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Short Communicaion

Role of Neutrophils in the Inflammation of Brain

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Abstract

The immune response after stroke is known to play a significant role in ischemic brain. The inflammatory messages let out by immune contacts activated by brain damage sets off a complex series of pathologic events which have been progressively recognized as an essential attendant to neuronal death. The primary immune mediators contained are glial cells and infiltrating leukocytes, including neutrophils, monocytes, and lymphocyte. After ischemic stroke, infiltrated leukocytes release inflammatory mediators into the site of the lesion, thereby exacerbating brain injury. This review describes how the roles of circulating neutrophils are a double-edged sword for neuroinflammation by focusing on their detrimental and protective effects in ischemic stroke. Here, we will concentrate on underlying characterize of glial cells and leukocytes under inflammation after ischemic stroke.

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Necrotic cell death within the infarcted area causes the release of inflammatory cytokines and migration of immune cells. Neutrophils are the first cells accumulated into the brain after stroke. The mechanism of neutrophil entry into the brain after stroke was investigated in permanent and transient experimental stroke models with in vivo imaging. Bloodborne neutrophils immediately migrate, even against blood flow, and then transmigrate out of blood vessels to reach the injured brain area [1]. The zenith of neutrophil invasion is achieved between two and three days after stroke [2]. The Blood Brain Barrier (BBB) blocks the entry of immune cells into the brain. But, neutrophil entry is enabled by regional BBB breakdown caused by ischemia [3]. The effect of immune cell migration is a controversial topic. Although immune cells might play a significant role in the tissue repair, their harmful impacts dominate. This was showed in experimental settings, where invading neutrophils increased ischemic neurotoxici ty through different effects [4].Neutrophils produce Reactive Oxygen Species (ROS), like superoxide radicals and hydrogen peroxide when they are activated. Nonetheless, they send enzymes(cathepsin G, collagenase, gelatinase, and heparinase), which promote to ROS-mediated vascular damage.Neutrophils can enable complement and release cell content, during suicidal extra cellular. This antibacterial mechanism involves in the neutrophil elastase, which was demonstrated to remain vessel permeability [5,7]. Additionally, neutrophil release of proinflammatory mediators initiates a self-energizing cascade of proinflammation and destruction. Resident microglia can fight this detrimental damage to a minor extent, by engulfing neutrophils [4]. These adverse effects of neutrophils make them a prime target for novel therapies for stroke. Indeed, in experimental focal brain ischemia models, a variety of therapeutic interventions successfully reduced lesion size. One approach was to block pro-inflammatory cytokines and mediators. For instance, antagonization of C-X-C motif chemokine receptor 2 (CXCR-2) protected reinforcement of cells to the infarct area [8]. Alternative neutrophil chemoattractant, chemokine (C-X-C motif) ligand 1 (CXCL-1), is induced by interleukin17 (IL-17), which is released by T-cells. Blocking this pathway with an anti-17-antibody decreased the size of lesion [9]. Additionally, neutrophil extravasation was demonstrated to be mediated by very-late-antigen 4 (VLA-4) in a study. Thereby, blocking VLA-4 cut down lesion size [26]. A different approach is to block the neutrophil pro-inflammatory effects. Oxidative stress, induced an overload of ROS, promotes various acute, chronic, and inflammatory diseases. Thus, this mechanism has suggested as a target for therapy. In the the trial, beneficial effects were managed by prohibitor type 4 nicotinamide adenine dinucleotide phosphate oxidase (NOX4). In experimental models, brain damage was also ameliorated by inhibiting myeloperoxidase oxidant (MPO) production, with N-acetyl lysyl-tyrosyl cysteine amide or with the flavonoid, eriodyctiol [10,11]. Additionally, neutrophil migration, evaluated by MPO activity, and infarct volume were considerably decreased following the administration of AM-36 ,that is a neuroprotectant [12]. Nitric oxide (NO) reproduced by inducible NO synthase (iNOS) promotes to brain injury. iNOS expression is overwhelmingly found out in swarming neutrophils after stroke. Neutrophils were changed into tissue of mice, infarct volume enhanced. iNOS is a primary mediator of tissue ravage [13]. The inhibition of oxidative radical production was showed to be a proper approach in lacunar infarctions [14]. In contrast, A free radical scavenger(Edaravone) increased hemorrhagic transformation in patients with cardiogenic embolism [15]. In patients receiving rtPA treatment, hemorrhagic complications are more prevalent in blacks and Asians it is possible that

the higher bleeding rate was caused by ethnic-related reasons [16] . Uric acid was thought to conserve the brain from oxidative damage. Until now studies investigating the protective effect of UA after stroke continue quastinable [17]. While descriptive studies find that higher concentrations of UA in serum are beneficial in patients with stroke treated with thrombolysis [18,19] the results of the a study demonstrated only a beneficial outcome for selected patient groups, for instance, women [20]. It is also known that different elements like old age, time to treatment, the extent of the ischemic injury before administration of therapy, higher baseline National Institutes of Health Stroke Scale score, increased systolic blood pressure, or diabetes enhance the risk of hemorrhagic incidence after stroke [21]. For this reason, treatment options might depend on the combination of individual factors. Another molecule is the HMGB-1, discussed in the modulation of post-stroke immune response. This DNA-binding protein is emitted during stroke from cells with necrosis. This damage-related molecular pattern can be secreted by immune cells and is emitted and sustained by platelets promoting thrombus formation. Elevated plasma HMGB-1 levels were showed in patients with acute ischemic stroke in clinical studies. A correlation between HMGB- 1 levels and circulating leukocytes was proved [22]. It was also demonstrated that HMGB-1 promoted to tissue destruction by recruiting neutrophil [23,24]. Reductions in plasma HMGB-1 levels with cannabinoids were related to decreases in infarct size and number of neutrophil [25]. The rapid early changes beholded in different trials could be prevented by blocking-adrenoceptors with propranolol or by neutralizing HMGB-1 activity with antibodies [26,27]. These treatments were performed before and after stroke induction.In addition to upsizing ischemic injury and the subsequent signaling cascades.As well as,neutrophils are contained in reperfusion injury. The risk of hemorrhagic transformation is increased by as much as tenfold after intravenous rtPA administration, mainly based on reperfusion injury [27]. Some parameters (high neutrophil counts and a high neutrophil-to-lymphocyte ratio) were related to poor outcomes for 3 months. [28,29]. Similar results were found in patients with intracerebral hemorrhage [30]. Interestingly, treatment with rtPA induced neutrophil degranulation in experimental trials [31]. Granulocyte colony stimulating factor (G-CSF) had a protective effect in many experimental trial. Administration of G-CSF diminished infarct size and recovered motor function [32]. A recent meta-analysis showed that G-CSF did not recruit stroke outcome in patients with stroke [33]. And no beneficial effects of additional G-CSF administration were showed in experimental model; behalf an increased risk of hemorrhage happened within the infarct region at 72 h after stroke [34]. In these models, neutrophil blood counts were enhanced, and neutrophilic activation arrived within 15 min after reperfusion, and it continued evident after 24 h [35]. Neutrophils may be transporter of hemorrhagic complications after thrombolysis; thus, they could represent new targets for neuroprotective strategies in patients treated with rtPA.

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