CLINICAL IMPLICATIONS OF BASIC RESEARCH

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Gaining on Pain

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Managing pain is a vast clinical challenge. The lack of side-effect–free analgesics has contributed to the recent opioid abuse tragedy, and life expectancy in the United States has fallen as a result. The urgency of the situation demands a major effort to identify new approaches to the treatment of pain. Repurposed Food and Drug Administration (FDA)–approved drugs with analgesic efficacy could be useful, given the lengthy drug-development process. Therefore, the work of Salvemini and coworkers (Stockstill et al.) is notable in unraveling the mechanisms that contribute to the neuropathic pain caused by bortezomib, an anticancer medication.[1]

Bortezomib contributes to the success of cancer treatment and the long-term survival of patients with multiple myeloma. This modified dipeptide binds and inhibits the 26S proteasome (a cytosolic protein complex that breaks down proteins) and fuels the apoptotic mechanisms that kill myeloma cells. Unfortunately, it also causes painful peripheral neuropathy in approximately 30% of patients, and in some cases this has led to discontinuation of treatment. A causal link between sphingolipids (such as sphingosine-1 phosphate) and neuropathic pain has been found in many studies in rodents. In addition, some mutations in the genes *SPTLC1* and *SPTLC2* — which encode serine palmitoyltransferase, an enzyme that in turn drives de novo synthesis of sphingolipids — lead to neuropathic pain in humans because of the production of a neurotoxic sphingoid metabolite. Studies in animals, including unbiased metabolomic studies of neuropathic pain mechanisms in the spinal cord, have highlighted the importance of this enzyme in neuropathic pain.[2,3] Because the levels of the proapoptotic lipid ceramide are up-regulated by bortezomib, and because ceramide is a precursor of sphingolipids and would therefore be expected to increase the levels of sphingosine, it was logical to investigate the association between the use of bortezomib and levels of sphingolipid metabolites.

In studies in rats, Salvemini and coworkers investigated the effect of the drug on the dorsal horn of the spinal cord, where primary afferent neurons impart information to the central nervous system. They observed higher levels of both ceramide and sphingosine derivatives such as sphingosine-1 phosphate, and they found that blockade of serine palmitoyltransferase reversed bortezomib-induced neuropathic pain. These data confirmed a role for sphingolipids in some of the undesirable side effects of bortezomib.

Serendipitously, an orally active functional antagonist of sphingosine-1 phosphate, fingolimod, is already in clinical use. Fingolimod impedes lymphocyte egress from lymph nodes into the central nervous system. It is a useful oral drug for the treatment of multiple sclerosis. Known for more than a decade to have analgesic properties,[4] it down-regulates S1PR1, one of the five G-protein–coupled receptors activated by sphingosine-1 phosphate. Salvemini's team found that a specific S1PR1 antagonist reversed neuropathic pain and that silencing S1PR1 with the use of small interfering RNA confirmed its role in mediating pain in animal models. Fingolimod is thus a potentially useful treatment for bortezomib-induced neuropathic pain in humans — but might it compromise the desirable antitumor actions of bortezomib? High doses of fingolimod had no such effect in an in vitro model of tumor-cell killing, and indeed fingolimod itself has some antitumor activity. A proof-of-concept trial of the effects of fingolimod on bortezomib-induced neuropathic pain in humans therefore seems justified.

How does altered sphingolipid metabolism

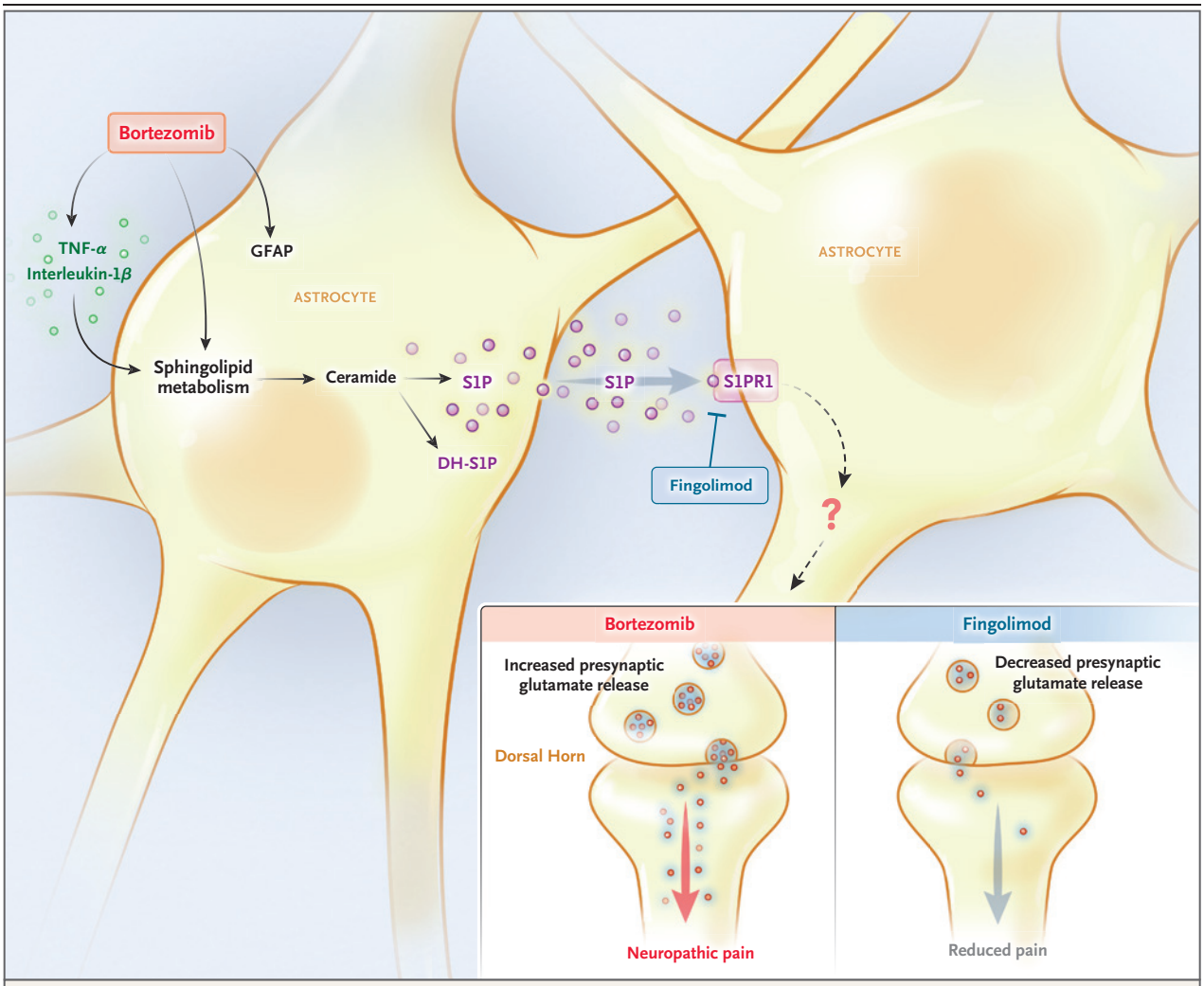

Figure 1. Astrocytes, Pain, and Bortezomib — A Model.

Within astrocytes, bortezomib causes an increase in sphingolipid metabolism, leading to an increase in the production of ceramide as well as sphingosine-1 phosphate (S1P) and dihydrosphingosine-1-phosphate (DH-S1P). Within the periphery, bortezomib increases the production of tumor necrosis factor α (TNF-α) and interleukin-1β, which in turn act to augment sphingolipid metabolism within astrocytes. Released S1P binds to the S1P receptor (S1PR1) on astrocytes, which ultimately leads to an increase in the release of presynaptic glutamate at the level of the dorsal horn of the spinal cord and to the development of neuropathic pain. Inhibition of S1PR1 by phosphorylated fingolimod reduces the release of presynaptic glutamate and therefore reduces neuropathic pain. GFAP denotes glial fibrillary acidic protein.

lead to neuropathic pain? S1PR1 is found at high levels in astrocytes (Fig. 1), and bortezomib induces the expression of glial fibrillary acidic protein in the dorsal horn of the spinal cord, which suggests an increase in the number or activation (or both) of astrocytes. Mice that lack S1PR1 specifically in astrocytes show little neuropathic pain on bortezomib treatment. It seems that activated astrocytes (which synthesize and secrete the neurotransmitter molecule glutamate) excite the dorsal horn. Also supporting this hypothesis is the finding that miniature excitatory postsynaptic currents in neurons of the dorsal horn increased in both frequency and amplitude in bortezomib-treated rats. S1PR1 agonists applied to the spinal cord also increased the frequency of these glutamatergic events. Future areas of investigation include the mechanism

through which S1PR1 activation in astrocytes leads to glutamatergic signaling, other potential mechanisms through which bortezomib causes neuropathic pain, and the question of whether fingolimod has any effect on neuropathy. The fascinating story of bortezomib-evoked pain provides a glimmer of hope that fingolimod might, in some persons, mitigate chronic pain.[5]

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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