

Platelet Activation in Alzheimer's Disease

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Short Communication

Platelets are small cellular fragments derived from megakaryocytes and circulate in the bloodstream at 250.000-400.000/ μ l. Platelets are responsible for hemostasis, but are also involved in thrombosis, inflammation and tissue repair. More importantly, recent evidence suggests a role for circulating platelets in Alzheimer's disease (AD). Actually, platelets express and contain high amounts of amyloid precursor protein, APP (isoform 751 and 770).

Platelets express all the secretases involved in APP metabolism (α -, β - and γ) the majority of APP is metabolized through the non amyloidogenic pathway, and release soluble APP which is known to regulate cerebral hemostasis Van Nostrand et al. [1] Small amount of A β peptides is also produced in platelets either in physiological and pathological conditions through the sequential action of β - and γ -secretases. Platelet A β peptides are stored in specific platelet granules, named α -granules, and are released upon activation at the site of vascular damage. Platelet-derived A β peptides in turn activate platelets Canobbio et al. [2]. We have demonstrated that A β peptides immobilized on a synthetic surface promote platelet adhesion Canobbio et al. [3].

This also happens *in vivo*: cerebral vascular deposits of A β are able to promote platelet adhesion and sustain platelet recruitment to vascular amyloid plaques Gowert et al. [4]. Platelet localization at the site of cerebrovascular injury has been reported by a different study, which demonstrated co-localization of activated platelets with deposits of A β peptides Roher et al. [5]. This is likely to play an important role in the establishment of a vicious circle of platelet activation, A β release and neuronal cell death. Once activated, platelets can release A β peptides in the circulation, increasing their local concentration and contributing to accumulation of A β peptides in the vessel of the cerebrovasculature. A β peptides also reinforce platelet activation through the increase of intracellular Ca²⁺, granule release, integrin activation, and stimulation of multiple signaling proteins, eventually leading to aggregation, thrombus formation and occlusion of cerebral vessels [6-8]. In addition, A β peptides contribute to the development of vascular amyloid deposits and to amyloid aggregation in the cerebral vessels through platelet integrin activation and clusterin release as demonstrated by Donner and collaborators recently this year [9]. Amyloid accumulation in cerebrovasculature eventually induces micro vascular inflammation contributing to generation of a chronic inflammation state Grammas et al. [10]. All these data point to a significant role for platelets in deposition, accumulation, and aggregation of amyloid peptides in cerebral vessels, with deleterious effects on brain circulation.

In this context, it is noteworthy that AD patients show an increased risk of thrombotic complications, stroke and ischemia and that multiple correlations exist between vascular disorders and AD Mielke

et al. [11]. Interestingly, a pre-activated state of circulating platelets has been observed in AD patients. AD platelets show a significant increase in surface expression of P-selectin (a marker of granule secretion) and integrin α IIb β 3 activation, and a higher percentage of circulating aggregates, platelet/leukocytes complexes, coated platelets (a subset of activated platelets with pro-coagulant activity), and platelet released microparticles [12-15].

In our recent publication, we have analyzed platelet activation in a well characterized mouse model of Alzheimer's disease [16]. We have demonstrated that circulating blood platelets from aged triple 3xTg (3xTg-AD) mice display a greater tendency to adhere to components of the sub endothelial matrix, such as collagen, von Willebrand factor and fibrinogen and to form thrombi over collagen under arterial blood flow, compared to platelets from age-matched wild type mice. 3xTg-AD mice contain three mutations associated with familial AD (APP KM670/671NL-Swedish, Tau MAPT P1301L and preselinin1 PSEN1 M146V) that result in overexpression of APP, overproduction of A β 42 and hyper phosphorylation of Tau in neurons [17]. Extracellular deposition of A β is evident in 6 months and Tau pathology in 12 months. A similar pre-activated state of platelets and a pro-thrombotic phenotype have been observed on a different AD mouse model, the APP23. Platelets from aged APP23 mice show enhanced integrin activation, degranulation and spreading on fibrinogen [18]. This finally results in accelerated thrombus formation on collagen under flow and increased vessel occlusion *in vivo*. Differently from 3xTg-AD, the APP23 mice carry only one mutation on APP, the Swedish mutation APP KM670/671NL. All these observations confirm an altered platelet activity that result from Alzheimer's disease progression and may account for the haemostatic abnormalities and vascular complications observed in AD patients.

In this context, it is important to mention that, typically, mouse models of AD carry human mutations under a neuronal promoter, thus the accumulation of A β peptides and Tau hyperphosphorylation are restricted to nervous cells. It is known that in pathological conditions, A β peptides are able to cross the blood brain barrier [19] and in this case the increased platelet activation observed in AD mouse models should be a consequence of this leakage and the increased amount of A β peptides in blood that in turn may activate platelets, as shown in (Figure 1). In familial AD patients, mutations are also present in platelets and may account for a more pronounced pro-thrombotic state than that observed in AD mouse models.

The observation that platelets from AD mice are in a pre- or hyper-activated state suggest that treatment with anti-platelet therapy may have beneficial effects on amyloid deposition in brain vessels and AD progression. To date, treatment of APP23 mice for three months with the P2Y₁₂ antagonist clopidogrel, results in a significant reduction of the deposition of amyloid peptides in cerebral vessels as well as in platelet activation [9].

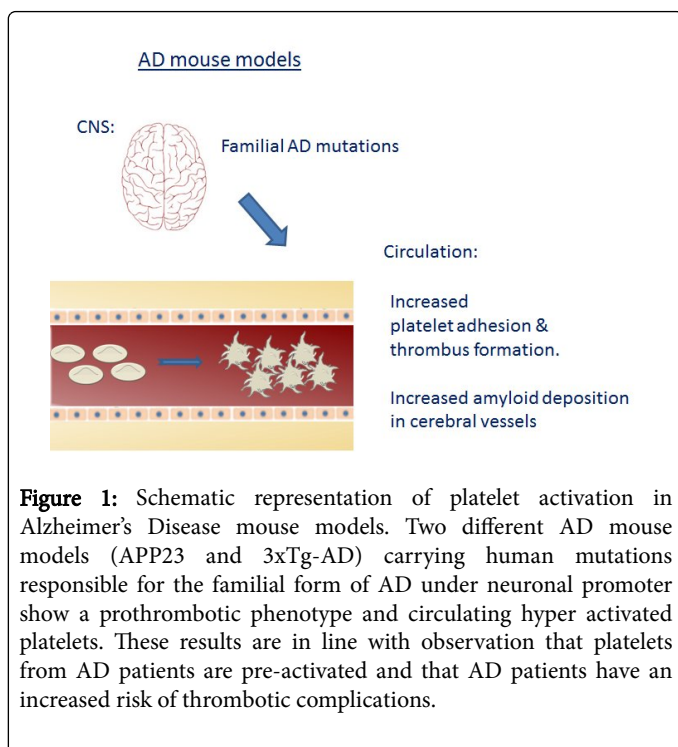


Figure 1: Schematic representation of platelet activation in Alzheimer's Disease mouse models. Two different AD mouse models (APP23 and 3xTg-AD) carrying human mutations responsible for the familial form of AD under neuronal promoter show a prothrombotic phenotype and circulating hyper activated platelets. These results are in line with observation that platelets from AD patients are pre-activated and that AD patients have an increased risk of thrombotic complications.

The use of AD mouse models, instead of human patients, to investigate possible alterations of blood platelet functions offers several important advantages that make this approach extremely informative: it allows analysing and comparing platelet reactivity in drug-free animals with an identical genetic background, thus reducing possible individual-related variability and interference due to pharmacological treatments administered to many patients. In addition, the temporal profile of AD onset and progression in mouse models is generally well characterized, and, it is therefore possible to follow the evolution of platelet reactivity over time across the whole life span of the animal and to correlate the results with the progression of the pathology and brain tissue damages. Finally, AD mice typically carry specific genetic mutations that are causative of the pathology in humans, and thus this approach may allow the dissection of the mechanisms linking selected mutations to specific alterations of platelet function.

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