A new oncoprotein catabolism pathway

Valérie Lallemand-Breitenbach and Hugues de Thé INSERM/CNRS/UNIVERSITÉ PARIS DIDEROT

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In this issue of Blood, Isakson et al identify autophagy as a new pathway for therapy-induced PML/RARA degradation, a critical determinant for leukemia eradication.

A circulatory system approach that involved depleting the SAP component has recently been published.8 Even if the current antibody does not bind to the heart or the liver, limited organ regression using an agent with a high therapeutic profile can set the stage for important immunotherapeutic approaches to the management of this devastating disease with successive generations of antiamyloid antibodies.

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

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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 clonogenic progenitors. Thus, modulation of autophagy in APL could have important therapeutic consequences.

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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.

A rticular thrombosis is initiated by platelets adhering to the damaged vessel wall. These adherent platelets become activated, leading to activation of the platelet integrin glycoprotein (GP) IIb-IIIa (αIIbβ3), which in binding fibrinogen and von Willebrand factor allows formation of a platelet aggregate or mural thrombus. At the same time, the damaged vessel wall and the activated platelet surface provide an acceleration of localized coagulation leading to thrombus stabilization by fibrin.1,2

Thrombosis precipitating ischemic stroke is a major cause of morbidity and death. The capacity to limit brain infarct formation and resultant permanent neurologic damage requires resolution of the arterial thrombus, ideally within a narrow therapeutic window of up to 4 hours postocclusion. Clinical studies with GPIIb-IIIa receptor antagonists3 or other fibrinolytic approaches4 are not optimal and are typically associated with a high incidence of bleeding. Current treatment of acute ischemic stroke with tissue plasminogen activator shows best utility within 4.5 hours of occlusion and can also be associated with clinically significant bleeding,5 highlighting the pressing need for better and safer therapeutic approaches.

Zhang and colleagues have previously described a unique antiplatelet autoantibody in patients with HIV– or hepatitis C–related thrombocytopenia that recognizes the sequence GPIIIa49-66 and induces platelet lysis, fused to the kringle 1 domain that recognizes fibrin (not fibrinogen). This construct can target an active thrombus (via activated αIIbβ3/polymerized fibrin) providing both dual antithrombotic activity and a unique therapeutic approach. Monovalent antibody also induces oxidative lysis via αIIbβ3, while kringle-containing plasminogen interacts directly with fibrin.

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The bifunctional SLK consisting of the scFv-A11, that binds to an epitope on activated αIIbβ3 (GPIIb-IIIa) and induces platelet lysis, fused to the kringle 1 domain that recognizes fibrin (not fibrinogen). This construct can target an active thrombus (via activated αIIbβ3/polymerized fibrin) providing both dual antithrombotic activity and a unique therapeutic approach. Monovalent antibody also induces oxidative lysis via αIIbβ3, while kringle-containing plasminogen interacts directly with fibrin.

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