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Fungal-derived oligoglucosides protect Candida albicans from the immune system attack

Platelets play a crucial role in hemostasis, thrombosis, and pathogen clearance. Many pathogenic fungi can interact with platelets in circulating blood. This interaction between the fungus and the host occurs at the level of the fungal cell wall, which consists mainly of polysaccharides associated with proteins and lipids. Its innermost layers are formed from a dense network of polysaccharides consisting of chitin and β-glucans. The human pathogenic fungus *Candida albicans* is the predominant cause of invasive forms of candidiasis. *C. albicans* infections continue to be a serious clinical problem with respect to increased morbidity and mortality. A recent study has shown that administrating β-1,3 glucan fractions reduces leukocyte infiltration, in particular neutrophils into the gut mucosa and enhances mouse survival in a chemically-induced colitis model. Clinically, β-1,3 glucans derived from the fungal cell wall are released in the circulation during infection and their detection allows the early diagnosis of an invasive fungal infection, but the rolef β-1,3 glucans in the modulation of platelet activities and platelet-neutrophil interactions is unknown.

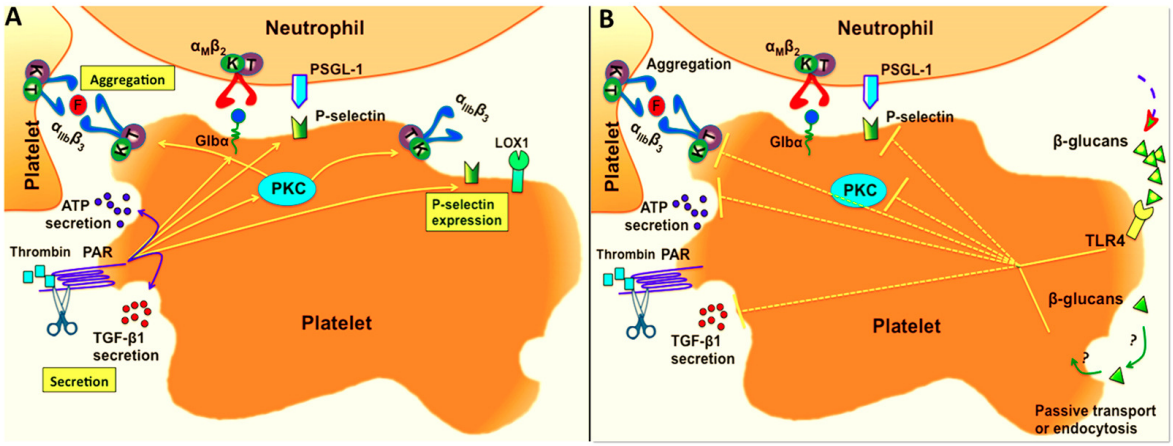

Fig. 1. Schematic overview showing the effect of β-1,3 glucan fractions on platelet activities. A, Thrombin interacts with protease activator receptors (PAR) leading to the activation of protein kinase C (PKC), αIIbβ3 (3), P-selectin, GIbα, and the secretion of ATP and TGF-β1. Inside out signaling leads to the activation of talin (T) and kindlin (K) resulting in conformational changes of integrin αIIbβ3 that mediate the formation of platelet aggregation by binding to soluble fibrinogen (F). B, β-glucan fractions modulate platelet activation mediated via TLR4 stimulation by decreasing ATP release, PKC phosphorylation and TGF-β1 production.

Our study show that short fractions of highly purified β-1,3 glucans derived from *C. albicans* modulate the immune system including the platelets. These β-1,3 glucan fractions decrease platelet aggregation, and modulate the coagulation process. The biological activities of these oligoglucosides depend on their degree of polymerization and their concentration. They also affect the regulation of platelet receptors (P-selectin and $\alpha_{IIb}\beta_3$). Clinically, β-1,3 glucans are released in the case of fungal bloodstream infection and are detectable several weeks before the isolation of the Candida species from the blood or before the onset of clinical symptoms. Interestingly, our study shows that the short fractions of β-1,3 glucans at a low concentration reduce platelet activation, and both platelet-*C. albicans* and platelet-neutrophil interactions,

which allow *C. albicans* to be protected from leukocyte activation. Mechanistically, these oligoglucosides block protein kinase C activation in platelets that affect the regulation of platelet receptors. Bedsides, we showed that the pentaglucosides did not modulate the expression levels of TLR2 in platelets. In contrast, the pentaglucosides reduced platelet activities through TLR4 mediated TGF-β1 production and ATP release, and blocking this receptor by an anti-TLR4 antibody abolished the effect of the pentaglucosides on platelets suggesting that TLR4 is involved in the immuno-modulatory effects induced by BGFs. Overall, our study offers new insights, showing that these fungal-derived oligoglucosides are not involved exclusively in the protection of *C. albicans* during infection but also in the coagulation process and in the modulation of platelet activation mediated via TLR4 stimulation. Thus, short fractions of β-1,3 glucans promote fungal escape from the host defense. Finally, we show for the first time that the soluble short fractions of β-1,3 glucans act as a shield for pathogenic yeasts and modulate the activation of platelets, which are placed to initiate an immune response against pathogen infection.

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