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Topic of Research: High altitude venous thrombosis: - An interplay between inflammation and coagulation

Findings of the study

The finding of the study is key events that lead to vascular inflammation which is the recruitment of leukocytes (monocytes) to the endothelium. The adhesion of monocytes to endothelial cells is usually considered an initial step in the development of atherosclerotic plaque. Hypoxia increases endothelial adhesion of monocytes appearing as a result from the interaction between β2 integrin (LFA-1) on monocytes and JAM-1/F11R on the endothelial cells. In this study, β2 integrin LFA-1 expression was markedly increased in THP-1 cells stimulated with hypoxia and DMOG and was attenuated in cells treated with DIM, MCC950, and SML0499. Based on these results, the HIF- 1α-NLRP3 inflammasome axis plays a significant role in the adhesion of monocytes to endothelial cells through β2 integrin and JAM-1 under hypoxia. Inhibiting this axis through DIM, MCC950, and SML0499 plays a crucial role in the genesis of vascular inflammation by abrogating monocyte adhesion to endothelialcells by inhibiting the interaction of β2 integrin of monocytes and JAM-1 on the endothelial cells.

Our studies revealed the role of NLRP3 inflammasome in regulating thromoinflammation under hypoxia. Systemic inflammation has been shown to be a strong prothrombotic stimulus, with processes involving increased procoagulant factors, inhibition of natural anticoagulants, fibrinolytic activity, and enhanced platelet reactivity (Esmon, 2003; Puhlmann et al., 2005). Here we provide a molecular mechanism by which hypoxia potentiates thrombosis through activation of NLRP3 inflammasome in macrophages. Coagulation induced by hypoxia was abolished by HIF-1α, NLRP3 inhibition, and catalytic activity of caspase-1, suggesting that hypoxia-induced coagulation depends on inflammasome activation.

A pharmacological inhibition of HIF-1α and NLRP3 could decrease the expression of HIF-1α, NLRP3, Caspase-1, cytokine IL-1β, FIII, FVII and PAI-1 when treated with hypoxia and HIF-1α activator. A pharmacological inhibitor of HIF-1α, DIM (Riby, Firestone, and Bjeldanes., 2008), NLRP3 inhibitor, MCC950 (Coll et al., 2019) and catalytic activity of caspase-1, SML0499 further confirmed the contribution of HIF-1α-NLRP3 in hypoxia induced thrombosis. To investigate how NLRP3 inflammasome contribute to hypoxia induced thrombosis, we demonstrated TF, a pivotal coagulation trigger, released from macrophages under hypoxia. Monocytes and macrophages appear to be the main sources of TF in blood after inflammasome activation, even though TF is produced in a variety of cell types (Grover and MAckman., 2018). We explored a pharmacological inhibitor of HIF-1α and NLRP3 could inhibit the expression and activity of tissue factor and PAI-1, thereby suggesting the role of HIF-1α-NLRP3 axis in hypoxia induced thrombosis by amplifying the expression of tissue factor. To identify the possible mechanism, we studied the correlation between cytokine HIF-1α-NLRP3, NLRP3-IL-1β, IL-1β-Egr-1 and Egr-1 and TFU. We found that HIF-1α- NLRP3 axis is highly correlated to TF expression, thereafter, promoting thrombosis. Although many group have proven the potential involvement of IL-1β in triggering TF expression (Pulmann et al., 2005; Liberale et al., 2019), we postulate the involvement of NLRP3 inflammasome in hypoxia induced coagulation through IL-1β.

In concurrent with our study, platelets have been identified to amplify the inflammation in rheumatoid arthritis through IL-1β, an IL-1β driven disease. Furthermore, a recent study showed that platelets had pro-atherogenic effects by skewing monocytes into pro-inflammatory macrophage morphologies (Boilard et al., 2010; Dinarello., 2011) These finding need further validation to identify the platelets factor that boost the inflammasome activation in leukocytes that further aggravates thrombosis.

Bullets points

- The study for the first time elucidated the molecular mechanistic pathway involved in venous thrombosis under hypoxic environment.
- Involvement of NLRP3 inflammasome in recruitment of monocytes, activation of monocytes/macrophage and amplification of the NLRP3 inflammasome activation.
- Regulation of Early growth response-1 in hypoxia induced coagulation.
- Activation of extrinsic pathway of coagulation cascade through tissue factor under hypoxia is regulated is HIF-1α-NLRP3 axis.
- Inhibition of HIF-1α, NLRP3 and Egr-1 prevents from inflammation mediated coagulation.
- Egr-1 connects HIF-1α, NLRP3 driven inflammation to the production of tissue factor, ultimately culminating in the process of thrombogenesis.