

The extravascular effects and direct cellular interactions of **thrombin** are mediated by PARs (PAR-1, PAR-3, and PAR-4) and their downstream signaling in multiple brain cell types. Such effects include inducing blood-brain-barrier disruption, brain edema, neuroinflammation, and neuronal death, although low thrombin concentrations can promote cell survival. Also, thrombin directly links the coagulation system to the immune system by activating interleukin-1 α . Such effects of thrombin can result in both short-term brain injury and long-term functional deficits, making extravascular thrombin an understudied therapeutic target for stroke. A review of Ye et al. examines the role of thrombin and PARs in brain injury following hemorrhagic and ischemic stroke and the potential treatment strategies which are complicated by their role in both hemostasis and brain ¹⁾.

Since the PAR1 antagonist has an increased **bleeding** risk in clinical practice, **PAR4** blockade has been suggested as a more promising treatment. Luo et al. explored the expression pattern of PAR4 in the brain of mice after **TBI**, and explored the effect and possible mechanism of BMS-986120 (**BMS**), a novel selective and reversible PAR4 antagonist on **secondary brain injury**. Treatment with BMS protected against TBI in mice. mRNA-seq analysis, Western blot, and qRT-PCR verification in vitro showed that BMS significantly inhibited thrombin-induced inflammation in astrocytes, and suggested that the Tab2/ERK/NF- κ B signaling pathway plays a key role in this process. These findings provide reliable evidence that blocking **PAR4** is a safe and effective intervention for TBI, and suggest that BMS has a potential clinical application in the management of TBI ²⁾.

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Ye F, Garton HJL, Hua Y, Keep RF, Xi G. The Role of Thrombin in Brain Injury After Hemorrhagic and Ischemic Stroke. Transl Stroke Res. 2020 Sep 29. doi: 10.1007/s12975-020-00855-4. Epub ahead of print. PMID: 32989665.

²⁾

Luo J, Wu X, Liu H, Cui W, Guo W, Guo K, Guo H, Tao K, Li F, Shi Y, Feng D, Yan H, Gao G, Qu Y. Antagonism of Protease-Activated Receptor 4 Protects Against Traumatic Brain Injury by Suppressing Neuroinflammation via Inhibition of Tab2/NF- κ B Signaling. Neurosci Bull. 2020 Oct 27. doi: 10.1007/s12264-020-00601-8. Epub ahead of print. PMID: 33111257.

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