Although the dawn of targeted treatments for primary intracerebral hemorrhage (ICH) seems in sight, many biological questions remain, which will drive the next clinical trial and animal model steps. The objective of this review is to describe the role of inflammatory signaling molecules and the clot lysis cascade, and the role of edema as a surrogate marker for inflammation.

The primary injury of hematoma formation and its expansion within brain parenchyma is mechanical damage to brain tissue causing disruption of white matter tracts and, at the most severe, resulting in herniation. The tissue at the epicenter of the clot is not likely to be salvaged because of dissection of blood, causing direct and rapid tissue destruction.1 The size of the epicenter remains unknown, some evidence suggests it is small when compared with ischemic stroke,2 thus secondary mechanisms of injury may be disproportionally important in ICH.

The secondary injury of ICH can be considered as emanating from a time-dependent progression of 3 intertwined degenerative cascades in the regions both adjacent to the hematoma: inflammation, red cell lysis, and thrombin production (coagulation cascade; Figure). All 3 lead to disruption of the blood–brain barrier, resulting in cerebral edema directly or indirectly, and death of brain parenchymal cells. These pathways are all feasible therapeutic targets as injury occurs over hours to weeks. Thus, perihematomal tissue is potentially salvageable by countering degenerative events at the appropriate time interval. Apoptosis and neuronal necrosis are common end points of the degenerative pathways, but without good clinical surrogates. Cerebral edema, on the contrary, may be a reasonable target.

Inflammation
ICH brings the immediate infiltration of blood components, including red blood cells, leukocytes, macrophages, and plasma proteins.1 Microglia are likely the first non-neuronal cells to react to brain injury—within 1 hour in animal models.4 Although their major role is to clear the hematoma and tissue debris (hence, long-term inhibition may not be fully beneficial), they also express and release a variety of toxic factors, such as cytokines, chemokines, reactive oxygen species, proteases, cyclooxygenase-II, prostaglandins, and heme-oxygenase 1.5–7 Reactive microglia peak at 3 to 7 days and persist for 4 weeks.

Neutrophils are the earliest leukocyte subtype to infiltrate the hemorrhagic brain—within 4 to 5 hours in animal models and peak at 3 days.8 They may damage the brain by producing reactive oxygen species, releasing proinflammatory proteases, affecting blood–brain barrier permeability, and aggravating neuronal death.9,10 Leukocytes die by apoptosis within 2 days after entering the hemorrhagic brain, which further damages brain tissue by stimulating microglia and macrophages to secrete proinflammatory toxic factors.11

Astrocytes become activated by plasma proteins together with microglia. They secrete inflammatory mediators and increase production of glial fibrillary acidic protein, causing reactive gliosis, which could inhibit axonal regeneration, but may also protect neurons by promoting secretion of neurotrophic factors or modulating expression of microglial inflammatory mediators.12–14 Astrocytes also express matrix metalloproteinases together with activated microglia—hence, controlling microglia–astrocyte interactions could be a potential means to minimize ICH–induced injury.6,15

Erythrocyte Lysis
Recruitment of the complement cascade results in red cell lysis, which occurs within 24 hours of ICH.16,17 Hemolysis causes release of hemoglobin and heme, both of which are taken up by microglia and neurons.18 Induction of heme oxygenase-1 and heme oxygenase-2 in microglia/macrophages catalyzes degradation of heme into biliverdin (which is converted to bilirubin by biliverdin reductase), carbon monoxide, and iron.19 Unconjugated bilirubin is detectable in the hematoma by 8 to 12 hours and, along with ferrous iron, contributes to pathological changes, such as increase in oxidative stress (free radical production), edema, infiltration of neutrophils, and neuronal death.20,21 Interruption of the complement cascade and increased iron chaperoning with free iron chelators are key strategies to alleviate pathological events in this cascade.
Inflammation in Intracerebral Hemorrhage

Coagulation

Thrombin is an essential component of the coagulation cascade and forms immediately after ICH, but is also formed because of prothrombin influx, resulting from ICH–induced blood–brain barrier disruption, which begins to occur several hours after ICH and results in a delayed thrombin generation.1

Activation of the extrinsic or intrinsic coagulation cascade results in production of factor Xa, which cleaves prothrombin to thrombin; thrombin then cleaves fibrinogen to fibrin.
and therefore has a crucial role in limiting hematoma size. At very low concentrations, thrombin is neuroprotective, but at high concentrations, thrombin kills neurons and astrocytes in vitro.22,23

Thrombin disrupts the blood–brain barrier, promoting formation of edema and neutrophil infiltration.24 The mechanism involves thrombin-induced stimulation of protease-activated receptors on microglia/macrophages, and activation of these cells via recruitment of mitogen-activated protein kinases, which enhance production of several inflammatory mediators, including tumor necrosis factor-α, interleukin-1β, and NO, thereby contributing to neuronal damage and edema.18 Thrombin and protease-activated receptor-1 are upregulated starting at 3 hours and peaking 2 days after ICH in animal models.25

Therapeutically, it may be possible to separate the beneficial and adverse effects of thrombin because they occur in different compartments and during different time frames or have different mechanisms. The beneficial effects of thrombin occur relatively soon after hemorrhage and are mostly vascular. The adverse effects may be parenchymal, and thrombin-induced injury may occur hours after the hemorrhage onset.

Cerebral Edema
Mitigating secondary injury in ICH, resulting from the above cascades, requires clinical surrogates that can be measured and allow sufficient time for prevention or reversal. Examples of such surrogates include ICH expansion, intracranial pressure, and edema. Although all 3 can be evaluated on readily obtainable imaging studies, edema is the most generalizable and occurs during a time interval similar to that of most pathophysiologic events. Edema is also a good surrogate because it is a common end point of multiple pathogenic events and can be measured in both animal and human studies with some validity. Edema has the potential to modify the overall outcome negatively of ICH attributable to its association with other events that lead to neuronal degeneration and in the early phase is associated with increase in midline shift, independent of hematoma enlargement.1,26

In experimental ICH, brain edema formation seems to occur in 3 phases. Initially, clot retraction, hydrostatic pressure, and plasma proteins induce brain edema as early as 1 hour after ICH27 with movement of serum from the clot into the surrounding tissue. The middle phase (peaking at 1–2 days) is related to thrombin production through the clotting cascade,28 and the third phase (delayed edema formation at approximately day 3 in the rat) is related to erythrocyte lysis and hemoglobin toxicity.29 In experimental ICH models, brain edema peaks around the third or fourth day after the hemorrhage, then declines slowly.29,30 In animals with substantial white matter, perihematomal edema is mainly located within that tissue. In human beings, perihematomal edema develops within 3 hours of symptom onset and peaks between 10 and 20 days after ictus.31 Edema growth, however, is fastest in the first 48 hours after ICH onset. Serum factors could account for wide temporal variation of peak edema in humans.32

Associations Between Perihematomal Edema, Clinical Outcomes, and Impact of Clot Removal
Several clinical studies have shown that the degree of brain edema around the hematoma is associated with poor outcome.26,33,34 Thus, for example, a clinical study of brain edema after ICH showed that delayed edema was related to substantial midline shift.35 Whether perihematomal brain edema contributes to neurological deficits beyond intracranial hypertension and herniation risk, however, is still debated.35,36 In the absence of directed therapies for ICH–induced brain edema, focus has been directed toward use of thrombolytic agents to lyse hematomas locally. In animal and small clinical studies, efficient reduction in perihematomal edema volume has been reported after frameless stereotactic aspiration and thrombolysis of the clot.37–40 These studies indicate a strong direct relationship between perihematomal edema volume and same-day hematoma volume, and suggest that early clot removal may
mitigate edema formation. The release of inflammatory factors may also be reduced by greater removal of hematoma. A clinical study of gross-total versus subtotal removal of hypertensive basal ganglia hemorrhages found that levels of thromboxane B2, 6-keto-prostaglandin F1α, tumor necrosis factor-α, and endothelin in hematoma drainage or cerebral spinal fluid were significantly lower in the gross-total versus subtotal resection group at different postoperative times.41

Pharmacological Manipulation of Inflammation and Oxidative Stress in ICH

Although ICH–induced inflammation, in particular, seems to be a key factor of secondary brain damage, it is not yet known whether manipulating oxidative stress and components of the blood coagulation cascade can improve prognosis after spontaneous hemorrhage. The Table shows a summary of anti-inflammatory strategies and targets, which have undergone animal and human investigation, and whether protection was demonstrated. Protection indicates a significant beneficial effect following systemic administration after ICH induction. Many therapies have been shown to reduce edema, apoptosis, and necrotic cell death in controlled animal models. Blocking inflammation in experimental models also improves some behaviors. A major problem with the models is that inflammatory reactions are exacerbated by placing a needle into the striatum, followed by foreign material (collagenase or blood). It has therefore been suggested that it is unlikely that anti-inflammatory approaches alone will be useful for generalized treatment of ICH.43 A few anti-inflammatory therapies have made their way into clinical trials. Cerebral Hemorrhagic And NXY-059 Treatment was halted prematurely because although the safety trial showed that the spin trap agent NXY-059 was safe, the drug was ineffective in treating acute ischemic stroke, leading the manufacturer to abandon further clinical trials with this agent.42,45 A pilot clinical study with rosuvastatin showed improved in-hospital mortality and National Institutes of Health stroke scale with further clinical trials planned.44 Despite preclinical associations between statin use and mortality, and perihematomal edema, the Simvastatin for ICH–induced attenuation of brain edema and neurological deficits in a rat model of brain injury after intracerebral hemorrhage. J Neurochem. 2003;256:3956–3962. The peroxisome proliferator–activated receptor γ agonist rosiglitazone is currently undergoing a phase II clinical trial: The Safety of Pioglitazone for Hematoma Resolution In ICH (SHRINC) study, a prospective, randomized, blinded, placebo-controlled, efficacy study evaluating treatment with 80 mg of simvastatin or placebo for 14 days on perihematomal edema was terminated because of poor recruitment.45 Peroxisome proliferator–activated receptor γ in microglia/macrophages has been found to promote hematoma absorption and protect other animal brain cells from ICH–induced damage.46 The peroxisome proliferator–activated receptor γ agonist rosiglitazone is currently undergoing a phase II clinical trial: The Safety of Pioglitazone for Hematoma Resolution In ICH (SHRINC) study, a prospective, randomized, blinded, placebo-controlled, dose-escalation safety trial.47 A small, retrospective study investigated the efficacy/safety of the cyclooxygenase-2 inhibitor celecoxib, in patients with ICH compared with a similar control group and reported a significant reduction in edema volume on follow-up imaging.48 The Administration of Celecoxib for Treatment of ICH: A Pilot Study began enrollment in 2007 and was completed in 2009. Results have not been published. Deferoxamine (DFO) is probably the most thoroughly evaluated treatment in animal models of ICH. The Dose Finding and Safety Study of Deferoxamine in Patients with ICH (DFO in ICH) Study was a phase I open label study, evaluating the safety and tolerability of varying doses of DFO.49 DFO was well tolerated, and not associated with an increase in serious adverse effects or mortality. Phase 2 evaluation of DFO is currently underway.

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References


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