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RED CELLS, IRON, AND ERYTHROPOIESIS

Comment on Viatchenko-Karpinski et al, page 623

Lipids drive chronic sickle cell disease pain

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In this issue of *Blood*, Viatchenko-Karpinski et al[1] demonstrate that chronic sickle cell disease (SCD) pain and associated sensory neuron hyperexcitability are driven, in part, by the activation of lysophosphatidic acid receptor 1 (LPAR1) by lysophosphatidic acid (LPA). This study adds SCD to the growing list of chronic pain conditions that may be effectively treated by therapies that target lipid signaling.

The study focuses on LPA, a single-tailed lipid produced by enzymatic hydrolysis by autotaxin of lysophosphatidylcholine (LPC), a critical membrane phospholipid. Previous work in both humans and mouse models has demonstrated that LPC is elevated in SCD due to the disruption of the Lands' cycle, the process by which erythrocytes recycle membrane lipids.[2] In addition to driving chronic SCD pain via transient receptor potential (TRP) channel activation,[3] erythrocyte-generated LPC may further perpetuate chronic SCD pain by being the primary source of LPA. Supporting this mechanism, Viatchenko-Karpinski et al found that pharmacological inhibition of autotaxin reduced both circulating LPA levels and behavioral hypersensitivities in SCD mice. Although it is not yet known whether autotaxin activity or LPA levels are elevated in individuals with SCD, LPC, the primary LPA precursor, is increased in patients, suggesting that this signaling pathway holds significant promise for SCD therapeutic development.

Using complementary small interfering RNA and pharmacological approaches, the authors further determined that LPA-associated pain is mediated, in part, by the activation of LPAR1, the only 1 of 6 G-protein–coupled LPA receptors whose expression was increased in SCD mouse sensory neurons. Future studies should examine additional LPA signaling pathways for therapeutic potential. For instance, although not increased in SCD mouse dorsal root ganglia (DRG; the structure that contains the cell bodies of peripheral sensory neurons), LPAR3 may be a more important LPA receptor in patients. New single-cell RNA sequencing studies reveal that, in human DRG, *LPAR3* is more widely expressed than *LPAR1*; although 17% of human DRG neurons express *LPAR1*, >50% of human DRG neurons express *LPAR3*.[4] This is not the case in mice; *Lpar1* is more broadly expressed than *Lpar3*, and therefore, existing pain literature has primarily focused on this protein family member.

In addition to the acute, excitability-based nociceptive effects documented by Viatchenko-Karpinski et al, persistent elevations in LPA-LPAR1 signaling may further drive chronic SCD pain by demyelinating peripheral sensory neurons. Both in vitro and in vivo administration of LPA disrupts Schwann cell myelination programs that are critical for the organization, metabolic support, and transduction capabilities of primary sensory afferents.[5] Although never systematically examined in individuals with SCD, pathological myelination (eg, decreased myelin thickness and abnormal Remak bundle packing) is observed in SCD mice.[6] SCD mice also exhibit alterations in epidermal innervation.[7] LPA-induced myelination disruptions may drive this phenotype that may underlie the chronic hypersensitivities observed in SCD.

Finally, electrophysiological recordings in this study identified ion channels that should also be explored as sickle cell therapeutics. Reproducing published observations, the authors clearly show that DRG neurons isolated from SCD mice are hyperexcitable relative to neurons isolated from normal hemoglobin control animals.[8] In other words, SCD neurons require smaller current injections to fire action potentials, fire more action potentials when sufficiently depolarized, and a higher proportion exhibit ongoing or spontaneous activity in the absence of experimenter-induced stimulation. Viatchenko-Karpinski et al suggest that SCD-associated reductions in outward potassium channel currents, which are normalized following LPAR1 knockdown, underlie these changes in excitability. Their suggestion contrasts with other groups that attributed SCD

neuronal hyperexcitability to sodium channel dysregulation.[8,9] This discrepancy is important considering the recent US Food and Drug Administration approval of suzetrigine, a new sodium channel–based analgesic.[10] Undoubtedly, preclinical laboratories and sickle cell clinicians are exploring the effectiveness of suzetrigine in SCD pain management. However, based on the new findings of Viatchenko-Karpinski et al, efficacy of this therapy is predicted to be negligible.

In conclusion, this work by Viatchenko-Karpinski et al expands our limited understanding of chronic SCD pain biology and in doing so, adds exciting new nonopioid targets that should be considered for use in this disease.

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