# 骨髄組織特異的インテグリンであるα9β1の機能抑制は、マウス脳卒中を抑制する

Nirav Dhanesha*, Manish Jain*, Amit K Tripathi*, Prakash Doddapattar*, Mehul Chorawala*, Girish Bathla**, Manasa K Nayak*, Madankumar Ghatge*, Steven R Lentz*, 今 重之, Anil K Chauhan*

Circ Res. **126**:1779-1794, 2020.

# Targeting Myeloid-Specific Integrin α9β1 Improves Short- and Long-Term Stroke Outcomes in Murine Models with Preexisting Comorbidities by Limiting Thrombosis and Inflammation

Nirav Dhanesha, Manish Jain, Amit K Tripathi, Prakash Doddapattar, Mehul Chorawala, Girish Bathla, Manasa K Nayak, Madankumar Ghatge, Steven R Lentz, Shigeyuki Kon, Anil K Chauhan

**Abstract ： Rationale**: Currently, there is no effective intervention available that can reduce brain damage following reperfusion. Clinical studies suggest a positive correlation between the increased influx of neutrophils and severity of brain injury following reperfusion. Integrin α9β1 is highly expressed on activated neutrophils and contributes to stable adhesion, but its role in stroke outcome has not been demonstrated to date.

**Objective:** We sought to determine the mechanistic role of myeloid-specific α9β1 in the progression of ischemic stroke in murine models with preexisting comorbidities.

**Methods and results:** We generated novel myeloid-specific α9-deficient (α9-/-) wild type (α9fl/flLysMCre+/-), hyperlipidemic (α9fl/flLysMCre+/-Apoe-/-), and aged (bone marrow chimeric) mice to evaluate stroke outcome. Susceptibility to ischemia/reperfusion injury was evaluated at 1, 7, and 28 days following reperfusion in 2 models of experimental stroke: filament and embolic. We found that peripheral neutrophils displayed elevated α9 expression following stroke. Irrespective of sex, genetic deletion of α9 in myeloid cells improved short- and long-term stroke outcomes in the wild type, hyperlipidemic, and aged mice. Improved stroke outcome and

enhanced survival in myeloid-specific α9-/- mice was because of marked decrease in cerebral thromboinflammatory response as evidenced by reduced fibrin, platelet thrombi, neutrophil, NETosis, and decreased phospho-NF-κB (nuclear factor-κB), TNF (tumor necrosis factor)-α, and IL (interleukin)-1β levels. α9-/- mice were less susceptible to FeCl3 injury-induced carotid artery thrombosis that was concomitant with improved regional cerebral blood flow following stroke as revealed by laser speckle imaging. Mechanistically, fibronectin containing extra domain A, a ligand for integrin α9, partially contributed to α9-mediated stroke exacerbation. Infusion of a specific anti-integrin α9 inhibitor into hyperlipidemic mice following reperfusion significantly reduced infarct volume and improved short- and long-term functional outcomes up to 28 days. **Conclusions:** We provide genetic and pharmacological evidence for the first time that targeting myeloid-specific integrin α9β1 improves short- and long-term functional outcomes in stroke models with preexisting comorbidities by limiting cerebral thrombosis and inflammation.

**抄録**　骨髄細胞の α９インテグリンを特異的に欠損させたマウスや中和抗体阻害により脳血栓や炎症を抑制することで短期的、長期的な脳卒中症状を抑制することができることが分かった。

*Division of Hematology/Oncology, Department of Internal Medicine, University of Iowa.

**Department of Radiology, University of Iowa