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Review article

Notch signaling and neuronal death in stroke

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ABSTRACT

Ischemic stroke is a leading cause of morbidity and death, with the outcome largely determined by the amount of hypoxia-related neuronal death in the affected brain regions. Cerebral ischemia and hypoxia activate the Notch1 signaling pathway and four prominent interacting pathways (NF-κB, p53, HIF-1α and Pin1) that converge on a conserved DNA-associated nuclear multi-protein complex, which controls the expression of genes that can determine the fate of neurons. When neurons experience a moderate level of ischemic insult, the nuclear multi-protein complex up-regulates adaptive stress response genes encoding proteins that promote neuronal survival, but when ischemia is more severe the nuclear multi-protein complex induces genes encoding proteins that trigger and execute a neuronal death program. We propose that the nuclear multi-protein transcriptional complex is a molecular mediator of neuronal hormesis and a target for therapeutic intervention in stroke.

1. Introduction

The most common proximate pathogenic event in stroke is the formation of a clot in a cerebral artery, resulting in severely reduced perfusion of brain tissue supplied by the affected vessel. The clot often resolves within several minutes to hours and blood flow resumes. In human patients and animal stroke models, neurons which are supplied with blood solely by the affected artery die rapidly by necrosis (the ischemic core), whereas neurons peripheral to the core which are also perfused to some extent by other arteries (the ischemic penumbra) undergo delayed apoptosis (Broughton et al., 2009; Fann et al., 2013). The pathophysiology of ischemic stroke-induced brain damage is complex. Ischemia and reperfusion can cause in bioenergetic failure, loss of cellular ion homeostasis, excitotoxicity, impaired mitochondrial function, generation of reactive oxygen species (ROS) and activation of caspases in neuronal cells. It can also lead to inflammatory responses in the brain by promoting generation of arachidonic acid products, production of cytokines, activation of complement pathways, inflammasomes, and various membrane receptors by damage associated molecular patterns (DAMPs), disruption of the blood-brain barrier, and infiltration of immune cells (Arumugam et al., 2005; Broughton et al., 2009; Brait et al., 2012; Fann et al., 2013) (Fig. 1). The triggering of membrane receptors such as toll-like receptors (TLRs), C-type lectin Mincle and the receptor for advanced glycation end products (RAGE) by DAMPs results in the stimulation of numerous signaling cascades and transcription factors, primarily in inflammatory glial cells but also in neurons (Tang et al., 2013a,b; Fann et al., 2013; Arumugam et al., 2017; Wang et al., 2017) (Fig. 1).

Preclinical studies have shown that many neurons in the ischemic penumbra can be rescued and their functional outcomes can be improved, by interventions that target one or more of the above-mentioned neurodegenerative processes. Such neuroprotective approaches include agents that inhibit glutamate receptors, ROS, leukocyte infiltration and immune responses, and interventions that bolster

Abbreviations: AP-1, activator protein-1; APP, amyloid precursor protein; AICD, APP intracellular domain; DAMPs, damage associated molecular patterns; FOXO3, forkhead box O3; HES, hairy-enhancer of split; HPCs, hematopoietic progenitor cells; HDAC, histone deacetylase; MAML, mastermind/Lag3; HIF-1α, hypoxia inducible factor 1 alpha; IGF-BP3, insulin-like growth factor binding protein-3; JIP, JNK-interacting protein 1; LTP, long-term potentiation; MCAO, middle cerebral artery occlusion; NICD, Notch intra-cellular domain; NF-κB, nuclear factor kappa B; PAG608, p53-activated gene 608; PIG, p53-inducible gene; NPC, neural progenitor cell; p53AIP1, p53-regulated apoptosis inducing protein-1; Pin1, peptidyl-prolyl cis-trans isomerase NIMA-interacting 1; ROS, reactive oxygen species; RAGE, receptor for advanced glycation end products; SRE, serum response element; SMRT, silencing mediator of retinoid and thyroid hormone receptor; TLRs, toll-like receptors; TNF, tumor necrosis factor

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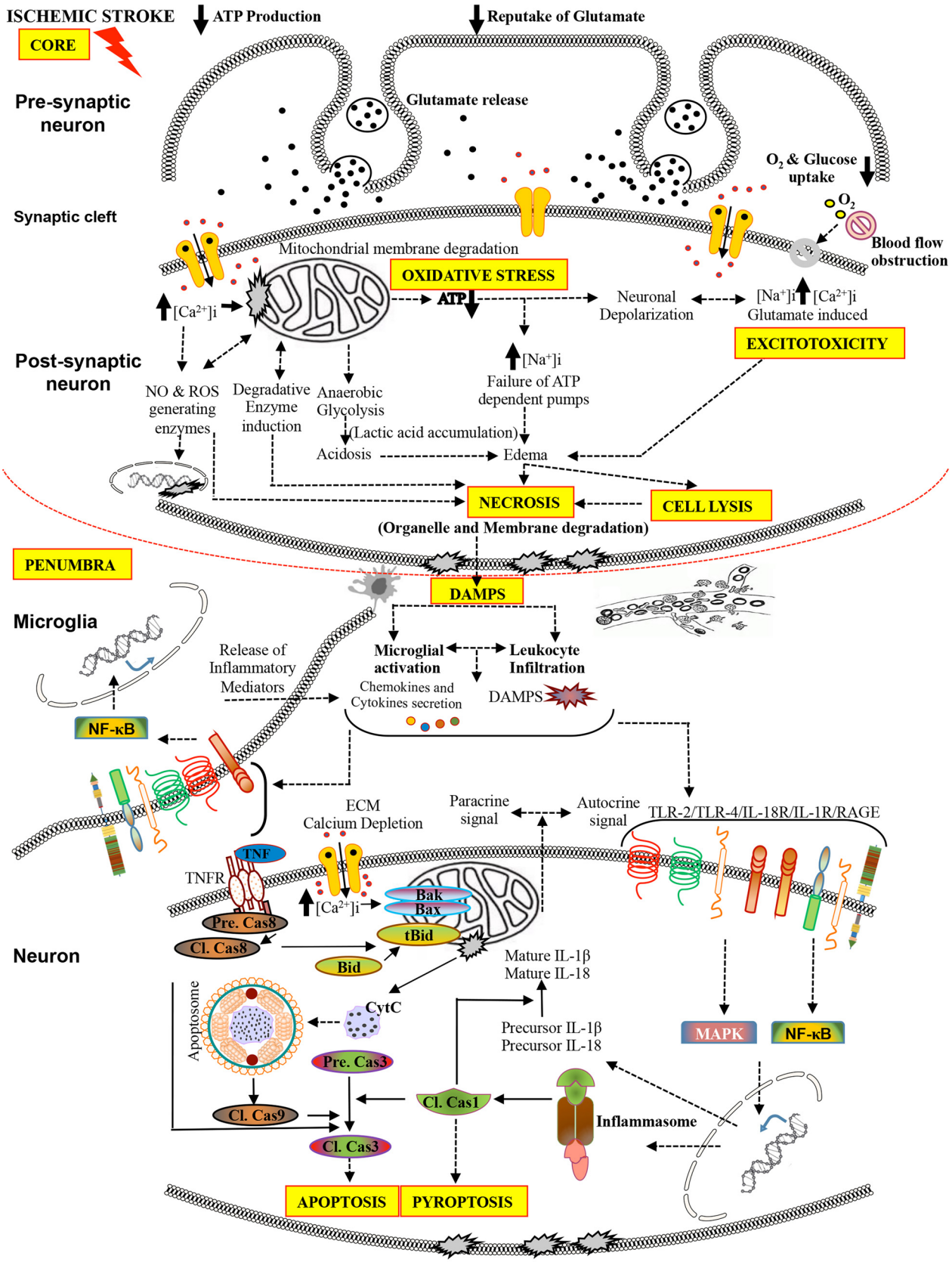

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mitochondrial function (Broughton et al., 2009; Lai et al., 2014). In addition, insight into the factors that determine inter-individual differences in stroke outcomes has come from studies showing that antecedent exercise, intermittent fasting, and pharmacological bioenergetic challenges can improve neurological deficit and reduce development of infarcted tissue in animal models of focal ischemic stroke