis is complex

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Chronic pancreatitis is a progressive inflammatory disorder of the pancreas most commonly occurring in 40 to 50-year-old men, and is associated with long-standing alcohol abuse (1,2). Prototypical features include recurrent episodes of abdominal pain which often progress to a severe refractory pain, leading to a significant impact on the quality of life, and disability (3-5). Many of these patients require multiple pharmacological, endoscopic, and even surgical treatments for the disabling pain, but with variable efficacy (6). When refractory and severe, a total pancreatectomy, in the hopes of giving a long-standing pain relief, may be the only option; however, it has its own complications (7).

Pain for those with chronic pancreatitis is complex. Multiple factors can cause pain, either singularly, or it could be a combination of problems like, structural, vascular, and neuropathic, as well as pain being generated locally and/or centrally (8-10). The mechanism(s) of pain generation are now becoming better understood. Current evidence has focused on a pancreatic neuropathy, whereby peripheral pain nociceptors send signals through the spinal cord to central receptors. These pancreatic sensory neurons are believed to undergo a sensitization and thus, increase nociceptor excitability. With a long-standing afferent neuronal signaling to the brain, central sensitization may then be the result. This manifests from an increase in the excitability of neurons in the spinal cord whereby a peripheral pain is no longer modulated by the features of pain, such as its duration and its severity. Such neuroplasticity has been strongly suggested, and any alterations in the brain, documented by a variety of neuroimaging techniques, has shown such changes in patients with chronic pancreatitis (9-12).

With that as a background, Liu and colleagues (13) explored specific mechanisms for neuronal signaling in the pancreas. Previous studies suggested that transforming the growth factor beta 1 (TGFB1) is up regulated in the presence of a chronic inflammation of the pancreas, in both the experimental models and the human's ones. Furthermore, it has been suggested that the SMAD pathway is the mediator of intracellular TGFB signaling. In this study (12), transgenic mice models were used, which overexpressed TGFB1 in the pancreas, as well as knockout models of the same receptor following the induction of chronic pancreatitis. Validated nociceptive tests by electrical stimulation were the primary outcome. The severity of pancreatic injury in the mice models was assessed histopathologically. The investigators then used inhibitors of the TGFB-SMAD signaling on the neurons in vitro, as well as a specific inhibitor of the SMAD3 phosphorylation. Lastly, they examined the effects of TGFB on the central mechanisms by an intrathecal infusion of TGFB1 for two weeks in the spinal cord.

They found *in vitro* effects of TGFB on the sensory nerves that mimic the *in vivo* exogenous and endogenous effects of TGFB 1 to have a substantiating role for TGFB 1 in the nociceptive sensitization observed in chronic pancreatitis. Lastly, using these inhibitors, they showed that targeting the TGFB receptor or the downstream mediator SMAD3, prevented neuronal excitability and thereby, hyperalgesia. Usage of small molecule inhibitors of TGFB-SMAD signaling also demonstrated a reduction in neuronal excitability by TGFB. These findings also had substantiated prior studies, suggesting that such a receptor blockade could alter pain behaviors in this rat model of chronic pancreatitis. Intrathecal infusion resulted in reduced hyperalgesia in rats with chronic pancreatitis (CP), but not

controls. This paradoxical response had been previously demonstrated in animal models.

What then does this data tell us about our management of the pain associated with chronic pancreatitis? The identification of the specific receptors and pathways that are associated with pain, give us the opportunity to develop specific inhibitors as shown in this study, and blocking these pathways, to allow for a reduced pain level. These exciting findings should also provoke further studies, to help to identify other mechanisms, and therefore potential therapeutic targets. While the development of new agents for receptor targeting could take years, these animal studies provide the opportunity to test the currently available agents, and if it has a positive result, it could yield immediate benefits for our patients. Sometimes determining who and how to treat is difficult particularly if it relies on imaging studies alone, given the lack of a correlation of imaging abnormalities to pain (14). Chronic pancreatitis pain has been enigmatic, and these studies suggest that we are breaking down these barriers and complexity.

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