

Individual Neuronal Apoptosis Provokes Determined Necrosis of the Regional Cerebral Infarct in Patients with Ischemic Stroke



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Abstract

Interplay pathway dynamics are constitutive agonists in an evolving ischemic focus within the brain that is triggered by apoptotic programmed cell death that is subsequently established as a necrotic focus of infarction within the cerebral cortex of many patients with stroke. The evolutionary dynamics further permit the activation of potentially neuroprotective measures that primarily attempt limitation of involvement of adjacent less injured neurons but subsequently by the establishment of transformed penumbra to a necrotic focus of infarction. Within such contextual transformations, the individual apoptotic neuron determines the characterized infarcted region as necrotic focus formulation. Individual neuronal apoptosis provokes determined necrosis of the regional cerebral infarct in patients with ischemic stroke.

Introduction

Stroke patients comprise a large number of patients with a highly significant degree of cerebral ischemia that is best exemplified by the transient focal ischemia models in experimental animals such as rat and mouse. Mechanisms include bioenergetic failure and loss of cell homeostasis, and also acidosis, excitotoxicity and disrupted blood-brain barrier [1]. A central issue is the series of set conditioning factors that induce apoptosis of individual neurons within the penumbral region of the cerebral cortex on the one hand and the development of neuronal necrosis on the other. Combined steroid administration inhibits ischemia-induced apoptosis of neurons through involvement of the intrinsic pathways [2]. It would appear that a combination of both apoptosis and necrosis of neurons evolves in at least some of the patients, and indeed neurons may exhibit features of both these forms of neuronal cell death when electron microscopic studies are combined with molecular and biochemical modes of analysis. Whether necrosis or apoptosis occurs often depends on cell type, cell age and location in the brain. Apoptosis leads to protein cross-linking, DNA fragmentation, ligand expression for phagocytic cell receptors and subsequent phagocytic uptake [3].

Neuroprotection

It is idealized that a set of potentially neuroprotective mechanisms is activated within the penumbral region of

an evolving cerebral infarct. Oxidative stress contributes to ischemia/reperfusion with blood-brain barrier disruption, inflammation necrosis and apoptosis; Nuclear factor- κ B-related factor 2 is central to regulated antioxidant defence and may protect against ischemia-induced neuronal injury [4]. Such coupled phenomena are central to the establishment of the expanding infarct secondary to delayed death of more neurons in the few days following the primary acute infarction of the core lesion. Glycine inhibits tumor necrosis factor alpha and protects against inflammation and gloss in hypoxia-ischemia of neurons [5]. Such considerations are believed to potentiate the possible beneficial attempts at reducing infarct size within the acute dimensions of ischemic injury to neurons.

Glial cells

Glial cells such as astrocytes and microglia are implicated in neuroprotection and indeed the cellular network of gap junctions between individual astrocytes are viewed as supportive elements in neuroprotection. The dimensions of complex control of ion-motive ATPase channels collaborate with the dynamics of possible recovery of related ischemic neurons that implicate a regional characterization and re-characterization of the ischemic injury not only to individual neurons but also to groups and sizeable aggregates of such neurons. Auto-antibodies to apolipoprotein A-1 are associated with poorer clinical recovery

and increased brain lesion volume 3 months after acute ischemic stroke [6].

Dynamics of ischemic injury

Genetic evidence exists that separates apoptosis from necrosis through different forms of nuclear pyknosis, with conservation of nuclear pyknosis in the propagation of necrosis [7]. Performance dynamics of the acute ischemic focus also implicates microglia that are implicated in removal of ischemic individual neurons following acute ischemic injury. The distributional coherence of integral groups of ischemic neurons is hence mirrored by presumably apoptotic individual neurons undergoing damage primarily to mitochondria and to lipid moieties of the plasma membrane of the cells. In such context, the evolving participation of apoptosis and necrosis would permit the progression of caspase pathway activation and the release of cytochrome c release from mitochondria. Also, destabilized cellular calcium homeostasis follows a stereotyped pattern of changes that invokes execution pathways of neuronal cell injury.

The phagocytic receptor CED-1 is activated through interaction with its ligand phosphatidylserine (PS) exposed on the surface of necrotic neurons; calcium influx activates a neuronal PS-scramblase for PS exposure [8]. A complex array of executing agonists include excitotoxic, oxidative and lipid peroxidation, and metabolic insults such as hypoglycemia participates within contexts of activated apoptotic pathways, as evidenced by the neuroprotective effects of administered caspase inhibitors in the acute phase of ischemic insults. Epigenetic regulatory networks in ischemic stroke may protect against oxidative stress with induced DNA methylation, histone modification and microRNAs, with affected redox state in neurons, glia and vascular endothelial cells [9].

Determined pathway events

Determined outcome of the ischemic individual neuron and also of groups of such neurons is affected by "ischemic pre-conditioning" whereby a mild episode of ischemia generates resistance to a second ischemic episode. Certainly, the panoramic contexts of evolving ischemic injury within neurons is programmed within the pathways primarily dictated by individual cellular responses to ischemia that however originates as a regional focus of groups of ischemic neurons. Platelet-activating factor receptor is expressed on cellular and nuclear membranes of leukocytes, platelets, endothelial cells, neurons and microglia; its deficiency is experimentally associated with prevention of caspase-3 activation and decreased vascular permeability and cerebral edema. Decreased brain levels of tumor necrosis factor-alpha, interleukin-1beta and the chemokine (C-X-C motif) ligand 1 may be crucial in global brain ischemia-reperfusion [10].

Particularly intriguing is the overlap of regional and individual cell ischemic episodes that determine the onset of a core of necrotic cerebral tissue in the first instance and the

subsequent creation of a penumbra of regional and partially injured neurons and glial cells. It is further to such phenomena that the ischemic episodes are regional also as evidenced by activated neuroprotective mechanisms such as the action of neurotrophic factors and of some cytokines such as tumor necrosis factor alpha and interleukin 1-beta. The PPAR gamma agonist 15d-PGJ2 regulates microglial activation and decreases tumor necrosis factor alpha and interleukin-1 expression. Fewer apoptotic cells and less CD68 positive staining in diabetic schema rats [11].

Chaperone dysfunctionality allows for an evolving train of events in the execution of both apoptosis and necrosis within the individually affected neurons and as further portrayed by the dynamics of the expanding penumbral region. 4'-O-beta-D-Glucosyl-5-O-Methylvisamminol, a natural histone H3 phosphorylation epigenetic suppressor is a neuroprotective factor by acting via the PI3K/Akt signaling pathway in focal ischemia in rats [12]. It is further to such processes that the integral identity of cell-death phenomena permits the execution of individual cell damage as dictated by regional injuries to the cerebral cortex in particular. pH gradient difference around cerebral foci of ischemia may allow delivery of polyethylene glycol-conjugated urokinase nano gels with effective thrombolysis of the ischemic stroke [13].

Performance attributes

Performance attributes characterize hence the emergence of a necrotic core to the ischemic focus in a manner that potentiates the evolutionary progression of the penumbral region of partially injured neurons. MicroRNA-9 is down regulated in mice with middle cerebral artery occlusion and oxygen-glucose deprivation neurons, with suppression of neuronal apoptosis on its up regulation [14]. The parameters of acquisition of cellular ischemic injury is mirrored in the evolutionary course dynamics of such events as the emergence of a multitude of agonists that portray the character of primary core necrosis by the penumbral region of conditioned delay of individual cell death within contexts of transforming apoptotic cascades within such individual neurons.

Apoptosis

The ischemic neuron undergoing apoptosis is generally associated with adjacent cells that do not show apoptosis phenotype characteristics and as such this has implicated microglial phagocytosis of the individually damaged neuron. Such a phenomenon however is contrary to the widespread focus of integral ischemic injury to the cerebral cortical region and is also at variance with a presumably programmed response to injury to cellular networks. Tissue necrosis in particular is a conceptual realization of regional fields of perfusion and re-perfusion events arising from compromised individual vessels of supply. Penethylidine hydrochloride down regulates the phosphorylation of JNK, p38MAPK, and

c-Jun and protects neurons against ischemia/reperfusion [15]. Ongoing phenomena such as the no-reflow events within the vessels of supply allow for complicated series of processes involving neuroprotective measures. Scite;;arom down-regulates expression of angiotensin-converting enzyme and AT1 receptor with neuroprotective effects [16]. The activation of heat shock protein such as HSP-70 and increased secretion of glucocorticoids during the acute ischemic episode allows for the emergence of constitutive pathways that on the one hand further injure the neurons and on the other hand actually enhance potential resistance to acute neuronal ischemia.

Apoptosis/necrosis interplay

The apoptotic neurons exhibit characteristic cell body shrinkage and condensation of chromatin that progresses as fragmentation of the DNA and the appearance of single- and double-strand breaks of the DNA molecules. Such events may be related to the cytoskeletal injuries that occur in individual neurons such as those caused by depolymerization of actin filaments by gelsolin. Release of calcium from endoplasmic reticulum stores is characterized as an end-pathway that is reflected in individual cell death. Mitochondrial dysfunction further correlates with the onset and participation of injurious events as evidenced by programmed cell death pathway activations. Apoptosis of individual ischemic neurons is hence a contextual setting for necrosis of core foci within the lesion as further indicated by the subsequent establishment of a truly necrotic focus of cerebral infarction. The delivery of multi-components would further confirm the derivation of programmed cell death as determining agonist series of pathway events in establishment of further increased injury to individual neurons and regional groups of ischemic neurons. Etanercept, a recombinant TNF receptor (p75)-Fc fusion protein, may with repeated administration prevent exacerbation of cerebral ischemic injury in the diabetic state, mainly through anti-inflammatory action [17].

Conclusion

Dynamics of calcium influx and of calcium release intracellularly include the participation of neuronal programming in cell death that is regionally characterized by dynamics of individual neuronal self-programmed cell death. As is evidenced by such dynamics of processed de-control of agonists such as mitochondrial dysfunction with release of cytochrome c and the lipid peroxidation pathways on the one hand, and of the oxidative end-products primarily affecting membrane lipids and calcium membrane channels, on the other, there evolves a regional/individual cell interplay of integral ischemic and hypoxic elements in the pathogenesis of cerebral infarcts. In such terms, evolutionary dynamics is collaborated pathway event in re-characterized potential neuroprotection of adjacent neurons within the adjacent cerebral cortex in many patients suffering from ischemic stroke. On the other hand, the transforming dimensions of injury to neurons are interplay

supportive elements that profile-determine cell apoptosis that, in turn, may lead to potential necrosis of cerebral tissue.

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