Current Topics

Mitochondria and Neuroprotection

Foreword

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Brain neurons do not proliferate, and they are destined to die after the birth. Therefore, the brain has various built-in self-defense mechanisms and maintains its important central functions for long periods of lifetime. The cell death of most cells, including neurons, after birth is often caused by energy failure and oxidation stress, and mitochondria play central roles in the determination of survival and death under these stresses. Accumulating reports revealed that a number of molecular machanisms are involved in the mitochondrial regulation of survival. This chapter for 'current topics' will briefly summarize several aspects of mitochondria and neuroprotection.

Ueda and Fujita summarize the current understanding of molecular mechanisms of necrosis and apoptosis, the represented modes of cell death. They also propose a new hypothesis, 'cell death mode switch for neuroprotection in the ischemic brain.' In this hypothesis, they claim that necrosis in the ischemic brain expands, while apoptosis in the penumbra surrounding the core terminates the expansion. It should be noted that they have attempted to characterize molecular mechanisms of necrosis.

Nomura focuses on the machineries of apoptosis through mitochondrial and endoplasmic reticulum (ER) stress pathways. He also attempts to suggest targets for drug discovery for neuroprotection. In this review, he mentions that the level of cellular nitric oxide in the brain derived from glia and neurons may determine the apoptosis status, and that protein disulfide isomerase (PDI), unbiquilin and HRD1 mediate ER stress and apoptosis.

Nakagawa summarizes details of the mitochondrial release of cytochrome c (cyto c), a trigger molecule of mitochondrial apoptosis. Here, he describes that caldiolipin retains cyto c in mitochondria through an action of ANT, a component of the mitochondrial permeability transition pore (mPTP), and that the production of caldiolipin hydroperoxide (CLOOH) is linked to cyto c release. He also proposes that phospholipid hydroperoxide glutathione peroxidase (PHGPx) plays a role as an anti-apoptotic factor by modulating CLOOH levels in the mitochondria.

Kume *et al.*, introduce their discovery of serofendic acid, which is isolated from calf serum and possesses protective action against glutamate neurotoxicity. They describe the purification process and mechanisms for survival activity. As serofendic acid is a sulfur-containing atisane type diterpenoid, this discovery may provide a new scope for the investigation of low-molecular-weight bioactive factors promoting the survival of CNS neurons.

Tanuma *et al.*, introduce their new Computer Screening Amino Acid Component Wave (ACW) method for genomic drug discovery of a novel caspase-3-specific inhibitory peptide and an agonistic peptide that binds to the Fas molecule. They claim that the ACW method based on the complementarities of interacting amino acids between comprehensive testing peptides and a target protein surface pocket can be used to further develop small peptidomimetic and nonpeptidic organic forms into a new generation of effective pharmaceuticals.

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