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Review

Physiological functions of non-apoptotic caspase activity in the nervous system

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ABSTRACT

Caspases are cysteine proteases that play important and well-defined roles in apoptosis and inflammation. Increasing evidence point to alternative functions of caspases where restricted and localized caspase activation within neurons allows for a variety of non-apoptotic and non-inflammatory processes required for brain development and function. In this review, we highlight sublethal caspase functions in axon and dendrite pruning, neurite outgrowth and dendrite branches formation, as well as in long-term depression and synaptic plasticity. Importantly, as non-apoptotic activity of caspases is often confined in space and time in neurons, we also discuss the mechanisms that restrict caspase activity in order to maintain the neuronal networks in a healthy and functional state.

Contents

1. Introduction

Caspases belong to a family of cysteine proteases which have important functions in apoptosis, a form of programmed cell death, and inflammation. Caspases are expressed in a wide range of organisms. Initially identified in worms, 18 mammalian homologs of the *C. elegans* Cell death protein 3 (CED-3) have been described to date. However, the set of caspases expressed within mammals is heterogeneous [1]. Pro-apoptotic caspases are responsible for the proteolytic cleavage of hundreds of caspase substrates in response to pro-apoptotic stimuli, ultimately leading to the controlled fragmentation of cellular components, a process essential for the removal of unwanted or damaged cells by specialized phagocytes [2]. In the context of inflammation, a subset of caspases are responsible for the proteolytic maturation of well-defined pro-inflammatory cytokines, as well as the initiation of an inflammation specific form of cell death called pyroptosis [3]. In healthy cells, caspases are expressed as inactive zymogen and their activation, which is usually initiated by proteolytic cleavage, is tightly regulated.

While the mechanisms controlling caspases activation and their targets are well established in the context of apoptosis and inflammation, accumulating evidence also support a non-apoptotic and

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non-inflammatory function of caspases. These functions comprise differentiation and cell fate determination (including differentiation of stem cells and terminal differentiation of keratinocytes, erythroblasts and myoblasts) as well as cell proliferation and tissue regeneration as a result of non-cell autonomous effect on survival and proliferation [4,5]. In addition, caspases exerts non-apoptotic function in the nervous system [5–9]. Over the recent years, studies have demonstrated that restricted and localized caspase activation within neurons allows for a variety of processes that are relevant to neuronal development and function. In this review, we briefly summarize our understanding of caspase activation before exploring the physiological sublethal roles of caspases in the nervous system. We illustrate the roles of caspases in shaping neuronal networks during development and reshaping neuronal connectivity during maturation of the nervous system. We finally discuss the mechanisms that potentially confine and restrict caspase activation in the nervous system.

2. Pathways for caspase activation

Apoptotic caspases can be subdivided into initiator and effector caspases where initiator caspases (caspase-2, -8, -9 and -10) are activated within molecular platforms and are responsible for the direct proteolytic activation of effector caspases (caspase-3, -6 and -7). These effector caspases are responsible for the cleavage of hundreds of cellular substrates and are the real effectors of the apoptotic program. Two molecular platforms, activated by two different pro-apoptotic pathways, are known to activate the apoptotic initiator caspases [4].

The extrinsic, or death receptor, pathway is initiated by ligand-dependent stimulation of cell surface receptors of the tumor necrosis factor (TNF) superfamily, including TNF receptor-1 (TNFR1), Fas/CD95, TNF-related apoptosis-inducing ligand (TRAIL) receptor-1 and -2 (TRAILR1, TRAILR2), death receptor 3 (DR3), and DR6. Upon ligand-induced trimerization, these receptors, identified by the presence of a death domain and commonly called death receptors, engage into the formation of a death-inducing signalling complex called DISC. This platform consists in the trimerized receptor, the adaptors Fas associated via death domain (FADD) and/or TNFR1-associated death domain protein (TRADD) and the pro-caspase-8 or −10. Within the DISC, pro-caspase-8 homodimerizes and undergoes auto-proteolytic activation. Fully activated caspase-8 can in turn, cleave and activate the effector caspase-3, −6 and −7 [10].

Alternatively, the intrinsic, or mitochondrial, pathway originates from the detection of intracellular stress and involves a signalling cascade leading to mitochondrial outer membrane permeabilization (MOMP) and release of proteins, such as cytochrome *c* and second mitochondria-derived activator of caspases (SMAC), from the mitochondrial intermembrane space. Members of the B cell lymphoma-2 (Bcl-2) family, which are characterized by the presence of Bcl-2 homology (BH) domains, play a key role in the control of MOMP. The pro-apoptotic members Bax and Bak are the effectors of this family, forming pores in the mitochondrial outer membrane upon oligomerization, allowing the release of mitochondrial proteins. Their activation is inhibited by interactions with anti-apoptotic members of the family (e.g. Bcl-2, Bcl-xl, Mcl-1, Bcl-b, Bcl-w, A1), while members containing a single BH domain, the so-called BH3-only proteins (e.g. Bid, Bim, Puma, Noxa, Bad, Bmf, Hrk, Bik), promote the activation of Bax and Bak by either direct interaction and/or inhibition of the anti-apoptotic Bcl-2 proteins [11,12]. In the cytosol, cytochrome *c* promotes the assembly of another caspase activating platform: the apoptosome. The adaptor apoptotic protease activating factor 1 (APAF-1) oligomerizes upon binding to cytosolic cytochrome *c* and ATP, promoting the recruitment and activation of pro-caspase-9. Formation of the apoptosome subsequently promotes the proteolytic activation of pro-caspase-3, -6 and -7 [13].

3. Pruning of axons and dendrites

During development, neurons extend their axons to innervate their target regions often resulting in superfluous connections. This outgrowth phase is followed by a regressive phase where excessive or inappropriate axons, dendrites and synapses are eliminated while suitable connections are maintained. The selective elimination of unwanted axons, dendrites, and synapses is known as pruning and occurs without the death of the parent neuron [14,15]. Pruning is essential for the refinement of neuronal connectivity and establishment of a mature and functional network. In vertebrates, pruning takes place largely during early postnatal development. Classical examples of developmental pruning occur in response to limited neurotrophic factors for sensory and sympathetic neurons, at the neuromuscular junction, in the midbrain where retinal ganglion cells project their axons as well as in the cortex and hippocampus [14,15]. During insect metamorphosis, large-scale pruning allows larval processes to remodel and form adult-specific connections [16]. Evidence that caspase activity is required for developmental pruning has emerged from both genetic and biochemical studies in multiple models.

Caspase function in pruning was first shown in the Drosophila model. During metamorphosis, remodelling of class IV sensory neurons innervating the epidermis involves the elimination of larval dendrites and the subsequent regrowth of adult-specific dendrites. Mutants of the initiator caspase Death regulator Nedd2-like caspase (DRONC) fail to prune the larval dendrites of these sensory neurons [17,18]. In this context, pruning requires Death-associated APAF1-related killer (DARK), the fly homolog of APAF-1 that is necessary for activating caspases *via* the apoptosome complex. Moreover, overexpression of p35, the baculovirus inhibitor of effector caspases, also inhibits dendritic pruning, suggesting that effector caspases are also important for dendrite pruning during metamorphosis [18]. Importantly, unlike in the context of cell death, caspase activity is spatially restricted to the dendrites of neurons undergoing pruning [17,18]. Effector caspases have also been implicated in the large-scale pruning of axons of the retinal ganglion cells (RGC) that occurs in the midbrain of mammals. During embryonic development, RGC extend their axons in the superior colliculus but largely overshoot their targets. Neuronal activity promotes the elimination of these inappropriate extensions during the first postnatal week in order to refine the eye-specific projection map [19,20]. In mice deficient in caspase-3, −6, or the caspase-3 target calpastatin, RGC axon projections remain outside of their targeted area in the superior colliculus beyond this refinement period [21,22].

The role of caspases in axon pruning has also been studied in the context of axon degeneration induced by neurotrophic factor deprivation in sensory and sympathetic neurons (Fig. 1). During development, neurotrophin-responsive neurons extend their axons to innervate target regions producing neurotrophins such as Neuronal Growth Factor (NGF). *In vitro*, depletion of NGF induces the apoptotic death of Dorsal Root Ganglia (DRG) and Superior Cervical Ganglia (SCG) neurons [23,24]. However, deprivation of NGF from only the distal axons of these neurons cultivated in compartmentalized chambers (referred to as “local NGF deprivation”), promotes axon pruning without causing neuronal death [25]. The involvement of caspases in axon pruning, initially reported using the caspases inhibitors zVEID and zDEVD [26], was confirmed with the observation that axons of DRG and SCG derived from caspase-3, caspase-6 or caspase-9-deficient mice are protected against axonal NGF deprivation [21,27]. Although caspases are present in

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