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Review

A primer on caspase mechanisms

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ABSTRACT

Caspases belong to a diverse clan of proteolytic enzymes known as clan CD with highly disparate functions in cell signaling. The caspase members of this clan are only found in animals, and most of them orchestrate the demise of cells by the highly distinct regulated cell death phenotypes known as apoptosis and pyroptosis. This review looks at the mechanistic distinctions between the activity and activation mechanisms of mammalian caspases compared to other members of clan CD. We also compare and contrast the role of different caspase family members that program anti-inflammatory and pro-inflammatory cell death pathways.

Contents

1. Introduction

1.1. General preamble on caspases

Caspases are proteases that elicit and propagate signaling events resulting in cellular death: apoptotsis implemented by apoptotic caspases and pyroptosis performed by inflammatory caspases (Fig. 1). Their name derives from the common use of a Cys side chain acting as nucleophile during peptide bond hydrolysis, and a rare primary specificity for cleaving after Asp – they are cysteine-dependent aspartate-specific proteases. The ancestor of caspases is ancient, and its descendants (officially peptidase clan CD) are found widespread across all life kingdoms [1], but the distinctive

Abbreviations: (PRRs), pattern recognition receptors; (PAMPs), pathogen-associated molecular patterns; (TLRs), Toll-like receptors; (AIM2), absent in melanoma 2; (ALRs), AIM2-like receptors; (NOD), nucleotide-binding oligomerization domain; (NLRs), NOD-like receptors; (PYD), pyrin domain; (CARD), caspase recruit domain; (DED), death effector domain; (ASC), apoptosis-associated speck like protein containing a C-terminal CARD; (GSDMD), gasderminD.

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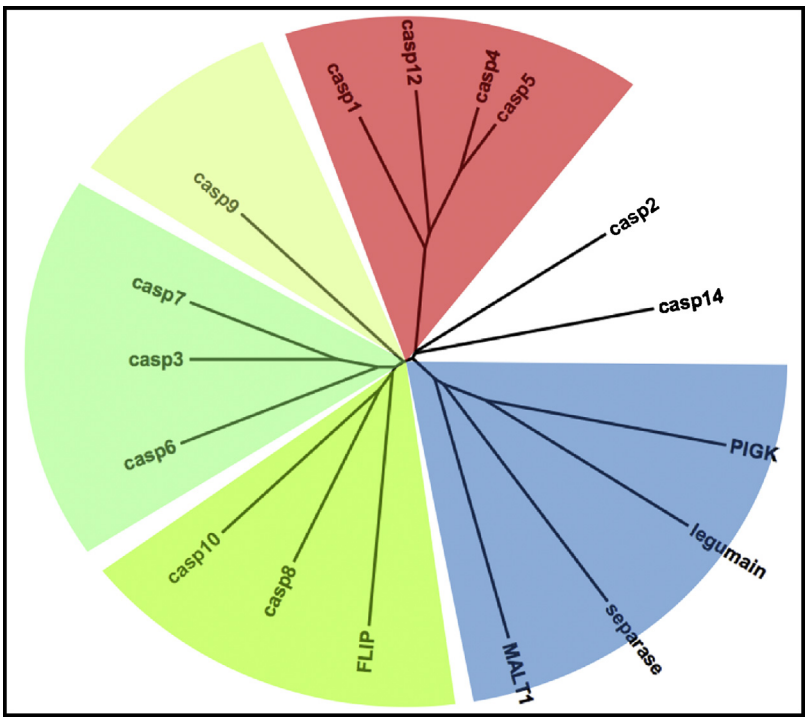

Fig. 1. Peptidase clan CD dendrogram illustrating evolutionary relationships of human caspases and their homologs. Apoptotic caspases are featured in green hues, inflammatory caspases in red, and the remaining four human members of peptidase clan CD are in blue. Caspases-2 and -14 are uncolored and unassigned, as they have primary roles unassociated with apoptosis or inflammation. Pseudoproteases, FLIP and caspase-12, are proteins with the characteristic fold but mutations in their catalytic machinery render them proteolytically incompetent.

Asp specificity is unique to metazoans [2]. In vertebrates the apoptotic caspases can be further subdivided into initiator (caspases-8, -9 and -10) and effector (caspases-3, -6 and -7) caspases [3]. The apoptotic and inflammatory caspases have moderately well defined biochemical and biological mechanisms, but confusion reigns regarding the role of caspase-2. Caspase-2 has been reported to serve many roles within and outside apoptotic networks, and recent data suggests its participation in cell cycle regulation [4]. Readers interested in the many (sometimes conflicting) conflicting functions of caspase-2 are directed to the following reviews [4–9]. Caspase-14, generally not considered an apoptotic or inflammatory caspase, seems to have a highly specialized, though mechanistically obscure, role in keratinization of the skin [10].

With the exception of caspase-1 - enriched in monocytes/macrophages, and caspase-14 - restricted to keratinocytes [11], caspases are widely expressed. Caspases are obligate cytosolic/nucleoplasmic proteins. Their sequences encode no export or import signals and, although they have been occasionally reported to be associated with mitochondria, these appear to have been artifactual [12]. Caspases begin life as single chain zymogens (enzymes awaiting activation) consisting of an N-terminal domain followed by a catalytic domain. The N-terminal domain is variable, can encode recruitment and activation signals, and defines the type of mechanism that caspases use. The C-terminal protease catalytic unit is a single domain, but often split into two chains by proteolytic cleavage during maturation. The catalytic dyad residues Cys and His reside in the large chain while the substrate recognition groove is formed primarily through residues from the small chain (Fig. 2).

2. Activation mechanisms of apoptotic caspases

Caspases are restrained as inactive zymogens awaiting appropriate activation signals. The zymogens of apoptotic effector caspases 3 and 7 are obligate dimers and their activity is held in check by a linker separating the large and small chains. Proteolytic processing of the linker allows assembly of the catalytic site through rearrangement of characteristic mobile loops. Autoproteolysis resulting in removal of the N-terminal pro domain or cleavage of the inter-chain linker sometimes follows activation. Although this has no impact on the inherent proteolytic activity [13,14] cleavage of the linker enhances dimer stability, and contributes to other downstream regulatory events [3,15]. There is essentially no dispute about this activation mechanism.

The zymogens of apoptotic initiator caspases are inert monomers, and there is little dispute about their activation mechanism (Fig. 3). The most parsimonious model for apical caspase activation, sometimes known as the induced proximity model [16,17], has been widely tested and holds that apical caspases require dimerization for activation, and that dimerization is the fundamental activating event. Initiator caspases are recruited by adaptor molecules to oligomeric activation platforms following an apoptotic signal. The induced proximity model postulates that local increase in concentration drive proximity-induced dimerization and therefore activation [15]. Much of the biochemical and structural work on activation of apical caspases has focused on caspases-8 and 9, but the same concept is thought to hold true for the activation of pro-inflammatory caspases, as we describe below. In cultured cells treated to undergo apoptosis, apoptotic caspases drive a characteristic morphology that includes membrane blebbing, chromosomal DNA fragmentation, packaging of cell constituents into “apoptotic bodies” and eventually cell death. In vivo few of these morphologies can be observed because apoptotic cell fragments are rapidly cleared by macrophages [18,19], but in the nematode *C. elegans* the entire process of cell death and disposal may be visualized. Apoptosis is an immunologically silent cell demise, indeed it may be anti-inflammatory, and therefore complex signaling networks activated by apoptotic cas-

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