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Classical Hematology (Red Cell Disease Thrombosis and Hemostasis)

IGFBP-6 AS A POTENTIAL REGULATOR OF PLATELET PROCOAGULANT ACTIVITY

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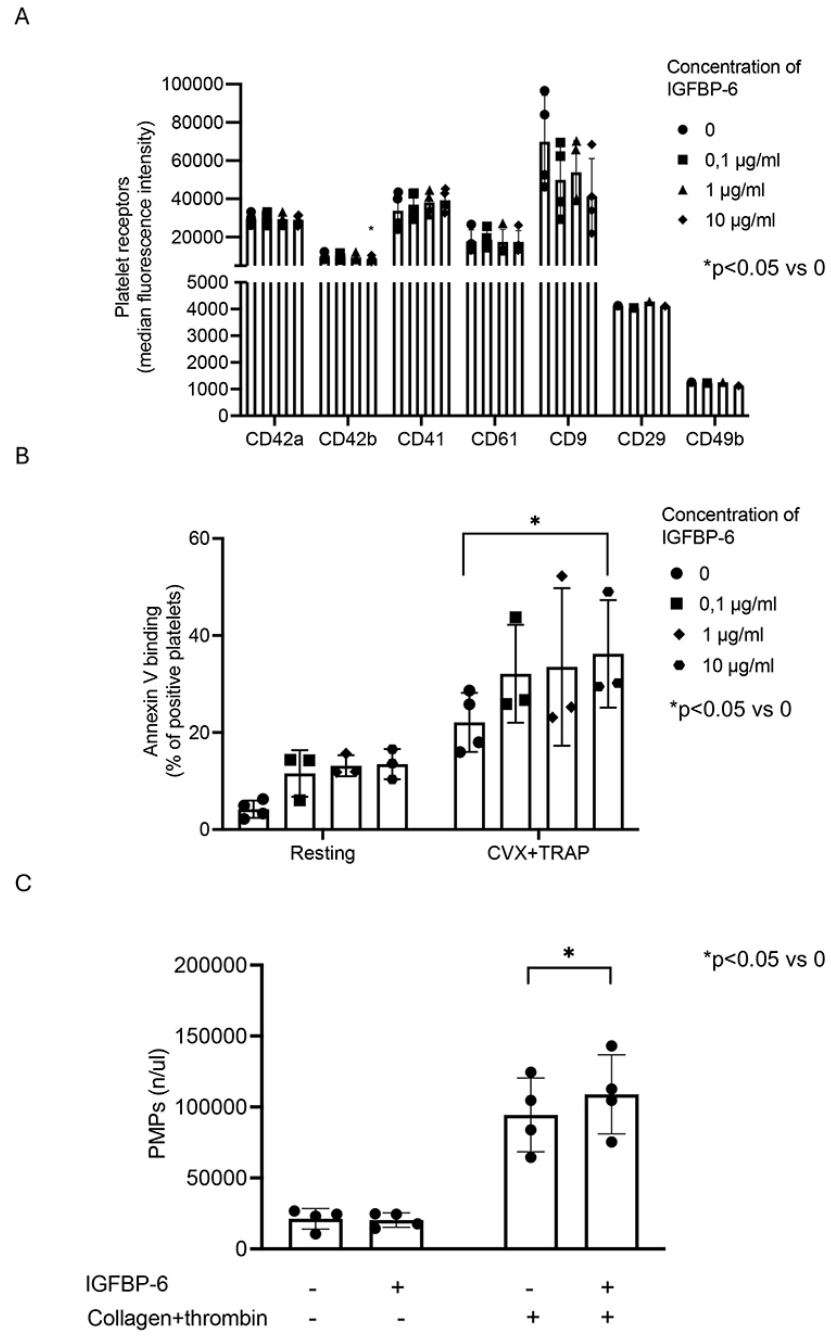
Introduction: Insulin-like growth factor binding protein-6 (IGFBP-6) is a multifunctional protein primarily known for its high affinity for IGF-II but with also IGF-independent immunomodulatory properties. It is expressed in several immune and stromal cell types, including dendritic cells, fibroblasts, endothelial cells, and eosinophils, and plays key roles in inflammation, tissue repair, and fibrosis by promoting immune cell chemotaxis, reactive oxygen species (ROS) production, and fibroblast activation (PMID:35457175), while also exerting vasculoprotective effects in models of atherosclerosis. In particular, reduced IGFBP-6 expression has been associated with unstable atherosclerotic plaques in human carotid arteries (PMID:32037372), whereas a recent study showed that endothelial IGFBP-6 limits vascular inflammation and atherosclerosis by modulating endothelial and macrophage responses (PMID:39794479). Given that platelets are central effectors in both hemostasis and vascular inflammation, these findings raise the hypothesis that IGFBP-6 may modulate platelet phenotype and procoagulant activity at the interface between inflammation and coagulation.

Methods: Spatial proteomics was carried out by molecular pixelation. Platelet rich plasma was incubated with IGFBP-6 at three different concentrations (0.1 – 1 – 10 ug/ml) for 60 minutes at room temperature. Expression of the major platelet receptors was assessed by flow cytometry. Platelet alpha-granule secretion was assessed as P-Selectin binding, and platelet alphaIIbbeta3 activation as PAC-1 binding by flow cytometry. Procoagulant platelets were assessed by measuring phosphatidylserine (PS) exposure on the platelet membrane by Annexiv V binding and Tissue factor (TP) expression by flow cytometry. Platelet extracellular vescicles (EVs) were counted in the supernatants of platelets stimulated with collagen and thrombin by flow cytometry.

Results: Spatial proteomics analysis revealed an altered expression of the platelet marker CD41 after incubation of a leukocyte–platelet suspension with IGFBP-6. Pre-incubation of isolated platelets with IGFBP-6 did not affect the expression of major platelet receptors, except for a slight but significant decrease in GPIb/IX/V at 10 µg/mL IGFBP-6. P-selectin expression and PAC-1 binding were also unchanged, suggesting that IGFBP-6 does not directly induce platelet activation. Flow cytometry revealed an increase in Annexin V binding, indicating an enhanced exposure of procoagulant phosphatidylserine on the platelet surface following pre-incubation with IGFBP-6 at 10 µg/mL. Consistently, tissue factor binding was increased, together with a higher release of extracellular vesicles in the supernatant.

Conclusions: Our findings identify IGFBP-6 as a novel regulator of platelet procoagulant activity, supporting a model in which IGFBP-6 contributes to the fine-tuning of thromboinflammatory responses at the vascular interface.

Figure 1


A
Platelet receptors (median fluorescence intensity)
100000
80000
60000
40000
20000
5000
4000
3000
2000
1000
0
CD42a
CD42b
CD41
CD61
CD9
CD29
CD49b
Concentration of IGFBP-6
0
0,1 µg/ml
1 µg/ml
10 µg/ml
*p<0.05 vs 0
B
Annexin V binding (% of positive platelets)
60
40
20
0
Resting
CVX+TRAP
*
Concentration of IGFBP-6
0
0,1 µg/ml
1 µg/ml
10 µg/ml
*p<0.05 vs 0
C
PMPs (n/ul)
200000
150000
100000
50000
0
*
*p<0.05 vs 0
IGFBP-6 - + - +
Collagen+thrombin - - + +