role of these molecules in chemotherapy resistance and treatment failure in Hodgkin lymphoma. Importantly, as side population cells share features with cancer stem cells,8 these findings will certainly also stimulate further work to elucidate potential relationships among expression of multidrug transporters, chemotherapy resistance, and putative HRS lymphoma “stem” cells.10

Conflict-of-interest disclosure: The author declares no competing financial interests.

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Comment on Kohli et al, page 456

New era dawns on sickle cell pain

Samir K. Ballas Thomas Jefferson University

In a commendable study in this issue of Blood, Kohli and colleagues describe a novel approach to unraveling the complexities of the pathogenesis of sickle cell pain and its management.1 Given the timing of this publication, it can be considered a celebratory centennial of the discovery of sickle cell disease in the United States in 1910.2

Sickle cell anemia is almost synonymous with pain. Acute painful episodes are its hallmark and the most common cause of hospitalization.3 Vaso-occlusion is believed to be the root cause of the pain; it causes damage to tissues supplied by the occluded vessel and is also responsible for creating a state of chronic vascular inflammation that explains many features of sickle cell pain.4,5 Tissue damage and vascular inflammation generate a number of inflammatory mediators that initiate an electrical impulse of pain transmitted along peripheral nerves (Aδ and C fibers) to the dorsal horn of the spinal cord. The impulse ascends along the contralateral spinothalamic tract to the thalamus, which interconnects reversibly with other centers, most notably with the limbic system (mediator of emotion and memory). At the same time, the central nervous system (CNS) inhibits the transmission of the painful stimulus at the level of the dorsal horn via a descending pathway, with norepinephrine and serotonin as neurotransmitters, which begins in the periaqueductal gray matter of the midbrain. Eventually the modified electrochemical impulse that started at the site of vaso-occlusion is sent to the cerebral cortex, where it is perceived as pain. Pain perception is thus a subjective phenomenon and is the result of a complex interplay among enhancing and inhibiting factors at the level of the CNS in addition to a host of coexisting psychosocial and environmental factors. Given the subjective nature of sickle pain coupled with the lack of experimental models to investigate, it generated an atmosphere of doubt about its authen-

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peripheral and/or central, the pain may be limited to musculoskeletal and cutaneous hyperalgesia alone or in combination with inflammatory and neuropathic pain. At the pharmacologic level, hyperalgesia in BERK and hBERK1 mice was attenuated by morphine and cannabinoid agonists. This finding implies that the use of medicinal cannabinoids may play an important role in the management of sickle cell pain similar to their reported role in the management of other types of pain. Used in combination with opioids, cannabinoids may decrease the amount of opioids needed to achieve adequate pain relief.

Another novel aspect of this study is the surprising similarity between the homozygous BERK and hemizygous hBERK1 mice. This is unlike persons with sickle cell trait who are asymptomatic under normal conditions. The reasons for this similarity between the 2 types of mice are unknown and require further future studies.

Some of the findings in this study provide welcome explanations for some of the perplexing observations in patients with sickle cell anemia. We and others, for example, reported that some hospitalized patients with acute painful crises become refractory to treatment with opioids about 3 or 4 days after admission and continue to have severe pain despite the administration of high doses of opioids. With no good explanation for this phenomenon, some providers attributed it to maladaptive behavior. It is interesting that the study by Kohli et al found decreased expression of mu opioid receptors in both BERK and hBERK1 mice. This is a possible explanation for the observed refractoriness to opioids in some patients who may benefit from the use of medicinal cannabinoids. It is unfortunate that so many of the presumed maladaptive behaviors of patients with sickle cell disease have had a plausible explanation later on. Thus, addiction turned out to be pseudoaddiction in many patients resulting from undertreatment of pain. Drug-seeking behavior turned out to be pain relief-seeking behavior resulting from tolerance and hyperalgesia. Refractoriness to opioids, if confirmed in patients, seems to be caused by decreased mu opioid receptors during acute painful episodes.

The present findings are of both basic and clinical value that will facilitate further translational research. Finally, we have an excellent animal model that opens the sluice gates to probe new avenues for understanding and treating sickle cell pain.

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Comment on Aurora et al, page 475

NF-κB–induced chromatin remodeling regulates angiogenesis

Doruk Keskin and Raghu Kalluri

In this issue of Blood, Aurora and colleagues identify a novel mechanism for the inhibition of angiogenesis by PEDF and TSP1, mediated via chromatin remodeling and transcriptional regulation by NF-κB. Angiogenesis, formation of new vessels from preexisting ones, occurs both in physiologic and pathologic settings including tumor growth. There is a yet unproven hypothesis that in the physiologic nonangiogenic state, an equilibrium between endogenous antiangiogenic and proangiogenic molecules maintains the “angiogenic balance,” while in conditions such as cancer, an increased secretion of proangiogenic molecules shifts this balance to favor an angiogenic phenotype. While our knowledge of how proangiogenic molecules function has increased in the past few years, the mechanism of action associated with endogenous angiogenesis inhibitors is still largely unknown. Aurora et al address this un answered question in this report.

NF-κB is a transcription factor that can participate in both activation and repression of transcription. This is achieved in part by its interactions with histone deacetylases (HDACs) or histone acetyl transferases (HATs), which are major mediators of chromatin remodeling. NF-κB plays a dual role in cancer. It is speculated to have dose-dependent apoptotic or proliferative effects on cancer cells. Additionally, it can promote angiogenesis through induction of survival of endothelial cells and secretion of angiogenic factors by cancer cells. However, emerging evidence indicates that NF-κB signaling in endothelial cells induces apoptosis, leading into inhibition of angiogenesis. In this study, Aurora et al show that endogenous antiangiogenic molecules pigment-epithelium–derived factor (PEDF) and thrombospondin–1 (TSP1) activate NF-κB, through the canonical pathway via phosphorylation and degradation of NF-κB inhibitor IkB, eventually leading into apoptosis of endothelial cells. It is also identified that TSP1 and PEDF regulate NF-κB to reduce the ability of endothelial progenitors to assume an endothelial morphology and serve to influence the angiogenic phenotype. These
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Samir K. Ballas