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Inflammation in intracerebral hemorrhage: From mechanisms to clinical translation

Yu Zhou [a], Yanchun Wang [a], Jian Wang [b], R. Anne Stetler [c], Qing-Wu Yang [a,*]

[a] Department of Neurology, Xinqiao Hospital & The Second Affiliated Hospital, The Third Military Medical University, Chongqing, China
[b] Department of Anesthesiology/Critical Care Medicine, Johns Hopkins University, School of Medicine, Baltimore, MD 21205, USA
[c] Center of Cerebrovascular Disease Research, University of Pittsburgh School of Medicine, Pittsburgh, PA 15213, USA

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ABSTRACT

Intracerebral hemorrhage (ICH) accounts for 10–15% of all strokes and is associated with high mortality and morbidity. Currently, no effective medical treatment is available to improve functional outcomes in patients with ICH. Potential therapies targeting secondary brain injury are arousing a great deal of interest in translational studies. Increasing evidence has shown that inflammation is the key contributor of ICH-induced secondary brain injury. Inflammation progresses in response to various stimuli produced after ICH. Hematoma components initiate inflammatory signaling via activation of microglia, subsequently releasing proinflammatory cytokines and chemokines to attract peripheral inflammatory infiltration. Hemoglobin (Hb), heme, and iron released after red blood cell lysis aggravate ICH-induced inflammatory injury. Danger associated molecular patterns such as high mobility group box 1 protein, released from damaged or dead cells, trigger inflammation in the late stage of ICH. Preclinical studies have identified inflammatory signaling pathways that are involved in microglial activation, leukocyte infiltration, toll-like receptor (TLR) activation, and danger associated molecular pattern regulation in ICH. Recent advances in understanding the pathogenesis of ICH-induced inflammatory injury have facilitated the identification of several novel therapeutic targets for the treatment of ICH. This review summarizes recent progress concerning the mechanisms underlying ICH-induced inflammation. We focus on the inflammatory signaling pathways involved in microglial activation and TLR signaling, and explore potential therapeutic interventions by targeting the removal of hematoma components and inhibition of TLR signaling.

Contents

Abbreviations: BBB, blood–brain barrier; DAMPs, danger associated molecular patterns; EP, ethyl pyruvate; GFP, green fluorescent protein; Hb, hemoglobin; HIF1á, hypoxia-inducible factor-1á; HMGB1, high mobility group box 1 protein; HO, heme oxygenase; HUCB, human umbilical cord blood; ICH, intracerebral hemorrhage; iNOS, inducible nitric oxide synthase; MPO, myeloperoxidase; MMP-9, matrix metalloproteinase; MyD88, myeloid differentiation factor 88; Nrf2, NF-E2-related factor-2; NSEs, neuronal stem cells; RBC, red blood cell; RIPK3, receptor interacting protein kinase 3; STICH, Surgical Trial in Intracerebral Hemorrhage; TIR, Toll-interleukin 1 receptor; TLR, toll-like receptor; TIRAP, TIR domain-containing adaptor protein; TRAM, TRIF-related adaptor molecule; TRIF, TIR domain-containing adaptor-inducing interferon; VAP1, vascular adhesion protein-1.

* Corresponding author at: Department of Neurology, Xinqiao Hospital & The Second Affiliated Hospital, The Third Military Medical University, Xinqiao Zhengjie No. 183, Shapingba District, Chongqing 400037, China. Tel.: +86 23 68755613; fax: +86 23 68755613.
E-mail addresses: yangqwmlys@hotmail.com, yangqwmlys@163.com (Q.-W. Yang).

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1. Introduction

Intracerebral hemorrhage (ICH) occurs when a diseased blood vessel ruptures, allowing blood to leak into the surrounding brain. ICH accounts for 10–15% of all strokes and is associated with high mortality and morbidity (Flower and Smith, 2011; Hwang et al., 2011; Mayer and Rincon, 2005). It has been reported that the fatality rate of ICH at 1 month is approximately 40%, which has not changed over the past twenty years (van Asch et al., 2010). This high rate of mortality and morbidity likely results from a lack of effective treatment options to improve a patient's survival following ICH, since standard management is limited to primarily supportive therapies such as control of intracranial pressure, treatment of brain edema, and maintenance of hemodynamic stability (Flower and Smith, 2011; Hwang et al., 2011; Mayer and Rincon, 2005; Xi et al., 2006). With an increasing elderly population, the incidence of ICH is expected to increase (van Asch et al., 2010). Thus, understanding the mechanisms underlying ICH and identification of novel therapeutic targets are of paramount interest to researchers in the development of new medical therapies for ICH.

1.1. ICH types

Depending on the underlying cause of hemorrhage, ICH is classified as primary or secondary (Mayer and Rincon, 2005). Primary ICH develops without any underlying vascular malformation or coagulopathy. Secondary ICH usually results from trauma, tumors, vascular malformation, coagulation, or use of thrombolytic agents (Mayer and Rincon, 2005; Wang and Dore, 2007a; Wang, 2010). Primary ICH occurs more often than secondary ICH. The most common causes of primary ICH are hypertensive arteriosclerosis and cerebral amyloid angiopathy, accounting for approximately 80% of primary ICH cases (Mayer and Rincon, 2005; Sutherland and Auer, 2006). No matter the cause, ICH can induce primary brain injury caused by the hemorrhage and growth of the hematoma, and secondary brain injury caused by physiological and pathological response to the hematoma. Thus, therapeutic strategies have been developed to target primary and secondary brain injury following ICH (Aronowski and Hall, 2005; Keep et al., 2012).

1.2. Primary and secondary brain injury after ICH

Primary brain injury caused by ICH occurs within the first few hours after the onset of bleeding and is mainly due to hematoma formation, which causes mechanical damage to adjacent tissues (Keep et al., 2012; Xi et al., 2006). The key factors that determine ICH outcome are hemorrhagic volume and hematoma expansion. Large hemorrhage is associated with poor prognosis, and patients often die when the hemorrhagic volume exceeds 150 ml (Broderick et al., 1993; Xi et al., 2006). Hematoma expansion contributes to midline shift and is associated with poor outcomes (Dowlatshahi et al., 2011; Zazulia et al., 1999). Because hematoma size is important for determination of ICH outcome, early removal of the hematoma and prevention of hematoma expansion are potential therapeutic targets. However, the Surgical Trial in Intracerebral Hemorrhage (STICH) has failed to provide convincing evidence to support the efficacy of early surgical removal of hematomas (Mendelow et al., 2005). Furthermore, recombinant activated factor VII significantly reduced hematoma growth but does not improve survival or functional outcomes in patients with ICH (Mayer et al., 2008). Because the optimal therapy for treating ICH-induced primary injury has not yielded conclusive benefits in clinical trials thus far, researchers have focused instead on the mechanisms underlying ICH-induced secondary injury in search for novel therapeutic targets for ICH.

Secondary injury plays a critical role in neurological deterioration in patients with ICH (Babu et al., 2012; Elliott and Smith, 2010). Secondary damage following ICH is triggered by the presence of intraparenchymal blood, which subsequently activates cytotoxic, excitotoxic, oxidative, and inflammatory pathways (Aronowski and Zhao, 2011; Felberg et al., 2002; Huang et al., 2002; Lee et al., 1997). Blood components, such as red blood cells (RBCs), coagulation factors, complement components, and immunoglobulins, contribute to ICH-induced secondary injury (Aronowski and Zhao, 2011; Babu et al., 2012; Xi et al., 2006). For example, thrombin, a serine protease, activates cytotoxic, excitotoxic, and inflammatory pathways, leading to edema formation and blood–brain barrier (BBB) damage in early brain injury following ICH (Aronowski and Zhao, 2011; Babu et al., 2012; Sharp et al., 2008). Hemoglobin (Hb) released from RBCs promotes the generation of free radicals that cause oxidative damage, resulting in death of the surrounding cells (Aronowski and Zhao, 2011; Babu et al., 2012; Nakamura et al., 2005b; Wagner et al., 2002). Hemin, the oxidative form of heme, induces brain injury via the release of excessive iron, depletion of glutathione, and production of free radicals (reviewed in Babu et al., 2012; Robinson et al., 2009). Many neuroprotective agents such as antioxidant drugs, anti-inflammatory drugs, thrombin inhibitors, and cytotoxic drugs have shown promise in preclinical studies, but their efficacy has not been

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