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COMMENT

How to Promote Hemoglobin Scavenging or Clearance and Detoxification in Hemorrhagic Stroke

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Hemorrhagic strokes such as intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH) are common diseases, but their effective treatments are limited. As a main cause of disabilities are fundamentally a series of pathological changes caused by a mass effect of hematoma and/or extravasated blood components, early blood clearance with little adverse effects is a reasonable treatment strategy [1, 2]. Recently, this journal published an interesting study, in which a natural bioflavonoid extract wogonin facilitated ICH clearance by activating peroxisome proliferator-activated receptor-γ (PPAR-γ) in mice [2], and two excellent review articles focusing on hemoglobin (Hb) clearance [3, 4], suggesting continued high levels of interest in this subject.

Erythrocytes contain Hb, peroxiredoxin-2, and carbonic anhydrase-1, all of which cause secondary brain injuries after hemorrhagic stroke [3]. Oxy-Hb and its degradation by-products disrupt endothelial nitric oxide signaling and induce vasoactive mediators, oxidative stress, and inflammatory reactions, followed by vasoconstriction, microthrombosis, cortical spreading ischemia, and seizures [4, 5]. Intracellular peroxiredoxin-2 is an important antioxidant, but becomes a damage-associated molecular pattern, a potent pro-inflammatory molecule, upon release to the extracellular spaces, as well as Hb and heme [3, 6]. Thus, removal of blood clots before erythrolysis is important to suppress secondary brain injuries. In clinical settings, direct surgical or irrigation removal of hematoma and cerebrospinal fluid (CSF) drainage with or without intrathecal thrombolysis has been performed to promote early blood clearance with limited efficacies [4]. From a practical standpoint, the procedures may carry their own risks such as increased bleeding and injuries of cerebrovascular tissues and is not applicable to many brain regions.

In a natural course, most of extravasated erythrocytes undergo osmotic cell lysis by activated complements and the other mechanisms, and are phagocytosed by microglia/infiltrating macrophages via CD36 [7], while a small fraction of erythrocytes may leave the brain via the glymphatic system [3]. Macrophages/microglia are the main cell types involved in extravasated erythrocyte clearance and highly express heme oxygenase (HO) to degrade heme to biliverdin, iron, and carbon monoxide, as well as ferritin to chelate irons, which are neurotoxic if released into the extracellular space [3, 8]. However, erythrophagocytosis may not be an ideal clearance mechanism because hyperphagic macrophages engulfing ≥ 2 erythrocytes undergo cell death, resulting in releases of deleterious hemes and irons into the extracellular spaces [8]. Although free Hb is scavenged by haptoglobin, and heme released by unscavenged Hb is sequestered with a high affinity by hemopexin [7], their scavenging effects are very limited due to their scarcity in the CSF [8]. A Hb scavenger haptoglobin, which irreversibly binds cell-free Hb to prevent its auto-oxidation, is mainly synthesized by the liver and the reticuloendothelial system, and to a limited extent diffuses into the CSF [8]. Haptoglobin is not normally synthesized within the brain, but is upregulated in astrocytes, oligodendrocytes, and neurons under pathological conditions or excessive levels of Hb [7, 8]. Macrophage/microglia endocytose the haptoglobin–Hb complex through the receptor CD163, exerting anti-inflammatory effects [7]. CD163 is upregulated on neurons under pathological conditions, but neuron with haptoglobin–Hb endocytosis leads to cell death [8]. Soluble CD163 and immunoglobulin G (IgG) also interact with free Hb, and the soluble CD163–Hb–IgG complex undergoes endocytosis into macrophage/microglia via the crystallizable fragment-γ receptor [7]. In contrast, about 90% of hemopexin in the brain is produced in neurons and glia under healthy conditions [8]. The hemopexin–heme complex is endocytosed by

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cells expressing the low-density lipoprotein receptor-related protein-1/CD91 receptor such as macrophages, astrocytes, neurons, pericytes, vascular endothelial and smooth muscle cells, and HO degrades post-endocytosis heme irrespective of cell types [8]. There are multiple CSF drainage routes including draining out along perivascular spaces (centrifugally from along capillary basement membranes between the endothelial layer and the surrounding astrocytes, basement membranes surrounding smooth muscle cells in the tunica media of arterioles, and then through the adventitia of pial and larger cerebral arteries), across the nasal epithelium, and along cranial and spinal nerves leading to the deep cervical lymphatic system, meningeal lymphatic vessels along the dural sinuses, and direct transport to blood across the arachnoid villi [3, 9]. In addition to full-length antibodies IgG (molecular mass [MM] of a monomer, about 150 kDa), erythrocytes (diameter, 7–8 μm), Hb (about 64.5 kDa), degraded blood products, and fibrinogen (about 340 kDa) in the subarachnoid space penetrate into brain tissues along the perivascular spaces of arterioles, capillaries, and venules, activating cascades of harmful neurovascular events [7–9]. Substances with a MM ≤ 100 kDa can leave the perivascular spaces by passing through the 50-nm clefts between the vascular endfeet of astrocytes, while the clearance of molecules with a MM > 200 kDa is restricted [7, 8]. Although the size of the simplest dimeric form of haptoglobin–Hb complex (162 kDa) is below the threshold, exit of the highest-order polymer of haptoglobin–Hb complex (1760 kDa) from the brain is severely impeded [7, 8]. The glymphatic system is impaired with aging [9], and meningeal lymphatic drainage or sinus-associated lymphatic vessels are blocked possibly by blood clots after SAH [1]. Erythrocyte-laden macrophages may cross back into the vascular system through the disrupted blood–brain barrier or the blood–CSF barrier within the choroid plexus [3]. In SAH, acute blood products in the subarachnoid space sometimes become invisible within a few days on neuroimages, but persistent impairment of the glymphatic system is common. Although abnormalities in CSF circulation and absorption can be diagnosed using intrathecal injections of a tracer, no neuroimaging can visualize blood components in the perivascular spaces, being a bottleneck for clinical research.

Hb-scavenging strategies to reduce its toxicity may include delaying erythrolysis to earn time for activation of endogenous defense mechanisms and augmentation of erythrophagocytosis before erythrolysis, haptoglobin–Hb, or hemopexin–heme binding, HO breakdown of heme, and glymphatic function to improve clearance of erythrocytes, degradation products, or erythrocyte-laden phagocytes. So far, experimental studies have reported the effectiveness of PPAR-γ activators (enhanced microglial phagocytic activity and CD36 upregulation), a transcriptional regulator nuclear factor erythroid 2-related factor 2 (haptoglobin upregulation), intrathecal tissue plasminogen activator (improved blood clearance in the perivascular space and glymphatic function), and a selective α-2-adrenergic agonist dexmedetomidine (inducing a slow-wave sleep-like state to enhance glymphatic function) [7, 9]. Glymphatic function may also be improved by pressors such as dobutamine through boosting the arterial pulsatility, which is a key force driving glymphatic flow, and by avoiding too frequent neuro-checks interrupting deep non-rapid-eye-movement sleep, during which glymphatic function is most active [9]. Understanding of blood clearance mechanisms may uncover additional potential interventions for translational researches, leading to the development of new therapies for hemorrhagic strokes.

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Declarations

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