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Elevated Transferrin at High Altitude: Trick or Treat?

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Living at high altitude for animals is a challenge due to low environmental oxygen availability (hypoxia), dehydration, and low temperature. Hypoxia is a state in which tissues are deprived of an adequate oxygen supply. Due to the key role of iron in mediating the oxygen-carrying capacity of blood, oxygen metabolism and iron homeostasis are closely linked. In high altitude, hypoxia induces erythropoiesis, thus leading to progressive iron consumption and eventually iron deficiency.[1]

Exposure to high altitude is a well-recognized risk factor for thromboembolic disorders, including venous thrombosis, pulmonary thromboembolism, mesenteric vein thrombosis, cerebral vein thrombosis, and deep vein thrombosis, consequent to blood hypercoagulation.[2] Under steady-state conditions, the normal coagulation pathway maintains a balance between the procoagulant and the anticoagulant pathways via fine-tuned interactions among nineteen clotting factors which participate in the coagulation cascade.

Recently, the main plasma iron carrier transferrin (Tf) has emerged as an important clotting regulator and an adjuster in the maintenance of coagulation balance with the ability to modify the coagulation cascade. Tf has the critical role to transport iron in the blood and deliver it to target cells through Tf receptor 1(TfR1)-mediated endocytosis. Under normal conditions, Tf (normal plasma concentration ~40 μM) is primarily bound to fibrinogen (normal plasma concentration ~10 μM) in a 4:1 stoichiometry. Thus, plasma Tf sequestration by fibrinogen leaves little Tf free in the circulation.[3,4]

Exposure to low atmospheric oxygen can lead to erythropoietin synthesis to stimulate red blood cell production, which in turn increases the demand for iron to synthesize hemoglobin. This requires low oxygen levels to activate the hypoxia-inducible factor (HIF)-1α, a transcription factor that regulates the expression of hundreds of genes promoting adaptive responses to hypoxia, including genes involved in red blood cell production and iron utilization.[5] Among these genes, the plasma iron transport protein Tf is regulated by HIF-1α at the transcriptional level through direct interaction with the enhancer region of the Tf gene. Under hypoxia, HIF-1α activation increases Tf expression in such a way that Tf levels exceed fibrinogen. Under these conditions, excess free Tf creates a procoagulant environment by enhancing thrombin and factor XIIa (FXIIa) while inhibiting antithrombin activities. Thus, Tf acts as a prothrombotic protein that promotes blood coagulation, inducing hypercoagulability.[3] Nevertheless, whether Tf elevation at high altitudes promotes hypercoagulability has remained unexplored.

This aspect was explored by Li and coauthors in a study recently published in Blood by monitoring the concentration and activity of coagulation factors in plasma from humans exposed to different altitudes, and mice exposed to hypoxia and low temperature as well as subjected to experimental thrombosis and stroke.[6] Little or no changes were observed in plasma fibrinogen, prothrombin and FXII with the increase in altitude. However, altitude was found associated with enhanced plasma enzymatic activities of thrombin and FXIIa in both humans and mice.

While serum iron levels were decreased, plasma Tf was significantly elevated in humans and mice at high altitude, suggesting a feedback mechanism to compensate for the reduced iron availability and a physiological attempt to replenish iron and oxygen at high altitude.[6] Exposure to hypoxia or cold temperature mimicking high altitude conditions upregulated Tf through HIF-1α activation in mouse livers. Treatment with Tf antibodies and HIF-1α inhibitors, or viral knockdown of Tf reversed both hypoxia- and low temperature-induced Tf upregulation. Importantly, the increase in Tf and HIF-1α was associated with a significant increase in the the enzymatic activities of thrombin and FXIIa in the plasma of hypoxia-induced mice, which was abrogated by Tf antibodies, HIF-1α inhibitors and viral knockdown of Tf. The induction of hypercoagulability was confirmed by the reductions in activated partial thromboplastin time, prothrombin time and bleeding time in mice subjected to hypoxia. These alterations decreased blood flow and aggravated thrombus formation in the carotid arteries and deep vein of mice exposed to hypoxia. The rescue of these parameters and phenotypes by Tf antibodies

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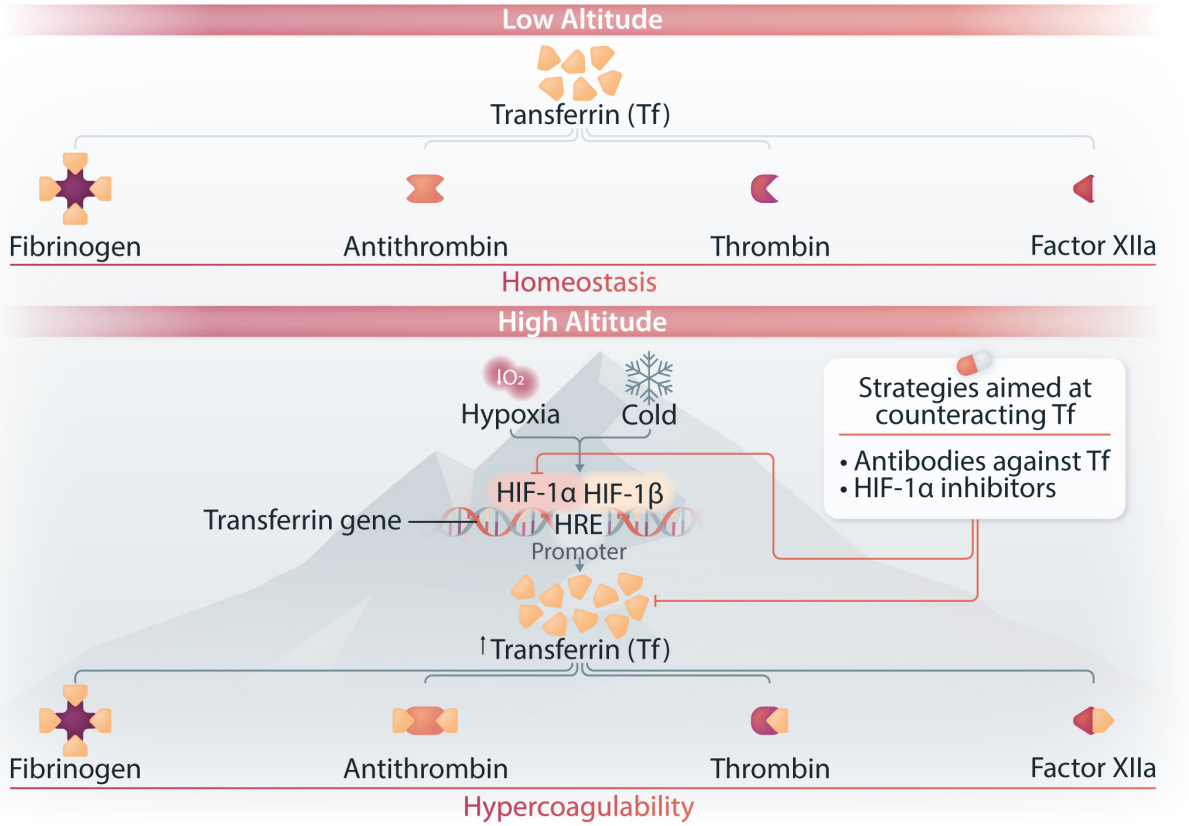

Figure 1. Hypoxia-induced Tf elevation promotes hypercoagulability at high altitude. At normal altitude, most Tf is sequestered by fibrinogen in plasma, which maintains coagulation balance. High altitude-related hypoxia, low temperature, and iron deficiency increase HIF-1α levels, which upregulate Tf to increase iron transport for erythropoiesis as an attempt to compensate for the limited oxygen supply. Under this condition, abnormally elevated Tf promotes hypercoagulability by interacting with plasma proteins of the coagulation cascade and potentiating thrombin and FXIIa while inhibiting antithrombin. Strategies aimed at counteracting Tf likely prevent the hypercoagulation state associated with high altitude and the risk of thromboembolic events. HIF = hypoxia-inducible factor; Tf = transferring.

and HIF-1α inhibitors as well as by ligand trap peptides which interfere with Tf-thrombin/FXIIa interactions, highlights the critical role of Tf in the hypercoagulable state associated with high altitudes.[6]

Ultimately, taking advantage of a mouse model of stroke obtained through transient middle cerebral artery occlusion, the authors show that Tf functional interference by Tf antibodies, HIF-1α inhibitors, viral Tf knockdown or ligand trap peptides inhibited thrombosis and ischemic stroke aggravation induced by hypoxia or low temperature.[6] Overall, these approaches improved the survival of mice subjected to stroke. Finally, Tf antibodies prevented the more severe hypercoagulable state and prothrombotic condition induced by the combination of hypoxia and low temperature.

Overall, these findings offer an explanation how hypoxia triggers thromboembolism and highlight Tf as a key mediator of hypercoagulability at high altitude. Although hypoxia and cold upregulate Tf to carry more iron as an attempt to compensate for erythropoiesis and oxygen supply, the abnormally elevated Tf causes hypercoagulability by potentiating the enzymatic activities of thrombin and FXIIa and inhibiting antithrombin. Through this mechanism Tf likely contributes to altitude-induced thromboembolism (Figure 1). The observation that Tf functional interference inhibits the hypercoagulability induced by hypoxia and low temperature and effectively reduces the susceptibility to thrombotic events, provides a promising strategy for the treatment of high altitude-induced thromboembolic disorders, and offers a potential therapeutic target for the development of novel therapies to treat hypoxia (Figure 1). Finally, this discovery has a potentially broader impact that goes beyond people exposed to high altitude, and is likely relevant to other diseases in which hypoxia or low iron levels, by leading to increased Tf expression, enhances the risk of thrombosis.[5] Patients with sepsis,[7] COVID-19 or other infections[8–10] as well as women who are on oral contraceptives,[4] who all can develop hypoferremia and elevated Tf levels, are among those that will likely benefit from approaches targeting Tf to decrease their thromboembolic risk.

AUTHOR CONTRIBUTIONS

FV conceptualized, wrote, and edited the manuscript.

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