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Multiple interacting cell death mechanisms in the mediation of excitotoxicity and ischemic brain damage: A challenge for neuroprotection

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ABSTRACT

There is currently no approved neuroprotective pharmacotherapy for acute conditions such as stroke and cerebral asphyxia. One of the reasons for this may be the multiplicity of cell death mechanisms, because inhibition of a particular mechanism leaves the brain vulnerable to alternative ones. It is therefore essential to understand the different cell death mechanisms and their interactions. We here review the multiple signaling pathways underlying each of the three main morphological types of cell death – apoptosis, autophagic cell death and necrosis – emphasizing their importance in the neuronal death that occurs during cerebral ischemia and hypoxia-ischemia, and we analyze the interactions between the different mechanisms. Finally, we discuss the implications of the multiplicity of cell death mechanisms for the design of neuroprotective strategies.

Contents

Abbreviations: AIF, apoptosis inducing factor; Ambra1, activating molecule in beclin1-regulated autophagy; Apaf-1, adapter protein apoptotic protease-activating factor-1; ASIC, acid-sensing ion channel; atg, autophagic related genes; Bad, Bcl-2-associated death promoter; BAF, boc-Asp-fmk; Bax, Bcl-2-associated X protein; Bak, Bcl-2 homologous antagonist killer; Bcl-2, B-cell lymphoma 2; Bcl-xL, B-cell lymphoma-extra large; BH, Bcl-2 homology domains; Bim, Bcl-2-interacting mediator of cell death; ER, endoplasmic reticulum; FADD, fas-associated death domain; FasL, fas ligand; HI, hypoxia-ischemia; IAP, inhibitor of apoptosis protein; KA, kainate; LAMP, lysosomal-associated membrane protein; LC3, microtubule-associated protein 1 light chain 3; MCAo, middle cerebral artery occlusion; mTor, mammalian target of rapamycin; NMDA, N-methyl-D-aspartate; PARP, poly(ADP-ribose) polymerase; PE, phosphatidylethanolamine; PI3K, phosphatidylinositol-3 kinase; PUMA, p53 upregulated modulator of apoptosis; Q-VD-OPH, (quinolyl-valyl-O-methylaspartyl-[2,6-difluorophenoxy]-methyl ketone); RIP1, receptor-interacting protein 1; Smac/Diablo, second mitochondria-derived activator of caspases/direct IAP binding protein with low pI; tBid, truncated BH3 interacting-domain death agonist; TNF, tumor necrosis factor; TRADD, TNF receptor-associated death domain; TRAIL, TNF-related apoptosis-inducing ligand; ULK1/2, UNC-51-like kinase 1/2; UVRAG, UV irradiation resistance-associated gene; 3-MA, 3-methyladenine.

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1. Introduction

Despite a considerable research effort, there is still no approved neuroprotective pharmacotherapy for acute neurological conditions such as stroke (Stankowski and Gupta, 2011; Yuan, 2009) and neonatal cerebral asphyxia (van Bel and Groenendaal, 2008). The reasons for this are multiple, but one of the problems appears to be the multiplicity of cell death mechanisms, because inhibition of a particular death mechanism will be ineffective if alternative mechanisms are able to kill the cell. It is therefore essential to understand the different cell death mechanisms and their interactions.

Morphological studies indicate that there are three main types of cell death (Fig. 1): type 1 or apoptosis, type 2 or autophagic death, and type 3 or necrotic/cytoplasmic death. Initial arguments for this trichotomy focused on cell death during normal development (Clarke, 1990), but a similar classification appears to be valid in both adult and neonatal pathological situations including ischemic brain damage (Bredesen, 2008; Clarke, 1999). The coverage of neonatal ischemic (including hypoxic-ischemic) models in the present review is limited to ages at which the brain damage is mainly in the gray matter – after postnatal day (P) 7. Very early cerebral ischemia (P2–P4) causes primarily white matter lesions, by entirely different mechanisms, which is beyond our present concern.

We here review critically, in the context of cerebral ischemia and hypoxia-ischemia, the available evidence on the multiple mechanisms underlying the three types of cell death. In particular, we focus on four problem areas. (1) The factors that determine whether a given type predominates. (2) The interactions between the multiple mechanisms and the hybrid forms of cell death that can result. (3) The current controversy about whether autophagy is a death mediator in type 2 cell death (Clarke and Puyal, 2012; Shen et al., 2012; Yuan and Kroemer, 2010). (4) The challenge that the multiple mechanisms constitute for the design of neuroprotective strategies.

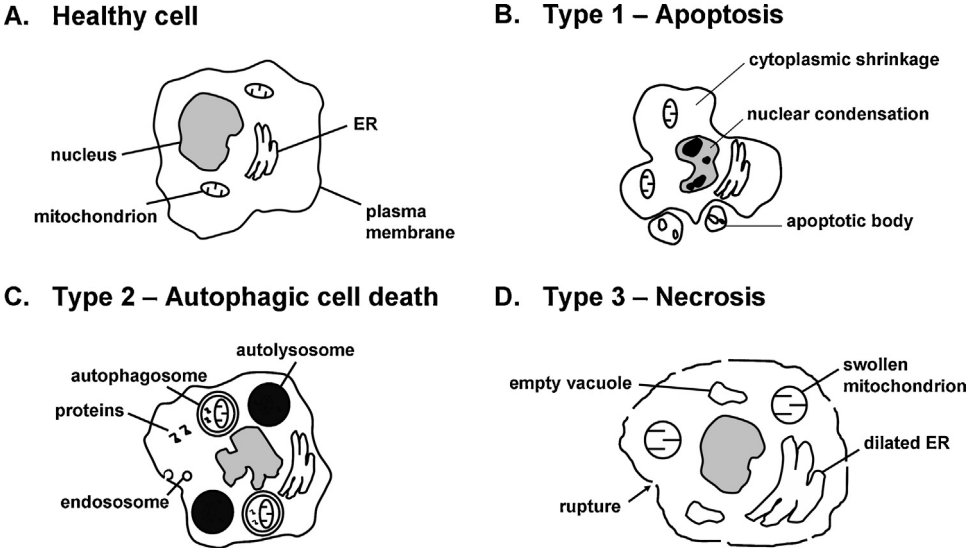

Fig. 1. Schematic description of the three main morphological types of cell death. (A) Healthy cell. (B) Type 1 – Apoptosis. Nucleus: shrinkage, chromatin condensation, pyknosis, fragmentation. Plasma membrane: convolution, budding, formation of apoptotic bodies. Cytoplasm: shrinkage, organelles appear almost normal, but loss of ribosomes from the RER and polysomes. (C) Type 2 – Autophagic cell death. Nucleus: sometimes shrinkage and moderate pyknosis. Plasma membrane: often intense endocytosis. Cytoplasm: numerous autophagosomes and autolysosomes, Golgi often enlarged. (D) Type 3 – Necrosis. Nucleus: little change, but swelling. Plasma membrane: swelling and rounding up of cell, sometimes with rupture of plasma membrane. Cytoplasm: dilation of organelles, vacuolization. ER: endoplasmic reticulum. (Other type-3 subtypes exist).
Inspired by Clarke (1990) and Clarke et al. (2008).