Protease activated receptor 1

Activation of a thrombin receptor, protease-activated receptor-1 (PAR-1), induces angiogenesis, cell proliferation, and invasion in tumors.

Protease-activated receptor 1 (PAR1) can be activated both by thrombin, inducing increased inflammation, and activated protein C (aPC), inducing decreased inflammation. Modulation of the aPC-PAR1 pathway may prevent the neuroinflammation associated with PAR1 over-activation.

They synthesized a group of novel molecules based on the binding site of FVII/aPC to the endothelial protein C receptor (EPCR). These molecules modulate the FVII/aPC-EPCR pathway and are therefore named FEAMs-Factor VII, EPCR, aPC Modulators. We studied the molecular and behavioral effects of a selected FEAM in neuroinflammation models in-vitro and in-vivo.

Results: In a lipopolysaccharide (LPS) induced in-vitro model, neuroinflammation leads to increased thrombin activity compared to control (2.7 ± 0.11 and 2.23 ± 0.13 mU/ml, respectively, $p = 0.01$) and decreased aPC activity (0.57 ± 0.01 and 1.00 ± 0.02, respectively, $p < 0.0001$). In addition, increased phosphorylated extracellular regulated kinase (pERK) (0.99 ± 0.13, 1.39 ± 0.14, control and LPS, $p < 0.04$) and protein kinase B (pAKT) (1.00 ± 0.09, 2.83 ± 0.81, control and LPS, $p < 0.0002$) levels indicate PAR1 overactivation, which leads to increased tumor necrosis factor-alpha (TNF-α) level (1.00 ± 0.04, 1.35 ± 0.12, control and LPS, $p = 0.02$). In a minimal traumatic brain injury (mTBI) induced neuroinflammation in-vivo model in mice, increased thrombin activity, PAR1 activation, and TNF-α levels were measured. Additionally, significant memory impairment, as indicated by a lower recognition index in the Novel Object Recognition (NOR) test and Y-maze test (NOR: 0.19 ± 0.06, -0.07 ± 0.09, $p = 0.03$. Y-Maze: 0.50 ± 0.03, 0.23 ± 0.09, $p = 0.02$ control and mTBI, respectively), as well as hypersensitivity by hot-plate latency (16.6 ± 0.89, 12.8 ± 0.56 s, control and mTBI, $p = 0.01$), were seen. FEAM prevented most of the molecular and behavioral negative effects of neuroinflammation in-vitro and in-vivo, most likely through EPCR-PAR1 interactions.

Conclusion: FEAM is a promising tool to study neuroinflammation and a potential treatment for a variety of neuroinflammatory diseases [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-κB 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)].

PAR-1 has a role in glioma growth and could be a new therapeutic target for gliomas [3)].

Thrombin and activated protein C (aPC) bound to the endothelial protein C receptor (EPCR) both activate protease-activated receptor 1 (PAR1) generating either harmful or protective signaling respectively.

Gera et al., examined the localization of PAR-1 and EPCR and thrombin activity in Schwann cells of normal and crushed peripheral nerve and in Schwannoma cell lines. In the sciatic crush model nerves were excised 1 hour, 1, 4, and 7 days after the injury. Schwannoma cell lines produced high levels of prothrombin which is converted to active thrombin and expressed both EPCR and PAR-1 which co-localized. In the injured sciatic nerve thrombin levels were elevated as early as 1 hour after injury, reached their peak 1 day after injury which was significantly higher (24.4 ±4.1 mU/ml) compared to contralateral uninjured nerves (2.6±7 mU/ml, t-test $p<0.001$) and declined linearly reaching baseline levels by day 7.

EPCR was found to be located at the microvilli of Schwann cells at the node of Ranvier and in cytoplasm surrounding the nucleus. Four days after sciatic injury, EPCR levels increased significantly (57785±16602AU versus 4790±1294AU in the contralateral uninjured nerves, $p<0.001$ by t-test) mainly distal to the site of injury, where axon degeneration is followed by proliferation of Schwann cells which are diffusely stained for EPCR. EPCR seems to be located to cytoplasmic component of Schwann cells and not to compact myelin component, and is highly increased following injury [4].

1)
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