(PF855) GALECTIN-1 AS A MEDIATOR OF THROMBOTIC RISK IN MYELOPROLIFERATIVE NEOPLASMS?

Topic: 15. Myeloproliferative neoplasms - Biology & translational research

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Background

Thrombotic events are a major cause of morbidity and mortality for patients with myeloproliferative neoplasms (MPNs), with an increased incidence of arterial and venous events including heart attacks, strokes and deep vein thrombosis, affecting ~10% of patients with myelofibrosis, ~20% with essential thrombocythemia and ~30% with polycythemia vera (PV). The increased incidence of thromboses is reduced, but not completely ameliorated, by current primary prevention strategies including aspirin and cytoreduction. We recently identified Galectin-1 (Gal1) as a novel driver of progression in MPNs (Li *et al., Sci Trans Med* 2024), showing induction of Gal1 expression by both the MPN clone and the cells in the bone marrow niche. We also observed increased platelet Gal1 mRNA as a sensitive biomarker of disease trajectory. Other groups reported increased platelet Gal1 protein in MPNs (Kelliher *et al., Blood Advances* 2024). Galectins, including Gal1, are β-galactoside binding proteins and have previously been implicated as platelet agonists. Gal1 has been shown to activate platelets through αIIbβ3, however, its impact on platelet function in MPNs has not been studied.

Aims

In the present study we investigate whether elevated Gal1 levels in patients with MPNs may contribute to the pro-thrombotic phenotype, and if pharmacological blockade of Gal1 might be a viable novel therapeutic strategy.

Methods

To interrogate platelet - Gal1 interactions we utilised fluorescence microscopy, multi-colour flow cytometry, biolayer interferometry and western blotting as well as a parallel flow chamber to probe for whole blood thrombus formation.

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Results

We show for the first time that Gal1 induces thrombus formation in a whole blood parallel flow chamber at arterial shear rates, including samples from patients with PV who were receiving aspirin therapy. Further, we demonstrate that Gal1 dose-dependently supports platelet adhesion. When assessed using flow cytometry, Gal1 induces αIIbβ3 activation ($p < 0.01$) in a dose-dependant manner, and exerts additive effects to low-dose thrombin ($p<0.05$), indicating that Gal1 might prime platelets to be more sensitive for activation upon secondary agonist exposure.

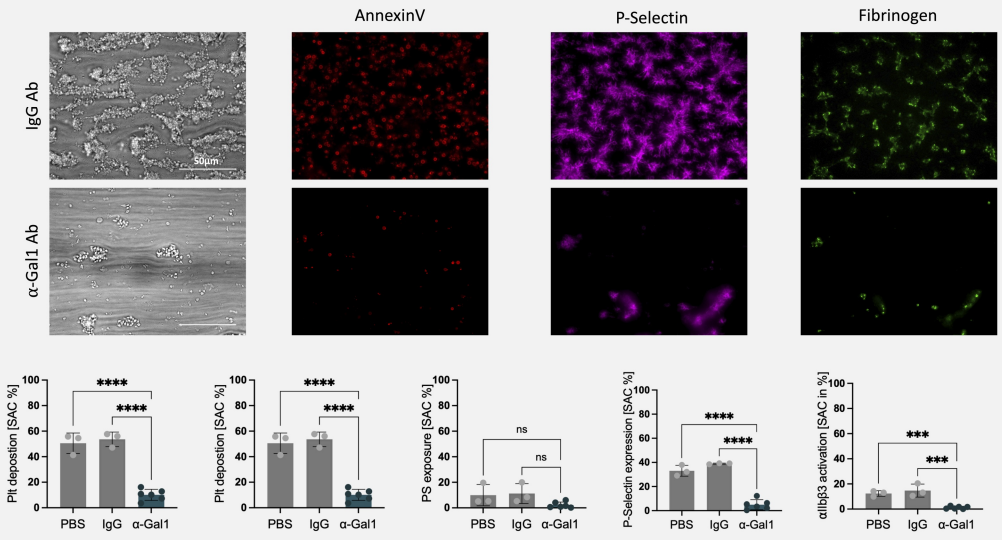
Gal1 supports formation of large platelet aggregates and pro-coagulant, phosphatidylserine(PS)-exposing platelets. As GPVI is known to trigger PS-exposure, this observation prompted us to examine whether GPVI may also play a role in Gal1-induced platelet activation, in addition to αIIbβ3. Indeed, biolayer interferometry assays confirmed specific and glycan-dependent binding of Gal1 to GPVI (K_D = 0.24 µM) and western blots of washed platelets stimulated with Gal1 indicated phosphorylation of GPVI downstream signalling molecules. Additionally, inhibition of GPVI signalling with PRT-318 significantly reduced platelet spreading ($p<0.0001$) as well as thrombus formation ($p<0.001$) on Gal1.

Finally, antibody-mediated neutralisation of Gal1 significantly impaired thrombus formation in response to Gal1, in whole blood from healthy donors as well as PV patients on aspirin therapy (for PV samples $p<0.0005$, Fig1).

Summary/Conclusion

Collectively, these findings indicate that Gal1 mediates platelet activation through αIIbβ3 outside-in signalling as well as via GPVI-dependent mechanisms. Given our prior work identifying a mechanistic role for Gal1 in myelofibrosis and leukaemic transformation in MPNs, targeting Gal1 in MPNs presents a potential multi-pronged strategy to improve patient outcomes in MPNs.

Figure 1: Antibody-mediated neutralisation of Gal1 abolishes thrombus formation in PV patients



PV patient whole blood perfused through a parallel flow chamber at arterial shear rates over Gal1+vWF-BP+PolyL. Thrombus formation and expression of platelet activation markers is abolished by an anti-Gal1 neutralising antibody, t-test, n=4.

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