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Preclinical and clinical research on inflammation after intracerebral hemorrhage

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ABSTRACT

Intracerebral hemorrhage (ICH) is one of the most lethal stroke subtypes. Despite the high morbidity and mortality associated with ICH, its pathophysiology has not been investigated as well as that of ischemic stroke. Available evidence from preclinical and clinical studies suggests that inflammatory mechanisms are involved in the progression of ICH-induced secondary brain injury. For example, in preclinical ICH models, microglial activation has been shown to occur within 1 h, much earlier than neutrophil infiltration. Recent advances in our understanding of neuroinflammatory pathways have revealed several new molecular targets, and related therapeutic strategies have been tested in preclinical ICH models. This review summarizes recent progress made in preclinical models of ICH, surveys preclinical and clinical studies of inflammatory cells (leukocytes, macrophages, microglia, and astrocytes) and inflammatory mediators (matrix metalloproteinases, nuclear factor erythroid 2-related factor 2, heme oxygenase, and iron), and highlights the emerging areas of therapeutic promise.

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Abbreviations: BBB, blood–brain barrier; GFAP, glial fibrillary acidic protein; HO, heme oxygenase; ICH, intracerebral hemorrhage; MIF, microglia/macrophage inhibitory factor; MIP, macrophage inflammatory protein; MMP, matrix metalloproteinase; Nrf2, nuclear factor erythroid 2-related factor 2; NSC, neural stem cell; ROS, reactive oxygen species; TNF, tumor necrosis factor; tPA, tissue plasminogen activator; WT, wild-type.

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1. Introduction

Intracerebral hemorrhage (ICH) results when a weakened blood vessel ruptures and bleeds into the surrounding brain. Spontaneous ICH accounts for 15–20% of all strokes and affects more than 2 million people worldwide each year (Qureshi et al., 2009; Ribo and Grotta, 2006). The prevalence of ICH is higher in certain populations, including blacks and Asians (Qureshi et al., 2009). Parts of the brain that are particularly vulnerable to ICH include the basal ganglia, cerebellum, brainstem, and cortex. Most cases of ICH are caused by primary hypertensive arteriolosclerosis and amyloid angiopathy (reviewed in Mayer and Rincon, 2005; Sutherland and Auer, 2006). Secondary ICH accounts for 15–20% of patients and usually results from vascular malformation, neoplasia, coagulopathy, and the use of thrombolysis in ischemic stroke (reviewed in Mayer and Rincon, 2005; Sutherland and Auer, 2006; Wang and Tsirka, 2005a). No matter the cause, the extravasated blood compresses the surrounding brain tissue, increasing the intracranial pressure. The prevalence of ICH is expected to increase slightly as improvements in blood pressure management are counteracted by the trends that favor ICH incidence, such as population aging, increasing use of thrombolytics and anticoagulants, and lack of effective prevention for cerebral amyloid angiopathy in the elderly.

The incidence of fatality is much higher among individuals who suffer ICH than among those who experience ischemic stroke. Those who do survive usually experience long-term physical and mental disability, although some patients can recover most neurologic function. Treatment for ICH is primarily support and control of general medical risk factors. The prognosis of ICH depends on the location, amount of bleeding, extent of subsequent brain swelling, the level of consciousness at admission, concomitant diseases, and the age of the patient. Interestingly, the data from a recent clinical ICH study indicate that the degree of perihematomal edema and subsequent edema expansion are positively correlated with the underlying hematoma size but are not major independent determinants in the outcome (Arima et al., 2009).

Although ICH research has received far less attention than has ischemic stroke (Donnan et al., 2010; NINDS ICH Workshop Participants, 2005), during the past few years, progress has been made toward identifying the roles of inflammatory signaling molecules, cells, and proteins in initiation and progression of post-ICH inflammation. We and others have reviewed the roles of cytokines, proteases, and reactive oxygen species (ROS) in ICH-induced brain injury (Aronowski and Hall, 2005; Wang and Doré, 2007b; Wang and Tsirka, 2005a; Xi et al., 2006). A recent review has highlighted the important functions of complement activation in ICH (Ducruet et al., 2009). The focus of this review will be primarily on recent progress made in the use of preclinical ICH models, understanding the changes in cellular components (leukocytes, microglia/macrophages, and astrocytes) and inflammatory mediators [matrix metalloproteinases (MMPs), nuclear factor erythroid 2-related factor 2 (Nrf2), heme oxygenase (HO), and iron toxicity], and emerging opportunities for novel therapeutic strategies such as stem cell therapy.

2. Preclinical models of ICH

Preclinical studies of ICH have been carried out in many species, but rodents are most commonly used. Rodent models of ICH are fundamentally different from the human condition, and the paucity of white matter, lower glia-to-neuron ratio, and differences in homeostasis limit their clinical relevance. Two main animal models are used to reproduce the clinical condition of ICH, the whole-blood model and the collagenase model. The whole-blood model, in which an animal's own blood or donor blood is injected directly into the striatum, has been used in various animals (Gu et al., 2009; Koeppen et al., 2004; Okauchi et al., 2009; Qureshi et al., 2001). Recently this model has been adapted for use in mice (Rynkowski et al., 2008; Tejima et al., 2007; Wang et al., 2008; Xue et al., 2006; Zhao et al., 2007b), thereby enabling the use of transgenic or knockout ($^{-/-}$) mice to study specific signaling pathways or brain injury mechanisms. The autologous whole-blood model mimics ICH better than the donor blood model because the latter induces more severe brain edema (Nakamura et al., 2004b). The advantage of the whole-blood model is that only blood is introduced into the model system. The drawbacks include: lack of underlying vascular pathology and rupture; variable lesion size caused by ventricular rupture or backflow of the injected blood along the needle track and corpus callosum; and potential effects of donor blood or anticoagulant on inflammation, complement, or the coagulation system. Given the limited volume of blood that can be infused into the mouse striatum, the technique of blood injection in mice remains challenging. Because of the shortcomings of the current blood infusion models, we established a modified double-blood infusion model in mice that does not use any anticoagulant (Wang et al., 2008). In the modified model, 10 μl of autologous whole blood is infused into the striatum at a speed of 0.2 μl/min in two phases, with a break of 7 min in between. We keep the needle within the injection site for another 20 min after blood infusion to prevent backflow of blood along the needle track. The hematoma developed in this model is confined to the ipsilateral striatum and produces the desired brain injury and neurologic deficits (Wang et al., 2008).

In another model, the proteolytic enzyme collagenase is injected into the striatum, breaking down the blood–brain barrier (BBB) and resulting in active bleeding (Rosenberg et al., 1990; Tang et al., 2004; Wang et al., 2003). In this model, the hematoma develops gradually over 4–5 h (Wang and Doré, 2007a). The procedure itself is simple, and it mimics an acute cerebrovascular injury. Furthermore, the resultant bleed is spontaneous and reproducible in location and size (Tejima et al., 2007; Wagner, 2007; Wang and Doré, 2007b). These advantages allow investigation of the collagenase-induced bleeding response and hematoma expansion. The model is relevant to the clinical condition because continued bleeding occurs in 14–20% of all ICH patients and lasts for over 6 h in 17% of cases (Brott et al., 1997; Kazui et al., 1996). Of course the collagenase model does have some drawbacks. There is no underlying vascular pathology, and bleeding results from the rupture of many vessels, whereas in humans, rupture of a small, deep-penetrating artery is the primary cause. In addition, the introduction of bacterial collagenase into the brain could potentially enhance inflammation, although three in vitro studies, including our own, argue against the possibility by showing that collagenase alone does not activate microglia, affect prostaglandin E2 production, or induce cell death (Chu et al., 2004; Matsushita et al., 2000; Wang et al., 2003). Both models have limitations and reflect only certain clinical features of ICH, but to our knowledge, these two models are the most useful tools currently available for the study of ICH. Interestingly, a new mouse model of spontaneous ICH has been developed in which ICH is induced by acute hypertension (Iida et al., 2005; Wakisaka et al., 2010); more studies into the pathophysiology of this model are clearly needed. In translational medicine, testing in multiple related preclinical models and in different laboratories is strongly encouraged before advancing any novel medicine or therapy to a clinical trial. Early reviews of preclinical animal models of ICH are available (Andaluz et al., 2002; Strbian et al., 2008).

3. Inflammation and the cellular response to ICH

ICH can cause primary and secondary brain injury. The immediate effects of ICH, such as hematoma expansion and the