PML/RARA is detected in cytoplasmic autophagic vesicles after treatment with these agents. Functionally, activation of autophagy by the mammalian target of rapamycin (mTOR) inhibitor triggers PML/RARA destabilization in the NB4 APL cell line, resulting in enhanced ATRA-induced differentiation. Conversely, the autophagy inhibitor BafA impedes treatment-induced PML/RARA degradation and biologic response.

These results are important in several respects. They identify a novel cytoplasmic PML/RARA catabolic pathway and explain why some studies had observed PML/RARA in the cytoplasm. Other oncogenic fusion proteins may share similar features of poor solubility and may be targets of autophagy. This study also raises interesting questions as to the possible links between autophagy and PML, which is highly stress-sensitive and may also assemble into cytoplasmic bodies. Finally, PML suppresses mTOR activity, a key inhibitor of the autophagic process. Then, release of PML from PML/RARA by ATRA or As2O3 treatment induces a self-perpetuating cycle accelerating PML/RARA degradation. The latter could be implicated in enhanced differentiation, as suggested in the Isakson study, but also in loss of self-renewal of APL clonalogenic progenitors. Thus, modulation of autophagy in APL could have important therapeutic consequences.

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

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Comment on Zhang et al, page 2336

Arterial thrombosis: going, gone!

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Most antithrombotic approaches target prevention rather than the more clinically relevant issue of resolution of an existing thrombus. In this issue of Blood, Zhang and colleagues describe a novel and effective therapeutic strategy for clearance of preexisting arterial thrombus in murine models of ischemic stroke.
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 \( \alpha_\beta_3 \) sharing the A11 epitope-bearing \( \beta_3 \) 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.

REFERENCES


shedding light on endomitosis

Amy E. Geddis

Endomitosis is an enigma fascinating to hematologists and cell biologists alike. Whereas aneuploidy can be associated with chromosomal instability and cancer,1 megakaryocytes become polyploid 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

Comment on Lordier et al, page 2345

PLATELETS & THROMBOPOIESIS

Mitotic and endomitotic cycling in early megakaryocytes. Progenitors that will become polyploid proceed through anaphase and then regress their cleavage furrows and re-enter G1 as 4N cells. Aurora B kinase is shown in orange, localized to kinetochores in metaphase, the spindle midzone in anaphase, and the midbody in telophase. Professional illustration by Marie Dauenheimer.

Observational studies have shown that endomitotic megakaryocytes deviate from mitosis in late anaphase, after the initiation of the cleavage furrow.3 Whereas cells undergoing diploid mitoses proceed through cytokinesis and complete division...
Arterial thrombosis: going, gone!

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