PHYSIOLOGY

Forget about thrombosis: Platelets and Alzheimer's disease, yet another sticky situation

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In this issue of *Science Signaling*, Donner *et al.* define a highly interesting role for platelets in mediating the pathogenesis of Alzheimer's disease via a mechanism linked to integrin $\alpha_{IIb}\beta_3$ outside-in signaling and adenosine diphosphate release. These findings raise the intriguing prospect of harnessing antiplatelet drugs for disrupting the nexus between Aβ-induced activated platelets and Aβ fibril and aggregate formation.

The fundamental role of platelets as important mediators of thrombosis and hemostasis is well appreciated, particularly in inciting major cardiovascular complications such as myocardial infarction and stroke (*1*). However, more recently it has become increasingly apparent that platelets are not merely one-dimensional actors that only mediate hemostasis and thrombosis. A large body of experimental evidence has emerged that highlights the importance of platelets in modulating immune and inflammatory responses. The nonhemostatic role that platelets play is in large part due to their ability to adhere to various cell types, in conjunction with the fact that the platelet releasate contains more than 300 proteins and is a rich source of proinflammatory cytokines and chemokines (*2*). Therefore, there is now considerable interest in how platelet functional responses may modulate a broad range of diseases, such as rheumatoid arthritis, sepsis, and malignancy (*3*). In this issue of *Science Signaling*, Donner *et al.* expand the nonhemostatic role of platelets by identifying a new and important role for platelets in the pathogenesis of Alzheimer's disease (AD) (*4*).

The involvement of platelets in the pathogenesis of AD opens up the highly attractive possibility of applying antiplatelet therapy for the treatment and/or prevention of AD. Donner *et al.* have demonstrated a novel mechanism whereby the major platelet adhesion receptor, integrin $\alpha_{IIb}\beta_3$, binds monomeric Aβ, which causes integrin outside-in signaling and downstream activation of SYK and PLCγ2, ultimately resulting in the release of clusterin and adenosine diphosphate (ADP) from activated platelets (Fig. 1A). The release of the chaperone clusterin plays an important role in facilitating the aggregation of Aβ fibrils and therefore the pathogenesis of AD. Preliminary experiments with the AD mouse model APP23 being treated with clopidogrel for a period of 3 months demonstrated that this therapeutic approach produced a trend toward a reduction of Aβ deposits in the hippocampus. However, no other significant effect was detectable. The reason for the relative lack of effect of clopidogrel monotherapy is not entirely resolved by Donner *et al.* Although it is quite possible that clopidogrel therapy may not be effective as an AD treatment, the duration of treatment and time point of therapeutic intervention may be important in determining therapeutic success. Importantly, as clopidogrel is the least potent of the $P2Y_{12}$ inhibitors currently approved, antiplatelet therapy with prasugrel or ticagrelor might be a more promising approach. However, given the multiple pathways mediating platelet activation, a further way forward might be a combination of antiplatelet therapy using a $P2Y_{12}$ inhibitor in conjunction with aspirin, as is commonly used in patients with a coronary stent implantation. It is important to note that clinical studies so far have not demonstrated any benefit of antiplatelet therapy using aspirin in patients with established AD (*5*). However, the data presented by the authors have provided novel mechanistic insights describing alternative platelet activation pathways important in AD pathogenesis, and therefore different therapeutic targets need to be considered.

However, it must be borne in mind that antiplatelet therapy comes with an inherent major downside. All currently approved antiplatelet drugs, especially when used in combination, are associated with substantial bleeding complications, including intracerebral hemorrhage. Therefore, this poses the question of how to safely inhibit platelet activation and Aβ aggregation without these potential risks.

With these limitations in mind, the findings presented by Donner *et al.* raise the exciting possibility that novel antiplatelet agents currently in preclinical development could be applied to inhibit the nexus of platelet activation and Aβ aggregate formation (Fig. 1B). Given the demonstrated central role of $\alpha_{IIb}\beta_3$ and ADP, one potential approach would be the direct inhibition of the interaction between Aβ and $\alpha_{IIb}\beta_3$. Currently approved $\alpha_{IIb}\beta_3$ antagonists can only be administered intravenously and can themselves induce conformational change in the integrin to induce outside-in signaling, thereby inducing paradoxical platelet activation (*6*). However, newer $\alpha_{IIb}\beta_3$ antagonists in preclinical development, such as RUC-2, bind and block nonactivated $\alpha_{IIb}\beta_3$ but do not cause a conformational change, and thus no outside-in signaling (*7*). However, the long-term blockade of $\alpha_{IIb}\beta_3$ of all circulating platelets is likely to pose a high bleeding risk. Therefore, a recombinant single-chain antibody (scFv)—which only blocks activated $\alpha_{IIb}\beta_3$, does not induce paradoxical platelet activation, and has been demonstrated to be associated with a lower risk of bleeding compared with standard $\alpha_{IIb}\beta_3$ antagonists—represents an alternative and potentially safer means to inhibit $\alpha_{IIb}\beta_3$ (*8*). Furthermore, in such an antibody approach, the pharmacokinetic drug profile can be easily tailored for a specific long-term effect.

In addition to the role of integrin $\alpha_{IIb}\beta_3$, Donner *et al.* demonstrate a fundamental role for ADP in promoting the aggregation of Aβ. Therefore, the ability to inhibit both the activated $\alpha_{IIb}\beta_3$ and ADP could be a highly desirable therapeutic strategy. A recently described recombinant scFv that specifically targets activated $\alpha_{IIb}\beta_3$ and contains the catalytic side of CD39 with apyrase activity (*9*), thereby degrading ADP, appears to be a particularly attractive novel therapeutic approach to be tested in the context of AD.

Another recently described approach would be the selective inhibition of integrin outside-in signaling using the small molecule mP_6 (*10*) to dissociate the ligation of Aβ to the integrin from platelet activation and clusterin release.

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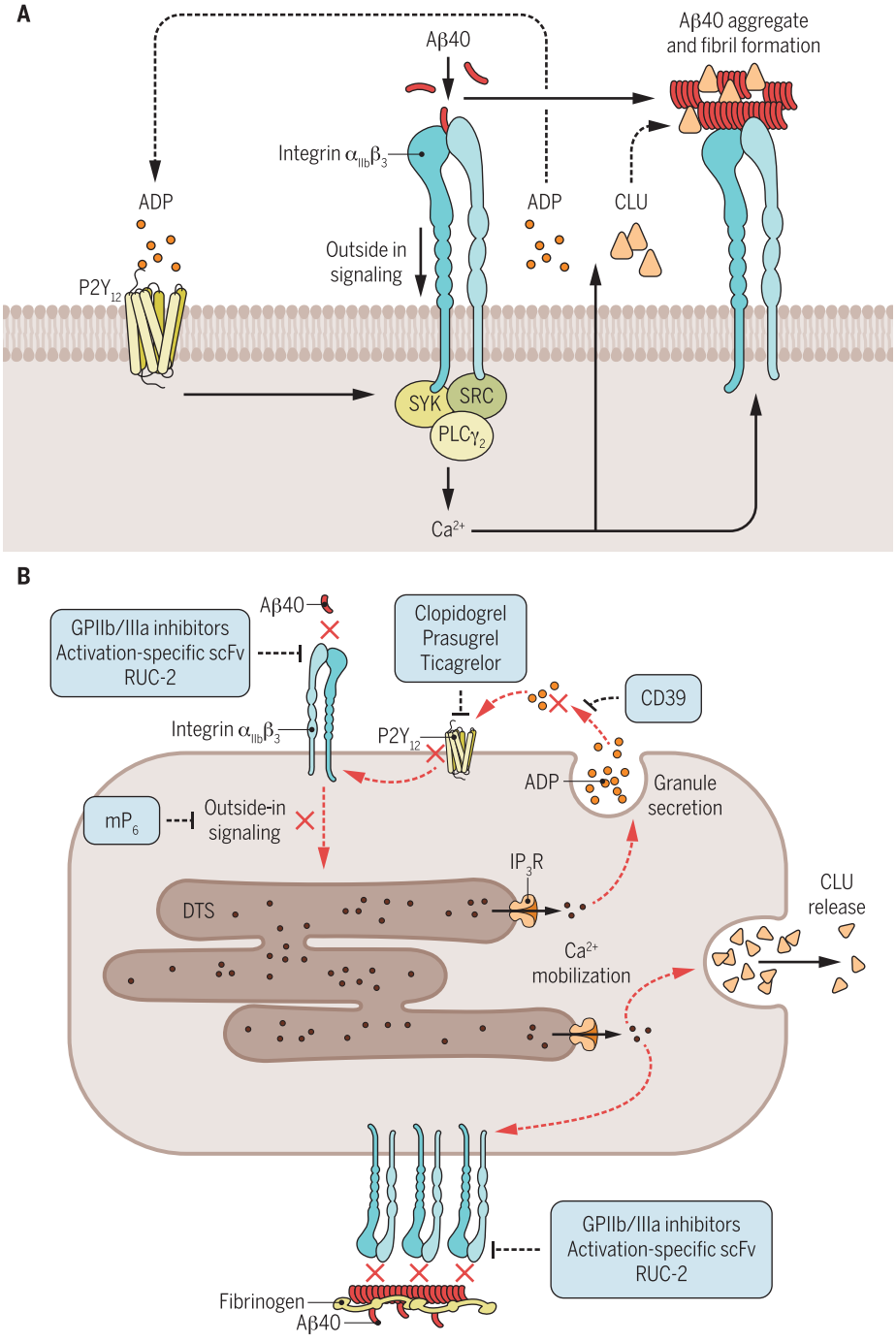

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Fig. 1. Antiplatelet agents currently in preclinical development could be applied to inhibit the nexus of platelet activation and Aβ aggregate formation in Alzheimer's disease. (**A**) The findings by Donner *et al.* (*4*) are summarized as a self-perpetuating cycle in which Aβ activates integrin-mediated secretion of ADP and clusterin (CLU) from platelets, which beget Aβ aggregation and further integrin activation. (**B**) This nexus might be therapeutically targeted at various points, likely most effectively by the combination of multiple antiplatelet agents (blue boxes).

Importantly, this compound has not been associated with hemostatic side effects, thus making it another potentially viable therapeutic strategy in the context of AD.

An intriguing question raised by these findings is what role platelets may play in the pathogenesis of other diseases associated with protein misfolding. The appearance of amyloid deposits as a consequence of misfolded proteins is not restricted to AD but is a common finding in a range of pathologies, including diabetes and atherosclerosis (*11*). Although it has previously been established that misfolded proteins can activate platelets (*11*), in light of the data presented here, it is tempting to speculate that platelet activation in this context may also establish a self-perpetuating cycle that precipitates the formation of further aggregates of misfolded proteins, thereby directly promoting the progression of disease. This is particularly pertinent because it has been shown that the interaction of platelets with several different amyloid fibrils can be inhibited by RGD (Arg-Gly-Asp) peptides, thereby indicating that platelet integrin $\alpha_{IIb}\beta_3$ is indeed the direct binding partner (*11*). Given the global epidemic of diabetes and cardiovascular disease, in conjunction with the limited efficacy of treatment for many amyloid diseases, these fundamental questions will no doubt form the basis for future investigations that will shed new light on the expanding nonhemostatic role of platelets and the pathogenesis of amyloid diseases. Most importantly, unfolding these mechanisms may herald the development of novel therapeutic strategies.

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