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Review

Intercellular cross-talk in intracerebral hemorrhage

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ABSTRACT

Intracerebral hemorrhage (ICH) is a devastating cerebrovascular disorder with high mortality and morbidity. Currently, there are few treatment strategies for ICH-induced brain injury. A recent increase in interest in the pathophysiology of ICH has led to elucidation of the pathways underlying ICH-induced brain injury, pathways where intercellular and hematoma to cell signaling play important roles. In this review, we summarize recent advances in ICH research focusing on intercellular and hematoma:cell cross-talk related to brain injury and recovery after ICH.

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Contents

Abbreviations: Ang, angiopoietin; BBB, blood–brain barrier; CD, cluster of differentiation; DAMP, danger associated molecular pattern molecule; HMGB1, high morbidity group box 1; HO, heme oxygenase; ICAM-1, intercellular adhesion molecule-1; ICH, intracerebral hemorrhage; IL, interleukin; LCN2, lipocalin 2; MCP-1, monocyte-chemoattachment protein-1; MMP, matrix metalloproteinase; Nrf2, nuclear factor-erythroid 2-related factor; PAR, protease-activated receptor; PPARγ, peroxisome proliferator-activated receptor-γ; RIPK1, receptor-interacting protein kinase 1; ROS, reactive oxygen species; SFK, Src family kinase; TGF-β, transforming growth factor-β; TLR, toll-like receptor; TNF-α, tumor necrosis factor-α; VAP-1, vascular active peptide-1; VEGF, vascular endothelial growth factor

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1. Introduction

Intracerebral hemorrhage (ICH) is a devastating form of cerebrovascular disorder with a particularly high mortality (about 40% at one month) (Feigin et al., 2009), and typically, it causes severe neurological deficits in those who survive. Thus, only 20% of ICH survivors are able to live their life independently at six months after onset (Adeoye and Broderick, 2010). The annual incidence of ICH is 10–30 per 100,000 population, with about 2 million cases occurring in the world annually (Qureshi et al., 2009; Xi and Keep, 2012). Furthermore, because ICH occurrence is strongly age-related, the rate of ICH is expected to increase as a result of the aging population (Qureshi et al., 2001, 2009). Few effective medical and surgical treatment strategies are currently available, and ICH-induced mortality at one month has not decreased in the past three decades (van Asch et al., 2010).

With increasing interest in the mechanisms of ICH-induced brain injury, many potential injury pathways have been elucidated in animal and clinical studies (Keep et al., 2012; Xi et al., 2014). In this review, we aim to describe recent advances in ICH research, mainly focusing intercellular communication and hematoma:cell signaling related to brain injury, consequent pathogenesis, and brain recovery.

2. Primary and secondary brain injury after ICH

2.1. *Primary brain injury*

An ICH causes immediate physical disruption to the brain cellular architecture adjacent to the hemorrhage, a mass effect. Little can be done to ameliorate this initial damage (Keep et al., 2012; Xi et al., 2006). After the first ictus of bleeding, about 20–40% of patients experience hematoma enlargement during the first day (Balami and Buchan, 2012; Delgado Almandoz et al., 2010; Dowlatshahi et al., 2011). The precise mechanisms of hematoma growth are still not known. Hypertension may influence hematoma growth (Anderson et al., 2010; Qureshi et al., 2010). Only a few experimental studies have investigated of the effects of blood pressure on hematoma growth. Wu et al. (2011) found that the volume of ICH induced by collagenase injection was the same in spontaneous hypertensive and normotensive rats. However, interestingly, more severe neuronal death, microglial activation, ferritin upregulation, and neurological deficits were observed in spontaneous hypertensive than in normotensive rats, suggesting that hypertension may contribute to brain injury other than by expansion of hematoma (Keep et al., 2012).

Whether perihematomal ischemia occurs and contributes to ICH-induced neuronal injury is controversial both in humans and animals. Interpretation of blood flow reductions in perihematomal tissue is complicated by changes in metabolism and edema formation (Keep et al., 2012; Xi et al., 2006). Zazulia et al. (2001) reported reduced perihematomal blood flow after ICH and that this area corresponded with reduced, rather than increased, oxygen extraction fraction. This finding suggests that perihematomal blood flow reductions are matched with reduced metabolic demand in tissue damaged by the ICH. Other clinical and experimental studies have reported reduced perihematomal blood flows. However, the reductions seem insufficient to cause ischemic injury and they were combined with perifocal edema (Herweh et al., 2007; Mayer et al., 1998; Qureshi et al., 1999).

2.2. *Secondary brain injury*

Secondary brain injury after ICH is caused by a cascade of events. Immediately after ICH, activation of hemostatic cascade occurs as an initial reaction to limit bleeding. Thrombin, an essential component of the hemostatic cascade, is produced in the brain immediately after hemorrhage (Hua et al., 2007). Thrombin can affect many type of cells including endothelial cells, astrocytes, neurons, and microglia (Keep et al., 2012). Much evidence suggests that thrombin contributes to early blood–brain barrier (BBB) disruption and edema formation after ICH (Keep et al., 2014; Lee et al., 1996, 1997; Xi et al., 1998).

Release of hemoglobin and iron from the hematoma is considered another major contributor to ICH-induced brain injury (Keep et al., 2012; Wagner et al., 2003; Xi et al., 2006). Erythrocyte lysis occurs within 24 h after ICH, peaking at day 1–7 (Nakamura et al., 2004; Wu et al., 2003; Xi et al., 2006), and hemoglobin- and iron-mediated brain injuries occur along with lysis of extravasated erythrocytes. Injection of hemoglobin and its degradation products into striatum also cause brain damage (Hua et al., 2003; Huang et al., 2002).

It was reported that neurotoxic effects of hemoglobin are mainly due to heme (Lara et al., 2009). Degradation of heme by heme oxygenases (HO) after erythrocyte lysis results in the release of iron, carbon monoxide, and biliverdin, which is then converted to bilirubin (Maines, 1988). Iron overload in the brain starts within 24 h to peak at 7 days after hemorrhage, and remains at least a month (Chaudhary et al., 2013; Wu et al., 2010, 2003). Iron toxicity may be based on the Fenton chemistry reaction that can produce highly reactive free radicals, and it can cause neurodegeneration via oxidative injury (Zecca et al.,