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Review

# Pathogenesis of acute stroke and the role of inflammasomes

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ABSTRACT

Inflammation is an innate immune response to infection or tissue damage that is designed to limit harm to the host, but contributes significantly to ischemic brain injury following stroke. The inflammatory response is initiated by the detection of acute damage via extracellular and intracellular pattern recognition receptors, which respond to conserved microbial structures, termed pathogen-associated molecular patterns or host-derived danger signals termed damage-associated molecular patterns. Multi-protein complexes known as inflammasomes (e.g. containing NLRP1, NLRP2, NLRP3, NLRP6, NLRP7, NLRP12, NLRC4, AIM2 and/or Pyrin), then process these signals to trigger an effector response. Briefly, signaling through NLRP1 and NLRP3 inflammasomes produces cleaved caspase-1, which cleaves both pro-IL-1β and pro-IL-18 into their biologically active mature pro-inflammatory cytokines that are released into the extracellular environment. This review will describe the molecular structure, cellular signaling pathways and current evidence for inflammasome activation following cerebral ischemia, and the potential for future treatments for stroke that may involve targeting inflammasome formation or its products in the ischemic brain.



**Contents**



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## 1. Introduction

Stroke is the second leading cause of mortality worldwide resulting in approximately 6 million deaths every year and is a major cause of long-term disability (World Health Organization, 2010). An estimated 16 million people suffered from a first-ever stroke in the year 2005, and in the absence of any clinical interventions, it is estimated that 23 million first-ever strokes will occur by 2030 (Strong et al., 2007; Mukherjee and Patil, 2012). Stroke occurs when blood flow to the brain is interrupted by an embolic or thrombotic occlusion of a cerebral artery (ischemic stroke) or by bleeding from a ruptured blood vessel (hemorrhagic stroke). The pathophysiological processes following stroke are complex and extensive, and include bioenergetic failure, loss of cell ion homeostasis, acidosis, increased intracellular calcium levels, excitotoxicity, reactive oxygen species-mediated toxicity, generation of arachidonic acid products, cytokine-mediated cytotoxicity, activation of neuronal and glial cells, complement activation, disruption of the blood–brain barrier and infiltration of leukocytes (Woodruff et al., 2011). Currently, intravenous recombinant tissue plasminogen activator (r-tPA) to induce thrombolysis following a thrombotic occlusion is the only pharmacological agent approved for acute stroke therapy. However, a major limitation of r-tPA therapy is its narrow therapeutic window of 3 h. An increased risk of intracerebral hemorrhage, neuronal excitotoxicity and an inability to rescue dying neurons preclude the use of r-tPA beyond this time frame (NINDS, 1995; Smith et al., 2008; Taschner et al., 2011). An alternative approach for treating acute ischemic stroke is neuroprotection. Despite neuroprotective agents decreasing neuronal cell death and infarct size in cell culture and animal stroke models, respectively, all such agents tested in patients have failed in clinical trials due to deleterious side effects and/or low efficacy (Ahmed et al., 2000; Chan et al., 1998; Cheng et al., 2004; Davis et al., 2000; Fosphenytoin– Internet Stroke Centre, 2007; Furuya et al., 2001; Van der Worp et al., 2002).

Recent findings have provided insight into a newly described inflammatory mechanism fundamental to the innate immune system that may contribute to neuronal and glial cell death during cerebral ischemia. There is emerging evidence to suggest that plasma membrane pattern recognition receptors on neurons and glial cells can play an important role in activating nuclear factor kappa B (NFκB) and mitogen activated protein kinase (MAPK) pathways (Tang et al., 2007, 2013). This occurs in response to endogenous danger signals initiated by substances released from necrotic cells in the ischemic core, leading to an increased production of pro-inflammatory cytokines and to neuronal and glial cell death. These effects are mediated by intracellular multi-protein complexes termed inflammasomes (Abulafia et al., 2009; Deroide et al., 2013; Kono and Rock, 2008; Legos et al., 2001; Tamatani et al., 2000). In particular, the NOD (nucleotide-binding oligomerization domain)-like receptor (NLR) Pyrin domain containing 1 (NLRP1) and NLRP3 inflammasomes, expressed abundantly in the brain and immune cells, may play important roles in detecting cellular damage and mediating inflammatory responses to aseptic tissue injury during ischemic stroke. This review will describe evidence for expression of NLRP1 and NLRP3 inflammasomes in the brain, their involvement in ischemic stroke, and the therapeutic potential of agents that modify inflammasome signaling.

## 2. Stroke

Stroke is an acute condition characterized by a sudden decrease in blood flow to brain tissue resulting in impairment or loss of neurological function. The condition typically involves an immediate deprivation of both glucose and oxygen, which are needed to maintain the metabolic demands of the brain as it holds no energy stores that can be drawn upon (Ahmad and Graham, 2010). Clinically, stroke can be classified as either ischemic or hemorrhagic. Ischemic stroke commonly accounts for approximately 80% of all stroke cases, and can be instigated by an embolic or thrombotic occlusion of a cerebral artery, whereas hemorrhagic stroke accounts for approximately 15–20% of all cases and is initiated by the rupture of a cerebral blood vessel (Gilgun-Sherki et al., 2002). Ischemic stroke can be further divided into two categories – global or focal ischemia (Bacigaluppi et al., 2010; Durukan and Tatlisumak, 2007). Global ischemic stroke occurs when blood flow to the entire brain or a majority part of the brain is stopped or severely reduced, which commonly occurs during a cardiac arrest associated with myocardial infarction (Bottiger et al., 1999; Yonekura et al., 2004). Conversely, focal ischemic stroke occurs when cerebral blood flow is attenuated in a specific brain region, prompted by an embolic or thrombotic occlusion (either transiently or permanently) in a major cerebral artery (Hata et al., 2000; McAuley, 1995). Amongst the two categories, focal ischemic stroke is by far the most prevalent.

### 2.1. Ischemic stroke

Ischemic stroke is characterized by the formation of two regions within the ischemic territory, a central ischemic core surrounded by an ischemic penumbra (or peri-infarct zone) due to focal hypoperfusion (Kumar et al., 2010; Lo, 2008a). The size of the ischemic core and penumbra will usually depend on the severity and duration of the cerebral artery occlusion and vulnerability of certain populations of neurons to ischemia (e.g. CA1 pyramidal neurons in the hippocampus are more susceptible to ischemic damage than dentate granule neurons) (Brouns and De Deyn, 2009; Mattson et



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