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Letter

Platelet antioxidants: A conundrum in aging

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Platelet activation requires production of reactive oxygen species (ROS) [1], and the levels of ROS are tightly regulated by antioxidants. Under the condition of oxidative stress such as during aging, an over-production of ROS or diminished levels of anti-oxidants may tip the balance towards a pro-thrombotic platelet phenotype. Indeed, age-related increase in platelet ROS and platelet activation has been observed [2–5], but a distinct mechanistic pathway has not been established.

The recent findings by Jain and colleagues [6] emphasize a possible age-related adaptation in platelets to increased oxidative stress. Through an elegant cross-sectional and longitudinal study-design in humans and mice, authors demonstrated that age is associated with a non-linear regulation of redox homeostasis. While the age-related increase in platelet activation has been established in humans [4], most studies lack data from the very-old-age group (>80 years) [5]. In this regard the report by Jain et al. [6] is very intriguing: While platelets from middle-age (40–59 years) to old-age (60–79 years) subjects displayed elevations in ROS, activation markers, and a decrease in antioxidants; the very-old-age subjects (>80 years) demonstrated lower ROS levels, increase in anti-oxidants and relatively quiescent and less apoptotic platelets. The authors recapitulated these findings in mice: 12-month-old mice displayed elevation in platelet-ROS and -activation that decreased at 18–24 months with corresponding increase in antioxidants. Authors concluded that the adaptive increase in antioxidants at advanced age protects from platelet activation. Although these findings are unique, the translational implication is questionable. First, even though authors showed decreased platelet function in very-old-age subjects, the existing literature does not suggest a lower risk of thrombosis in this age-group, implying that the observed functional-adaptability in platelets may not affect thrombotic susceptibility. Second, the findings in mice does not corroborate with previous reports where mice ≥18 months exhibited increased intra-platelet ROS, platelet activation and arterial thrombosis [2,3], despite increase in platelet-antioxidants such as superoxide-dismutase (Sod1) and catalase [2].

One explanation for disparate findings could be the differential role of antioxidant pathways in adaptive vs. protective responses. For example, an increase in antioxidant enzyme Sod1 may represent adaptation to increased superoxide production during aging. However, such adaptive response will result in an inadvertent increase in H_2O_2 and thus adaptive increase in catalase may occur to get rid of excess H_2O_2. Dayal et al. [2] demonstrated that despite increases in platelet-Sod1 and -catalase in aged mice, overexpression of glutathione-peroxidase, the enzyme that hydrolyzes H_2O_2, rescued aged-mice from increased platelet activation and thrombosis. This suggests that changes in Sod1 and catalase with age were adaptive rather than protective. Second, Jain and colleagues [6] used non-specific methods to detect ROS levels, so the findings should not be considered conclusive [7]. Finally, despite the similar burden of comorbidities in old-age and very-old-age groups, differences in the ROS levels and platelet-activation existed. The authors try to account for these differences using longitudinal studies in mice in absence of comorbidities and demonstrated that survival of mice beyond 18 months correlates with the increased levels of platelet-catalase and -Sod1. But, it is not clear why mice had such high mortality at 18 or 20 months in their hands, given that the lifespan of C57Bl6J mice is beyond 24 months. Was the early death related to a thrombotic consequence, or to the presence of other age-related inflammation/malignancy?

Overall, a major strength of the study by Jain et al. [6] is that they used clearly defined age ranges with adequate sample size within each group, and they confirmed the findings using mice. They also quantified the relative expressions of antioxidants at the mRNA and protein levels and corroborated the levels with enzymatic activity. Based on their observation, authors advocate for less aggressive anti-platelet therapy in elderly patients citing several reports of increased major bleeding on aspirin [8], or dual anti-platelet therapy (DAPT) with clopidogrel [9]. Interestingly, a high percentage of elderly patients (age > 75 years) have residual platelet reactivity despite being on DAPT [10], suggesting that in addition to an increase in bleeding risk, the thrombotic risk may also be high in the very-old-age due to uncontrolled platelet activation. Therefore, taking advantage of initial findings of Jain et al. [6], a more comprehensive longitudinal study is needed in healthy young, middle-aged, old-age and very-old-age subjects to track what pathways are potentially altered at different stages of aging and whether it dictates the thrombotic susceptibility.

Authorship contribution

K.S.I. prepared the first draft and helped with final preparation and editing of the manuscript. S.D. conceived the idea, designed format, and co-wrote the manuscript.

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Declarations of interests

The authors declare no conflicts of interest.

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