likely to activate complement or invoke an inflammatory phagocytic cytokine response because it lacks an Fc domain.

The current study did not address SLK’s use as a thrombolytic in other vascular beds, for example, in coronary artery thrombosis, where it might act as an alternative in some circumstances to coronary artery stenting and other more interventional approaches. Any potential effect of A11 and/or SLK on the endothelial integrin α,β3 sharing the A11 epitope-bearing β3 chain also remains to be elucidated. If these promising preclinical studies can be replicated in first studies in humans, they are likely to provide better and safer treatment options in ischemic stroke.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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Comment on Lordier et al, page 2345

Shedding light on endomitosis

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Endomitosis is an enigma fascinating to hematologists and cell biologists alike. Whereas aneuploidy can be associated with chromosomal instability and cancer,1 megakaryocytes become polyplid in the course of terminal differentiation. In this issue of Blood, Lordier and colleagues delve further into the function of Aurora B kinase in endomitosis.2

Mitotic and endomitotic cycling in early megakaryocytes. Progenitors that will become polyploid proceed through cytokinesis and complete division.
or abscission, megakaryocytes exhibit regression of the cleavage furrow and re-enter G1 as polyploid cells (see figure). This observation has led investigators to focus on proteins that are involved in the regulation of furrowing and cytokinesis as candidates for promoting polyploidy. The chromosomal passenger proteins, which include Aurora B kinase, survivin, borealin, and INCENP, are key regulators of anaphase and cytokinesis (reviewed in Carmena et al1). These proteins form a complex that translocates from the inner centromere in early mitosis, to the spindle midzone in anaphase, and subsequently to the equatorial cell cortex and midbody. In these different locations, Aurora B kinase is required for the biorientation of chromosomes and the spindle assembly checkpoint, positioning and regression of the cleavage furrow, and coordination of abscission. Loss of Aurora B kinase activity leads to the failure of cytokinesis and polyploidization.4 Therefore, it is not surprising that researchers interested in endomitosis have scrutinized the activity of Aurora B kinase in megakaryocytes. Indeed, initial reports supported the hypothesis that polyploid megakaryocytic cell lines and megakaryocytes have reduced transcription or stability of Aurora B kinase.5,6 However, subsequent studies using confocal microscopy demonstrated that the localization of Aurora B kinase in primary megakaryocytes during endomitosis was similar to that of diploid controls, and that this Aurora B kinase was functional.8

Lordier and colleagues take these studies further and confirm that Aurora B kinase is present and functional in human endomitotic megakaryocytes. Using the chemical inhibitor AZD1152-HQPA, they studied the effects of inhibiting Aurora B kinase on megakaryocyte polyploidy. This is a complex problem, requiring a distinction between the effects on mitotic megakaryocyte precursors and their endomitotic progeny. Although evaluation of the bulk culture suggested that addition of AZD1152-HQPA increased megakaryocyte ploidy, by careful analysis the authors were able to determine that inhibition of Aurora B kinase led to the selective loss of low ploidy, mitotic cells. AZD1152-HQPA caused a chromosomal segregation defect in both mitotic and endomitotic megakaryocytes. However, mitotic cells underwent apoptosis, whereas endomitotic cells survived and continued to cycle at a slightly reduced rate. This difference in survival may be due to the relative overexpression of the antiapoptotic protein BclxL and consequent resistance to the activation of p53 in mature megakaryocytes. In addition, retinoblastoma protein (Rb) was hypophosphorylated in the presence of AZD1152-HQPA, consistent with previous reports that Rb is a target for Aurora B kinase and providing a possible mechanism for the observed delayed cell-cycle entry. Taken together, this study confirms that Aurora B kinase is functional during megakaryocyte endomitosis and provides convincing evidence that loss of Aurora B kinase activity does not promote polyploidization in this cell type. In addition, these studies may have uncovered part of the mechanism by which megakaryocytes avoid apoptosis in response to perturbations of the cell cycle.

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