

骨髓組織特異的インテグリンである $\alpha 9\beta 1$ の機能抑制は、マウス血栓を抑制する

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Blood.135:857-861, 2020.

Targeting myeloid-cell specific integrin $\alpha 9\beta 1$ inhibits arterial thrombosis in mice

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Abstract Evidence suggests that neutrophils contribute to thrombosis via several mechanisms, including neutrophil extracellular traps (NETs) formation. Integrin $\alpha 9\beta 1$ is highly expressed on neutrophils when compared with monocytes. It undergoes affinity upregulation on neutrophil activation, and stabilizes adhesion to the activated endothelium. The role of integrin $\alpha 9$ in arterial thrombosis remains unexplored. We generated novel myeloid cell-specific integrin $\alpha 9^{-/-}$ mice ($\alpha 9\text{fl}/\text{flLysMCre}^{+}$) to study the role of integrin $\alpha 9$ in arterial thrombosis. $\alpha 9\text{fl}/\text{fl}$ littermates were used as controls. We report that $\alpha 9\text{fl}/\text{flLysMCre}^{+}$ mice were less susceptible to arterial thrombosis in ferric chloride (FeCl_3) and laser injury-induced thrombosis models with unaltered hemostasis. Neutrophil elastase-positive cells were significantly reduced in $\alpha 9\text{fl}/\text{flLysMCre}^{+}$ mice concomitant with reduction in neutrophil count, myeloperoxidase levels, and red blood cells in the FeCl_3 injury-induced carotid thrombus. The percentage of cells releasing NETs was significantly reduced in $\alpha 9\text{fl}/\text{flLysMCre}^{+}$ mouse neutrophils stimulated with thrombin-activated platelets. Furthermore, we found a significant decrease in neutrophil-mediated platelet aggregation and cathepsin-G secretion in $\alpha 9\text{fl}/\text{flLysMCre}^{+}$ mice. Transfusion of $\alpha 9\text{fl}/\text{fl}$ neutrophils in $\alpha 9\text{fl}/\text{flLysMCre}^{+}$ mice restored thrombosis similar to $\alpha 9\text{fl}/\text{fl}$ mice. Treatment of wild-type mice with anti-integrin $\alpha 9$ antibody inhibited arterial thrombosis. This study identifies the potential role of integrin $\alpha 9$ in modulating arterial thrombosis.

抄録 骨髄細胞の $\alpha 9$ インテグリンを特異的に欠損させたマウスでは、血栓を抑制できることが分かった。さらに $\alpha 9$ インテグリンの中和抗体を用いても血栓を抑制できることが分かった。本結果から、動脈硬化に $\alpha 9$ インテグリンが関与していることが分かった。

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