Intracerebral Hemorrhage: Mechanisms and Therapies

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We welcome you to this special issue of *Translational Stroke Research* on intracerebral hemorrhage (ICH). There are about two million cases of ICH in the world each year, accounting for about 10–15 % of all strokes in the USA, Europe, and Australia and 20–30 % of strokes in Asia. It has a very high mortality rate (~40 %), and most survivors face long-term disability [1, 2]. Despite this, ICH has historically received much less focus than ischemic stroke. However, in the last years, there has been a marked increase in interest. Thus, Medline reported 374, 442, 590, 945, and 1,614 articles on intracerebral hemorrhage in the years from 1986–1990, 1991–1995, 1996–2000, 2001–2005, and 2006–2010, respectively. This upswing in interest is reflected by this special issue which includes 19 papers by leading experts in the field including clinical and preclinical studies, reviews and new research, and three editorials.

Rincon and Mayer [3] provide an extensive clinical overview of current management of ICH as well as ongoing clinical trials. Those trials include several aimed at clot evacuation with or without the use of tissue plasminogen activator (tPA) to aid in clot lysis [4, 5]. Tissue plasminogen activator is also being examined in the CLEAR IVH trial [6] for intraventricular hemorrhage (IVH). Ventricular extension worsens ICH-induced injury [7]. In this issue, Strahle et al. review evidence on the mechanisms of IVH-induced injury [8]. This is particularly important in relation to hemorrhage of the germinal matrix in premature neonates.

Neonatal hemorrhage is also the subject of an editorial by Bouz [9].

In treating cerebral ischemia with tPA, patients developing ICH is a major concern. Similarly, treating ICH patients with hemostatic agents to prevent hematoma expansion may cause thromboembolic events [10]. In addition, as discussed by Fisher et al. in this issue, ischemic and hemorrhagic cerebrovascular disease frequently coexists in the same patient (mixed cerebrovascular disease) raising a conundrum of how to treat such patients. Fisher et al. discuss potential ways to solve that problem [11].

Questions have also been raised over whether tPA may have some adverse consequences in the brain including causing delayed edema formation. In this issue, Keric et al. present data in a porcine ICH model that plasminogen activator inhibitor-1 can reduce that edema formation [12].

Polymorphisms in the APOE gene are associated with the risk of developing ICH and prognosis after ICH [13, 14]. In this issue, Lei et al. [15] report finding an interaction between APOE polymorphism and gender in determining ICH-induced injury. TOMM40 is a gene in close proximity to APOE. Valant et al. have examined the role of TOMM40 in cerebral amyloid angiopathy [16]. They report that single nucleotide polymorphisms in TOMM40 are associated with vascular amyloid deposition but not ICH.

The mechanisms that appear to underlie ICH injury differ substantially from those of cerebral ischemia [17]. Indeed, there is evidence that ischemia plays little role in most ICH [17], and it is dangerous to infer a potential therapeutic approach from one type of stroke to another. A case in point is hyperglycemia where there has been considerable interest in regulating glucose levels in ischemic patients (e.g., the GASP and current SHINE clinical trials; [18]) but, as indicated by the study of Feng et al., the evidence for a role of

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hyperglycemia in exacerbating ICH-induced brain injury is much less clear [19]. This deserves further investigation.

Perihematomal edema is a hallmark of ICH. In this issue, Bodmer et al. [20] review the molecular mechanisms underlying edema formation and potential therapeutic targets to reduce formation. ICH causes blood–brain barrier disruption and vasogenic edema formation. Liu and Sharp also review their work on the role of the Src family of kinases in blood–brain barrier disruption (and repair) as well as in neuronal cell death [21]. Lok et al. describe experiments indicating that neuregulin may be a novel mechanism to reduce blood–brain barrier disruption after brain injury [22].

Much work is ongoing in relation to the role of inflammation in ICH-induced neural and vascular injury. In this issue, Yao and Tsirka review the role of chemokines and particularly monocyte chemoattractant protein-1 (CCL2) in the influx of leukocytes into the brain after ICH and hemorrhagic brain injury [23]. Hammond et al. report their results on the types of inflammatory cells that infiltrate the brain after ICH and the changes in inflammatory mediators that may drive that infiltration [24]. Similarly, Lively and Schlichter examine the evolution of the inflammatory response after ICH by measuring inflammatory mediators levels [25]. They have found differences between young and old rats which may be important since ICH is mostly a disease of the elderly. Loftspring et al. examine the potential role of neutrophils in ICH-induced injury, but found no effect of neutrophil depletion [26]. Simard et al. used a different approach to manipulate inflammation in subarachnoid hemorrhage, systemic delivery of heparin [27]. They found significantly reduced neuroinflammation, demyelination, and apoptosis.

While it is well known that there is a profound astrocyte reaction after ICH, less attention has been paid to this cell type as a potential therapeutic target. Here, Sukumari-Ramesh et al. discuss the potential beneficial and detrimental effects of ICH-induced astrogliosis [28].

Advances in our understanding of ICH will be assisted by new methodologies. Two examples are presented in this edition. Hasan et al. present data using ferumoxytyl-enhanced MRI to image inflammation in human brain arteriovenous malformations (AVMs) [29]. This promises to be a new diagnostic tool for potential AVM rupture and a method of studying the natural course of AVM development. Xie et al. examine the vascular response after mouse ICH using micro CT after vascular perfusion with microfil [30]. This technique allows 3D vascular reconstructions in order to examine vasodilation and neovascularization in relation to the hematoma.

The potential of mixed cerebrovascular disease, the desire to treat patients as early as possible after ictus when it may not be certain whether a stroke is hemorrhagic or ischemic, and the possibility that some potential therapies

may have beneficial and detrimental effects in different forms of stroke mean that it is important to test strategies in both ischemic and hemorrhagic stroke models. The effects of conditioning stimuli (induced tolerance) on ischemic brain damage are well known and are proceeding to clinical trial. The effects of ischemic preconditioning (IPC) on ICH-induced injury have not been studied. In this issue, He et al. show that IPC can reduce ICH-induced injury, although there were some effects on hemostasis that require further investigation [31].

As yet, there are still no therapies for ICH. However, as emphasized by the editorial by Morgenstern in this issue, there are now multiple clinical trials aimed at rectifying that situation, and this issue as a whole shows some of the breadth of work being undertaken to try and improve ICH treatment [32]. We would like to thank the contributors for the effort and time they put into this issue.

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