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Short Communication

Binary Role of Hemoglobin in Thrombosis

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ABSTRACT

Hemolysis often coincides with thrombotic events in clinical settings. The liberated hemoglobin has been postulated as a potential contributor to thromboembolism. To elucidate the role of hemoglobin in hemolytic thrombosis, we have recently conducted a study employing mice lacking Von Willebrand Factor (VWF), and provided intriguing evidence suggesting the potential non-VWF-dependence of hemolytic thrombosis. Remarkably, the observed thrombotic phenotypes in these VWF-deficient mice closely resembled those manifested in wild type mice following repeated hemoglobin administration. Additionally, we found that hemoglobin can bind to the active A1 domain of VWF blocking the VWF-GPIb interaction and a single administration of hemoglobin effectively inhibited VWF-mediated thrombosis in wild type mice. These multifaceted findings underscore the potential of acellular hemoglobin to exert both deleterious and beneficial effects on hemostasis and overall health.

Keywords: Hemoglobin; Thrombosis; Von willebrand factor; Platelets; Thrombocytopenia

DESCRIPTION

Hemolysis is the breakdown of erythrocytes. In disease, the anomalous destruction of red blood cells leads to the release of encapsulated hemoglobin into the surrounding milieu. This aberrant degradation can originate intrinsically due to hereditary defects in red blood cells, as observed in sickle cell disease, or extrinsically triggered by factors like autoimmune antibodies or toxic agents targeting red blood cells [1]. Within the context of Thrombotic Microangiopathy (TMA), microangiopathic hemolysis ensues. The mechanistic cleavage of red blood cells, evidenced by the presence of schistocytes, occurs when these cells traverse micro thrombi under conditions of heightened shear stress. Intriguingly, it has been observed that hemoglobin released during hemolysis not only constitutes a consequence but also actively accelerates micro thrombus formation [2]. Several *in vitro* studies have demonstrated that hemoglobin can facilitate the interaction between Von Willebrand Factor (VWF) and platelets, a crucial event in thrombosis initiation [3]. Consequently, this phenomenon of hemolytic thrombosis has been pathologically linked to VWF-dependence. Nevertheless, to date, a definitive correlation between the patient's VWF level and the severity of hemolytic thrombosis remains elusive. Furthermore, the identified weak interaction between hemoglobin and VWF proves insufficient to ascertain thrombotic risk in patients with mild hemolysis.

We have recently performed a study on the potential non-VWF-dependence of hemolytic thrombosis [4]. The study encompassed a comprehensive evaluation of the thrombotic risk induced by hemoglobin in mice deficient in VWF. Remarkably, the observed thrombotic phenotypes in these VWF-deficient mice closely resembled those manifested in the wild type mice when subjected to repeated hemoglobin administration. This compelling evidence indicates that the thrombotic manifestations are likely independent of VWF, thus suggesting an alternative underlying mechanism for hemoglobin-induced thrombosis.

Although the precise mechanism underlying hemoglobin-induced thrombosis remains uncertain, evidence from our study suggests that the accumulation of hemoglobin plays a crucial role. Our investigations indicate that multiple intravenous injections of hemoglobin, as opposed to a single injection, are capable of inducing thrombosis and thrombocytopenia. Notably, the rapid clearance of hemoglobin from the plasma by its native scavenger

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protein, haptoglobin, may account for the observed phenomenon. The half-life of hemoglobin, as measured in our study, approximates 16 minutes. Interestingly, single administration of hemoglobin within this brief timespan did not impact platelet count or VWF levels, implying that hemoglobin may not directly interact with platelets or VWF. This is important for the inconsistency between the results from *in vivo* study and *in vitro* study. The thrombocytopenia induced by repeated hemoglobin administration appears to involve an indirect pathway between hemoglobin and platelets, necessitating either a certain threshold of hemoglobin accumulation or its sustained presence. Encouragingly, upon suspension of hemoglobin accumulation, platelet count showed a gradual recovery to baseline levels within 72 hours, as observed in our experiments. These findings suggest that while hemoglobin resulting from hemolysis in Thrombotic Microangiopathy (TMA) may indeed accelerate the formation of micro thrombi, thereby perpetuating hemolysis, it alone may not be sufficient to catalyze thrombosis in the *in vivo* context. The multiple hemoglobin administrations in our experimental model, although not fully replicating the continuous hemoglobin release seen in patients with ongoing hemolysis, effectively elicited comparable phenotypes, including micro thrombosis and thrombocytopenia, akin to those found in such patients. As we advance, it would be advantageous to conduct clinical studies on individuals with hemolysis; particularly those with Von Willebrand Disease (VWD), to corroborate the insights gleaned from our mouse model and ascertain the translational implications for human pathology.

The interaction between hemoglobin and the activated A1 domain of von Willebrand factor (VWF) observed in our investigation diverges from the reported binding between hemoglobin and the inactivated A1 domain of VWF. This interaction occurs specifically when the binding sites in loop 1-2 and loop 3-2 on the A1 domain are exposed, which typically transpires under conditions of shear stress that elongate the VWF molecule [5]. Upon binding, hemoglobin effectively obstructs the association of platelet Glycoprotein Ib (GPIb) and impairs VWF-mediated thrombosis. The notably high binding affinity of this interaction renders the reaction sensitive to even low concentrations of hemoglobin.

We further ascertained that at micro molar concentrations, hemoglobin efficiently attenuates $FeCl_3$-induced thrombosis, a process well-regulated by VWF. The low binding affinity between hemoglobin and the inactivated A1 domain of VWF at this concentration indicates that hemoglobin would not significantly interact with circulating VWF. This discrimination in binding VWF offers the benefit of selectively exerting an inhibitory role on VWF-mediated thrombosis without detrimentally impacting VWF plasma levels. Given VWF's direct involvement in platelet activation and its role as a carrier of factor VIII (FVIII), its plasma level holds crucial clinical importance for bleeding control. From a therapeutic perspective, hemoglobin-based strategies present a potentially lower bleeding risk compared to alternative approaches. In the tail bleeding test, mice administered hemoglobin exhibited only a twofold increase in bleeding time, significantly less than observed in mice administered an anti-VWF polyclonal antibody, which effectively depletes VWF/FVIII from plasma. This finding underscores the potential of hemoglobin-like medicines for the treatment of VWF-mediated thrombosis.

CONCLUSION

Hemoglobin, being an intrinsic constituent in red blood cells, typically remains sequestered within cellular confines. As presented in our study, the acellular hemoglobin presents the potential for both deleterious and beneficial effects on hemostasis and overall health. Further investigations are warranted in future to elucidate the underlying mechanisms and functions of hemoglobin in the context of coagulation, which will contribute to a more sophisticated understanding of this native component within our physiological milieu.

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