

 METABOLOMICS

Gaining insight into pain

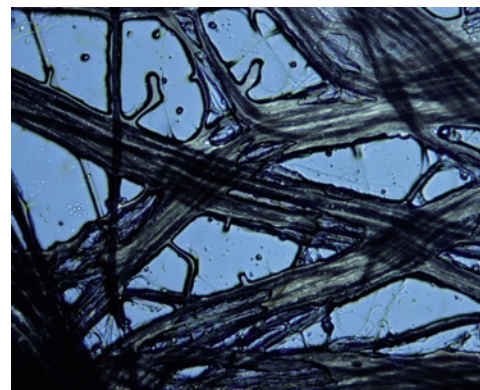
Treatment options for neuropathic pain, which develops as a result of injury to the nervous system, are limited and have not advanced substantially for many years, in part owing to a lack of understanding of its molecular basis. A recent metabolomics study by Patti *et al.*, published in *Nature Chemical Biology*, implicates an endogenous lipid metabolite in neuropathic pain and might provide a new pathway to target with potential analgesics.

In a well-established rat model of neuropathic pain — tibial nerve transection (TNT) — allodynia (pain in response to light touch) persists for at least 9 weeks after the initial transection of the tibial branch of the sciatic nerve, despite the wound appearing healed. Patti and colleagues took an untargeted mass spectrometry-based metabolomics approach to analyse metabolites from plasma, the tibial nerve, dorsal root ganglia and the rat dorsal horn of TNT rats and control (sham-operated) animals 21 days after surgery. A total of 733 metabolic features showed over a twofold change between the two groups, and 94% of these were derived from the dorsal horn.

Focusing on this site, where the damaged nerve meets the spinal cord,

the authors discovered that sphingomyelin–ceramide metabolism was markedly affected. In particular, levels of ceramide (d18:1) and several phosphatidylcholines were increased, whereas those of several diacylglycerols were decreased, consistent with an increased degradation of sphingomyelin to ceramide. *N,N*-dimethylsphingosine (DMS) was one of several sphingomyelin–ceramide metabolites that were significantly upregulated.

Having determined the concentration of DMS present in the dorsal horn 21 days after TNT, the research team then demonstrated that intrathecal injection of a similar concentration of DMS could induce mechanical allodynia in healthy rats within 24 hours. Intrathecal DMS injection also increased the expression of glial fibrillary acidic protein in the spinal cord, which is indicative of astrocyte activation. Among the many substances released by activated astrocytes, interleukin-1 β (IL-1 β) and monocyte chemoattractant protein 1 (MCP1) are inflammatory mediators with roles in nociceptive responses, and the authors showed that cultured astrocytes released increased levels of both IL-1 β and MCP1 following DMS treatment.



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These data indicate that sphingomyelin–ceramide metabolism is altered in the dorsal horn of rats subjected to neuropathic pain, resulting in increased levels of the endogenous ceramide catabolite DMS, which can elicit mechanical hypersensitivity *in vivo* and cytokine release *in vitro*. They also demonstrate the power of using an untargeted approach to identify potential new drug targets, with future efforts likely to focus on identifying the specific enzymes involved in DMS biosynthesis as potential points for therapeutic intervention.

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ORIGINAL RESEARCH PAPER Patti, G. J. *et al.* Metabolomics implicates altered sphingolipids in chronic pain of neuropathic origin. *Nature Chem. Biol.* 22 Jan 2012 (doi:10.1038/nchembio.767)