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Caspase Functions in Cell Death and Disease

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Caspases are a family of endoproteases that provide critical links in cell regulatory networks controlling inflammation and cell death. The activation of these enzymes is tightly controlled by their production as inactive zymogens that gain catalytic activity following signaling events promoting their aggregation into dimers or macromolecular complexes. Activation of apoptotic caspases results in inactivation or activation of substrates, and the generation of a cascade of signaling events permitting the controlled demolition of cellular components. Activation of inflammatory caspases results in the production of active proinflammatory cytokines and the promotion of innate immune responses to various internal and external insults. Dysregulation of caspases underlies human diseases including cancer and inflammatory disorders, and major efforts to design better therapies for these diseases seek to understand how these enzymes work and how they can be controlled.

Caspases are a family of genes important for maintaining homeostasis through regulating cell death and inflammation. Here we will attempt to summarize what we currently know about how caspases normally work, and what happens when members of this diverse gene family fail to work correctly.

Caspases are endoproteases that hydrolyze peptide bonds in a reaction that depends on catalytic cysteine residues in the caspase active site and occurs only after certain aspartic acid residues in the substrate. Although caspase-mediated processing can result in substrate inactivation, it may also generate active signaling molecules that participate in ordered processes such as apoptosis and inflammation. Accordingly, caspases have been broadly classified by their known roles in apoptosis (caspase-3, -6, -7, -8, and -9 in mammals), and in inflammation (caspase-1, -4, -5, -12 in humans and caspase-1, -11, and -12 in mice) (Fig. 1). The functions of caspase-2, -10, and -14 are less easily categorized. Caspases involved in apoptosis have been subclassified by their mechanism of action and are either initiator caspases (caspase-8 and -9) or executioner caspases (caspase-3, -6, and -7).

Caspases are initially produced as inactive monomeric procaspases that require dimerization and often cleavage for activation. Assembly into dimers is facilitated by various adapter proteins that bind to specific regions in

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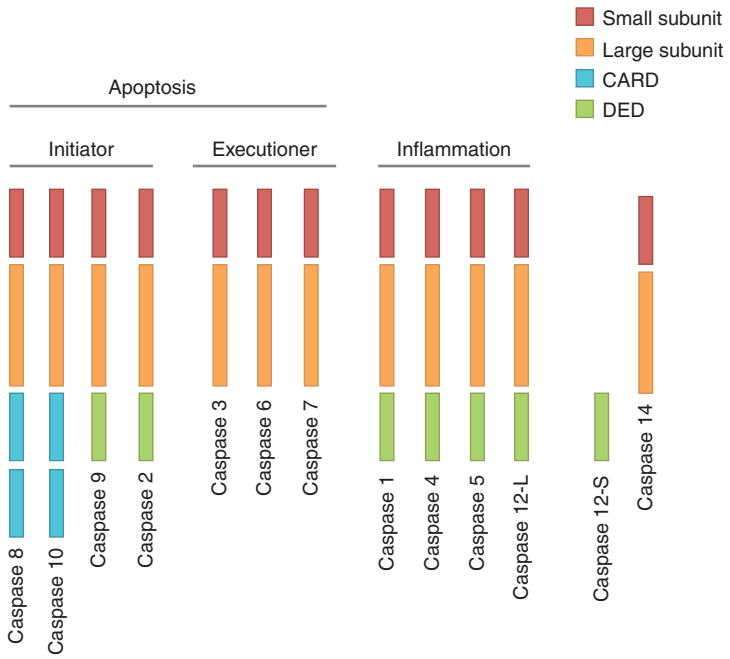

Figure 1. Domain structure of human caspases.

the prodomain of the procaspase. The exact mechanism of assembly depends on the specific adapter involved. Different caspases have different protein–protein interaction domains in their prodomains, allowing them to complex with different adapters. For example, caspase-1, -2, -4, -5, and -9 contain a caspase recruitment domain (CARD), whereas caspase-8 and -10 have a death effector domain (DED) (Taylor et al. 2008).

PHYSIOLOGICAL CASPASE FUNCTIONS

Caspases in Apoptosis

Apoptosis is programmed cell death that involves the controlled dismantling of intracellular components while avoiding inflammation and damage to surrounding cells. Initiator caspases activate executioner caspases that subsequently coordinate their activities to demolish key structural proteins and activate other enzymes. The morphological hallmarks of apoptosis result, including DNA fragmentation and membrane blebbing.

Initiator Caspases

The initiator caspases-8 and -9 normally exist as inactive procaspase monomers that are activated by dimerization and not by cleavage. This process is generalized as an "induced proximity model" (Muzio et al. 1998; Boatright et al. 2003; Chang et al. 2003), in which upstream signaling events induce caspase dimerization and activation. Dimerization also facilitates autocatalytic cleavage of caspase monomers into one large and one small subunit, which results in stabilization of the dimer.

Executioner Caspases

Inappropriate activation of the executioner caspases-3, -6, and -7 is prevented by their production as inactive procaspase dimers that must be cleaved by initiator caspases. This cleavage between the large and small subunits allows a conformational change that brings the two active sites of the executioner caspase dimer together and creates a functional mature protease (Riedl and Shi 2004). Once activated, a single executioner caspase can cleave and activate

other executioner caspases, leading to an accelerated feedback loop of caspase activation.

Pathways of Apoptosis

Various apoptotic pathways exist that can be distinguished by the adapters and initiator caspases involved. Most apoptotic programs fall into either the extrinsic or intrinsic category (Fig. 2).

The Extrinsic Pathway of Apoptosis. Extrinsic apoptosis is triggered by extracellular cues delivered in the form of ligands binding to death receptors (DRs). Death receptors are members of the tumor necrosis factor (TNF) superfamily and include TNF receptor-1 (TNFR1), CD95 (also called Fas and APO-1), death receptor 3 (DR3), TNF-related apoptosis-inducing ligand receptor-1 (TRAIL-R1; also called DR4), and TRAIL-R2 (also called DR5 in humans). Rodents have only one TRAIL-R protein and it resembles DR5. Death receptor ligands include TNF, CD95-ligand (CD95-L; also called Fas-L), TRAIL (also called Apo2-L), and TNF-like ligand 1A (TL1A). The binding of a DR ligand to a DR causes the monomeric procaspase-8 protein to be recruited via its DED to the death-inducing signaling complex (DISC) formed at the cytoplasmic tail of the engaged DR that also includes the adapter protein FAS-associated death domain (FADD) or TNFR-associated death domain (TRADD). Recruitment of caspase-8 monomers results in dimerization

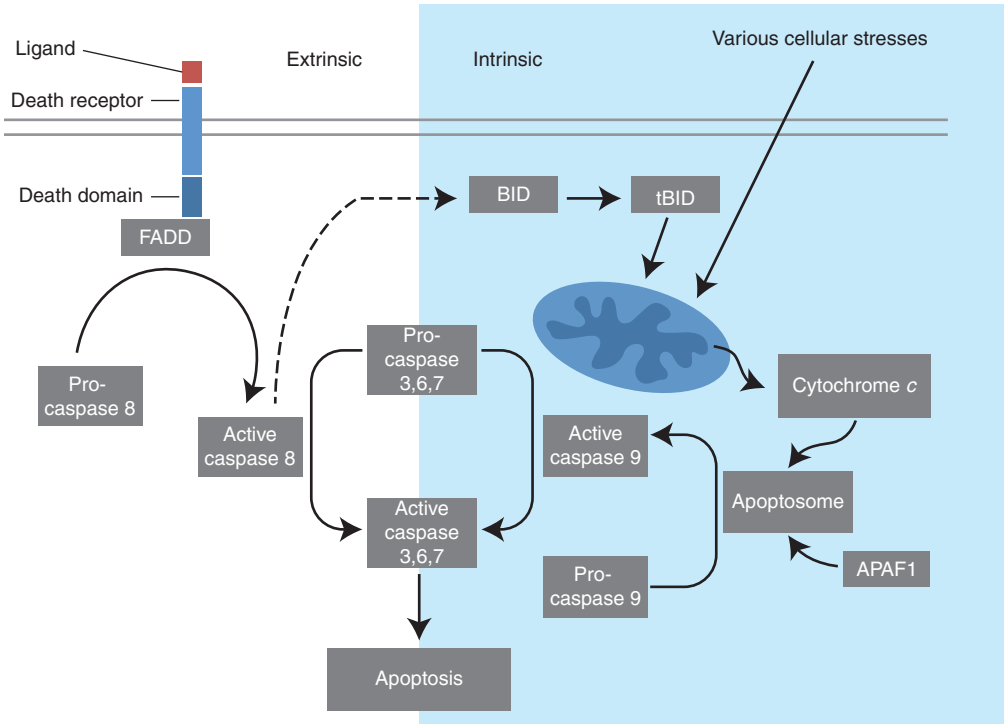

Figure 2. Extrinsic and intrinsic pathways of apoptosis. The extrinsic apoptosis pathway is activated through the binding of a ligand to a death receptor, which in turn leads, with the help of the adapter proteins (FADD/TRADD), to recruitment, dimerization, and activation of caspase-8. Active caspase-8 then either initiates apoptosis directly by cleaving and thereby activating executioner caspase (-3, -6, -7), or activates the intrinsic apoptotic pathway through cleavage of BID to induce efficient cell death. The intrinsic or mitochondrial apoptosis pathway can be activated through various cellular stresses that lead to cytochrome *c* release from the mitochondria and the formation of the apoptosome, comprised of APAF1, cytochrome *c*, ATP, and caspase-9, resulting in the activation of caspase-9. Active caspase-9 then initiates apoptosis by cleaving and thereby activating executioner caspases.

and activation. Cells from gene-targeted mice deficient for caspase-8 (casp8$^{-/-}$ mice) are thus resistant to DR-induced apoptosis (Juo et al. 1998; Varfolomeev et al. 1998; Kang et al. 2004), as are cells from mutant mice lacking either FADD (Yeh et al. 1998) or TRADD, which are specifically defective for TNF-α-mediated apoptosis (Chen et al. 2008b).

The outcome of DR-mediated activation of caspase-8 depends on the cell type. In so-called type I cells, caspase-8 initiates apoptosis directly by cleaving and thereby activating executioner caspases. In type II cells, caspase-8 must first activate the intrinsic apoptotic pathway (discussed below) to induce efficient cell death (Samraj et al. 2006). Type I and II cells differ in their content of intracellular inhibitor of apoptosis proteins (IAPs), which block executioner caspase function unless suppressed by proteins released from the mitochondria (Jost et al. 2009; Spencer et al. 2009).

The Intrinsic Pathway of Apoptosis. Intrinsic apoptosis is also known as mitochondrial apoptosis because it depends on factors released from the mitochondria. This pathway is activated by a vast array of cellular stresses, including growth factor deprivation, cytoskeletal disruption, DNA damage, accumulation of unfolded proteins, hypoxia, and many others. It can also be activated by developmental signals that instruct cells to die, such as hormones (Brenner and Mak 2009). The initiator caspase responsible for the intrinsic apoptosis pathway is caspase-9, which is activated by dimerization induced when the caspase-9 CARD domain binds to the adapter protein apoptotic protease-activating factor-1 (APAF1) (Shiozaki et al. 2002).

Both APAF1 and caspase-9 exist in a resting cell as cytosolic, inactive monomers. A cell experiencing stress first releases cytochrome *c* from the mitochondria. The binding of cytochrome *c* to the WD domain of the APAF1 monomer leads to a conformational change that exposes a nucleotide-binding site in the nucleotide-binding and oligomerization (NACHT) domain of APAF1. The nucleotide deoxy-ATP (dATP) binds to this site and induces a second conformational change in APAF1 that exposes both its oligomerization and CARD domains. Seven such activated APAF1 monomers then assemble into an oligomeric complex, the center of which contains the CARDs that recruit and activate caspase-9 (Acehan et al. 2002). The complex containing cytochrome *c*, APAF1, and caspase-9 has been termed the apoptosome (Cain et al. 2002).

Cytochrome *c* has a long established role in electron transport, and it was shown in 2000 that mammalian cells lacking cytochrome *c* could not activate caspases in response to mitochondrial pathway stimulation (Yeh et al. 2000). However, it was not until 2005 that Hao et al. (2005) formally established that the electron transport function of cytochrome *c* is independent of its ability to engage APAF1 and induce apoptosome formation and caspase activation. Cells from a knockin mouse mutant in which cytochrome *c* was mutated at lysine 72, a key residue for APAF1 interaction, were able to carry out electron transport but not apoptosis (Hao et al. 2005).

The critical role of intrinsic apoptosis in mammalian development is illustrated by the phenotypes of gene-targeted mice deficient for components of this pathway (Table 1). During the development of the normal brain, apoptosis is critical for culling massive amounts of brain cells to allow selection of those making the best neural connections (Madden and Cotter 2008). Caspase-9-deficient mice suffer from large brain outgrowths characterized by decreased apoptosis and excessive neurons (Hakem et al. 1998; Kuida et al. 1998), as do casp3$^{-/-}$ mice (Kuida et al. 1996; Woo et al. 1998). In vitro, embryonic stem cells and embryonic fibroblasts derived from casp9$^{-/-}$ mice are resistant to several intrinsic apoptotic stimuli, including UV and γ irradiation. Apaf1$^{-/-}$ mice show a similar phenotype including reduced brain cell apoptosis, as well as striking craniofacial abnormalities associated with neuronal cell hyperproliferation. Apaf1$^{-/-}$ cells cannot activate caspases in response to mitochondrial pathway stimulation, are resistant to many apoptotic stimuli, and display reduced processing of caspases-2, -3, and -8 (Yoshida et al. 1998).

Dual Role of Caspase-8 in Apoptosis and Necrosis. As mentioned earlier, caspase-8 plays an

Table 1. Summary of caspase-deficient mouse phenotypes

Caspase	Mouse mutant phenotype	Function derived from deficient phenotype	References
Caspase-1	Develop normally; have no defects in apoptosis	Are more susceptible to virus infection (Thomas et al. 2009); show enhanced tumor formation (Hu et al. 2010); have reduced apoptosis in several models such as neuronal cell death, myocardiac infarct, and heart failure (Frantz et al. 2003; Arai et al. 2006; Merkle et al. 2007); caspase-1-deficient mice are protected against cisplatin-induced apoptosis and acute tubular necrosis (Faubel et al. 2004)	Kuida et al. 1995; Li et al. 1995; Thomas et al. 2009; Hu et al. 2010
Caspase-2	Develop normally and are fertile; have only minor apoptotic defects in some cell types; MEFs show resistance to killing by HS and specific drugs	Caspase-2 has been proposed to be involved in different proapoptotic pathways, but the data from the gene-deficient mice do not support the majority of the in vitro results	Bergeron et al. 1998; O'Reilly et al. 2002; Tu et al. 2006
Caspase-3	Mice die perinatally in mixed background; some can survive to adulthood; show brain hyperplasia	Essential for neuronal cell death; caspase-3 is an essential component in some apoptosis pathways, dependent on the stimulus and cell type; essential for the regulation of B-cell homeostasis	Kuida et al. 1996; Woo et al. 1998, 2003
Caspase-6	Develop normally	No apoptotic defects	Unpublished (see Zheng et al. 1999)
Caspase-7	Develop normally	No apoptotic defects	Lakhani et al. 2006
Caspase-8	Embryonic lethal; defects in heart muscle development	Cells from caspase-8-deficient mice are resistant to death-receptor-induced apoptosis; inactivating mutation in humans shows immunodeficiency; tissue-specific deletion of caspase-8 revealed functions in T-cell homeostasis, in the generation of myeloid and lymphoid cells and the differentiation into macrophages, and in skin inflammation and wound healing; suppresses RIPK3-dependent necrosis	Juo et al. 1998; Varfolomeev et al. 1998; Chun et al. 2002; Salmena et al. 2003; Kang et al. 2004; Beisner et al. 2005; Kovalenko et al. 2009; Lee et al. 2009a; Li et al. 2010; Kaiser et al. 2011; Oberst et al. 2011; Zhang et al. 2011
Caspase-9	Perinatal lethal, but not 100% penetrant	Brain hyperplasia caused by decreased apoptosis and excess neurons; cells from caspase-9-deficient mice show resistance to apoptosis induced by a variety of cytotoxic drugs and irradiation	Hakem et al. 1998; Kuida et al. 1998
Caspase-10	No mouse homolog	Human inactivating mutations are associated with ALPS II	Wang et al. 1999
Caspase-11	Develop normally and are fertile	Mutant mice are resistant to endotoxic shock induced by LPS; IL-1 production after LPS stimulation is blocked; is necessary for caspase-1 activation; regulates cell migration in lymphocytes	Wang et al. 1998; Li et al. 2007

Continued

Table 1. *Continued*

Caspase	Mouse mutant phenotype	Function derived from deficient phenotype	References
Caspase-12	Develop normally	Mice are resistant to ER stress-induced apoptosis, but their cells undergo apoptosis in response to other death stimuli; thus, caspase-12 mediates an ER-specific apoptosis pathway; show an enhanced bacterial clearance and are more resistant to sepsis	Nakagawa et al. 2000; Saleh et al. 2006
Caspase-14	Develop normally and are fertile; their long-term survival was indistinguishable from that of wild-type mice	Mice show increased sensitivity to UVB irradiation; caspase-14-deficient epidermal cells show no defect in apoptosis; caspase-14 is responsible for the correct processing of (pro)filaggrin during cornification	Denecker et al. 2007

MEF, mouse embryonic fibroblast; HS heat shock; ALPS, autoimmune lymphoproliferative syndrome; LPS, lipopolysaccharide; ER, endoplasmic reticulum; RIPK3, receptor-interacting serine/threonine-protein kinase 3.

important role in extrinsic apoptosis, combining with FADD to form the DISC. Interestingly, the deletion in mice of caspase-8, FADD, or the DISC regulatory protein FLICE-like inhibitory protein (FLIP) leads to embryonic death caused by a variety of defects. Some of these defects appear to be related to apoptosis, such as impaired heart muscle development in the absence of caspase-8 (Varfolomeev et al. 1998), cardiac failure in the absence of FADD (Yeh et al. 1998; Zhang et al. 1998), and disrupted heart development in the absence of FLIP (Yeh et al. 2000). However, tissue-specific deletions of caspase-8 have revealed new roles for this caspase, which appear to be unrelated to apoptosis. Caspase-8 function is also critical for T-cell homeostasis (Salmena et al. 2003), the generation of myeloid and lymphoid cells and macrophage differentiation (Kang et al. 2004; Beisner et al. 2005), and skin inflammation and wound healing (Kovalenko et al. 2009; Lee et al. 2009a; Li et al. 2010). Recently, three reports provided evidence that some of the defects associated with loss of caspase-8, and result in embryonic death, are not owing to impaired apoptosis but rather to defective suppression of receptor-interacting serine-threonine kinase 3 (RIPK3) -dependent necrosis (Kaiser et al. 2011; Oberst et al. 2011; Zhang et al. 2011). Thus, caspase-8 appears to have dual roles in activation of apoptosis and suppression of necrosis, and caspase-8-dependent suppression of necrosis, but not caspase-8 activation of apoptosis, is critical for mouse embryonic survival.

Caspases in Inflammation

Inflammatory Caspases

Several caspases function as critical mediators of innate immune responses rather than pro-apoptotic factors. Caspase-1, -4, -5, and -12 comprise the inflammatory subset in humans, whereas caspase-1, -11, and -12 serve the same function in mice. Interestingly, the genes encoding inflammatory caspases are located in close proximity on human chromosome 11 and murine chromosome 9, suggesting that they may have arisen from gene duplication events. At the protein level, inflammatory caspases, like their proapoptotic counterparts, are produced as inactive procaspases in resting cells. Only after cellular stimulation via engagement of pattern-recognition receptors (see below) are inflammatory caspases activated through the formation of a cytosolic complex termed the inflammasome (Martinon et al. 2002).

Inflammasome Formation

Inflammasome formation resembles apoptosome formation and has been best studied for

the nucleotide-binding domain, leucine-rich repeat-containing (NLR) proteins, which are a family of pattern-recognition receptors (PRRs), and other proteins (Fig. 3). In a resting cell, NLR monomers are held in an inactive conformation until an external or internal stimulus promotes their assembly (similar to the assembly of APAF1 monomers in the apoptosome). NLR monomers interact through their NACHT domains and bind to the adapter protein apoptosis-associated speck-like protein containing a CARD (ASC/PYCARD) (Ting et al. 2008b). The presence of ASC permits the recruitment of an inactive inflammatory procaspase, typically procaspase-1, to the inflammasome, followed by cleavage and activation of caspase-1 through induced proximity autocatalysis (Davis et al. 2011). Activated caspase-1 in turn cleaves pro-IL-1β and pro-IL-18, which facilitates the secretion of these proinflammatory cytokines (Ting et al. 2008b).

Different NLR-driven inflammasomes contain different NLR members and respond to different stimuli, so that inflammasome formation and the resulting immune response are appropriately tailored to the specific context. However, precisely how inflammasomes are activated in various situations remains poorly understood. It is known that signals initiating inflammasome formation can be delivered by environmental irritants, pathogen-derived molecules, self-derived molecules associated with cell damage, or inappropriate metabolite accumulation (Davis et al. 2011). Whether these signals are received directly by NLR proteins or relayed through secondary pattern-recognition receptors remains unclear and is likely to be context dependent (Monie et al. 2009).

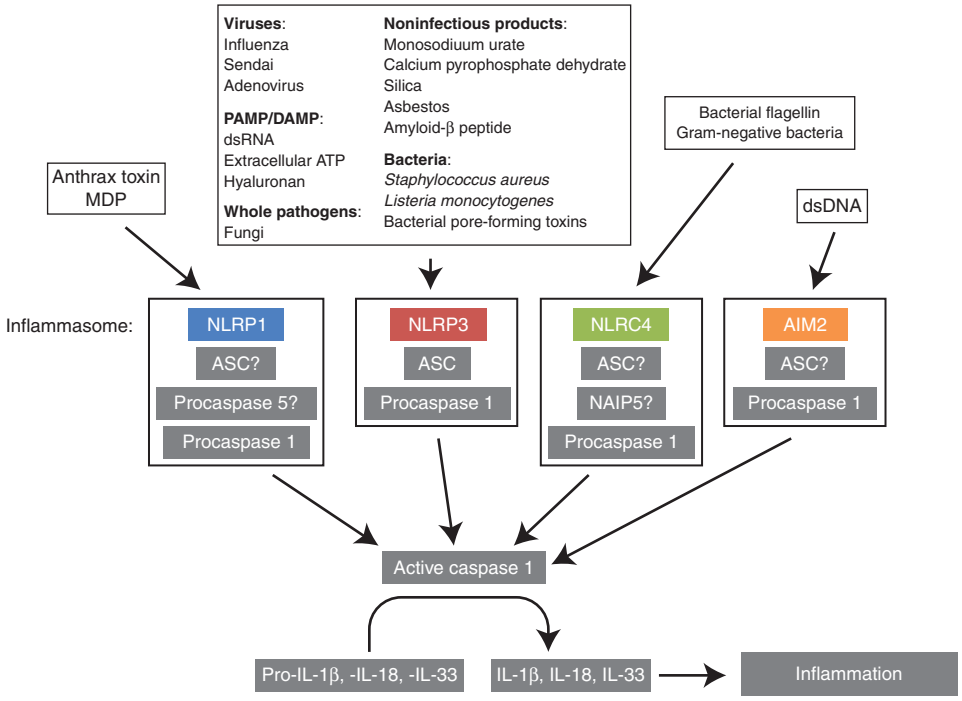

Figure 3. Signaling and composition of inflammasomes. Activation of inflammatory caspases such as caspase-1 is achieved through inflammasome formation. A multitude of cellular stimuli are recognized by a family of pattern-recognition receptors, engagement of which leads to the binding of the adapter protein ASC and the recruitment and activation of the inactive inflammatory procaspase, typically procaspase-1. Activated caspase-1 in turn cleaves pro-IL-1β, pro-IL-18, and pro-IL-33, which facilitates the secretion of these proinflammatory cytokines leading to inflammation.

Role of Pattern-Recognition Receptors. PRRs are molecules that can detect pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) and initiate inflammasome formation. PRRs are frequently expressed by cells that make contact with invading microbes, such as epithelial cells and cells of the innate and adaptive immune responses. Several different classes of PRRs exist, including Toll-like receptors (TLRs) that recognize a variety of PAMPs derived from bacteria, viruses, and fungi and work in synergy with the cytosolic, C-type lectin receptors (CLRs) (which sense fungi), retinoic acid-inducible gene (RIG)-I-like receptors (RLRs) (which sense viruses), and NLR proteins (which sense bacteria) (Davis et al. 2011) (for recent reviews on CLRs and RLRs see Loo and Gale 2011; Osorio and Reis 2011).

TLRs. TLRs were originally named for their similarity to the *Drosophila* protein Toll (Anderson et al. 1985a,b) and were first described in 1997 (Medzhitov et al. 1997). Different TLRs recognize different bacterial components, including lipopolysaccharides (LPS), flagellin, lipoproteins, double-stranded viral RNA, and the unmethylated CpG islands of bacterial and viral DNA. TLR engagement promotes inflammasome formation at least partially through signaling that activates the transcription factors NF-κB and AP-1. TLR-induced inflammasomes facilitate IL-1β and IL-18 secretion as well as the expression of interferon regulatory factor (IRF) transcription factors that mediate type I interferon (IFN)-dependent antiviral responses. Sometimes a second signal is required to complete TLR-mediated inflammasome formation and induce IL-1β secretion. For example, although monocytes circulating in the blood can secrete IL-1β in response to LPS stimulation alone (Netea et al. 2008), primary macrophages must undergo TLR engagement and receive an additional signal such as ATP before they can secrete IL-1β (Wewers and Herzyk 1989; Herzyk et al. 1992). It is unclear whether TLRs are inflammasome components, or whether they act as signaling molecules for inflammasome formation.

NLRs. Members of the highly conserved NLR family participate in innate immune defense against infection in all animals as well as in plants (Jones and Dangl 2006). There are 22 NLR proteins in humans and even more in mice (Schroder and Tschopp 2010). The largest NLR subclass (14 members) contains the NLR pyrin domain-containing proteins (NLRPs). Other NLR family members include the NODs (NOD1 and NOD2), class II transactivator (CIITA), NAIP, and NLRX (Ting et al. 2008a). The amino terminus of NRL proteins is comprised of either a caspase recruitment domain (CARD) or a pyrin domain (PyD) that permits the direct or indirect recruitment of inflammatory procaspases. At the carboxyl terminus, all NRL proteins (except NLRP10) have a central NACHT domain followed by leucine-rich repeats (LRRs). These LRRs are believed to confer specificity for a particular PAMP/DAMP.

The first NLR to be characterized was CIITA, which is essential for MHC class II gene expression and currently the only NRL member that functions as a transcriptional activator. "Bare lymphocyte syndrome" in humans is owing to a loss-of-function mutation in the *Ciita* gene (Steimle et al. 1993). All other NRLs are thought to perform cytoplasmic surveillance for PAMPs/DAMPs.

NOD1 and NOD2 were the first NLRs reported to be PAMP PRRs. Both recognize products of bacterial peptidoglycan degradation, with NOD1 binding to mesodiaminopimelic acid derived mainly from Gram-negative bacteria (Chamaillard et al. 2003; Girardin et al. 2003a), and NOD2 detecting the muramyl dipeptide common to both Gram-negative and Gram-positive bacteria (Girardin et al. 2003b; Inohara et al. 2003). After engagement, NOD1 and NOD2 oligomerize and transiently recruit receptor-interacting protein 2 (RIP2) through CARD–CARD interaction, leading to NF-κB activation and proinflammatory gene expression (Kufer et al. 2005).

Types of Inflammasomes

NLRP3 Inflammasome. NLRP3 is a scaffold protein that uses PyD–PyD interactions to bind to both ASC and procaspase-1, forming the NLRP3 inflammasome that promotes au-

tocatalytic caspase-1 activation. The NLRP3 inflammasome is expressed by myeloid cells and is formed ("activated") in response to a broad range of PAMPs as well as whole pathogens, including fungi (Jin and Flavell 2010). In the latter case, inflammasome activation involves Syk tyrosine kinase activity, the production of reactive oxygen species (ROS), and potassium efflux, but is independent of its transcriptional regulation of *Il-1β* (Gross et al. 2009). NLRP3 inflammasome activation is also triggered by bacteria such as *Staphylococcus aureus* and *Listeria monocytogenes,* which produce pore-forming toxins (Mariathasan et al. 2006); influenza virus, Sendai virus, and adenovirus, double-stranded RNA (Kanneganti et al. 2006; Muruve et al. 2008); and host-derived molecules such as ATP (Mariathasan et al. 2006) and hyaluronan (Yamasaki et al. 2009) that are released by injured cells. The NLRP3 inflammasome is also a sensor for amyloid-β peptide, the accumulation of which is a hallmark of Alzheimer's disease (Halle et al. 2008). Noninfectious materials that activate the NLRP3 inflammasome include crystals of monosodium urate and calcium pyrophosphate dehydrate, which cause gout and pseudogout, respectively (Martinon et al. 2006); asbestos and crystalline silica (Cassel et al. 2008; Dostert et al. 2008); the skin irritants trinitrophenylcholride, trinitrochlorobenzene, and dinitrofluorobenzene (Sutterwala et al. 2006; Watanabe et al. 2007); and UVB radiation (Feldmeyer et al. 2007). It is surprising that a single molecule can "sense" all these different stimuli. A new hypothesis therefore states that this multitude of danger signals is integrated by mitochondria and that the NLRP3 monitors mitochondrial status, reacting to changes in mitochondrial activity that then trigger NLRP3 inflammasome formation (Tschopp 2011).

NLRC4 Inflammasome. The NLRC4 (NLR family, CARD domain-containing 4) inflammasome is formed in response to bacterial flagellin and conserved regions of the type III and type IV secretion systems of Gram-negative bacteria such as *Salmonella typhimurium*, *Burkholderia pseudomallei* (BsaK), *Escherichia coli* (EprJ and EscI), *Shigella flexneri* (MxiI), *Pseudomonas aeruginosa* (PscI), and *Legionella pneumophila* (Amer et al. 2006; Franchi et al. 2006, 2007; Miao et al. 2006, 2008, 2010; Molofsky et al. 2006; Sutterwala et al. 2007). The exact composition of the NLRC4 inflammasome is not fully understood and it is unclear if NLRC4 requires ASC for physiological caspase-1 activation (Poyet et al. 2001; Mariathasan et al. 2004; Franchi et al. 2007; Suzuki et al. 2007). The NLR member NAIP5 (NLR family, apoptosis inhibitory protein 5) is variably required for activation of this inflammasome (Lightfield et al. 2011).

NLRP1 Inflammasome. The NLRP1 inflammasome is activated in response to *Bacillus anthracis* lethal toxin (LeTx) (Boyden and Dietrich 2006) and muramyl dipeptide (MDP) (Faustin et al. 2007). The sequence of the *NLRP1* gene has diverged between humans and rodents, and the murine genome contains three orthologues that are highly polymorphic (Boyden and Dietrich 2006). This variation is presumably responsible for the differences in LeTx susceptibility observed among inbred mouse strains (Boyden and Dietrich 2006). The precise mechanism by which the NLRP1 inflammasome induces caspase-1 activation is still controversial. Human NLRP1 contains a carboxy-terminal CARD domain and so can interact directly with procaspase-1; however, the addition of ASC to this complex in vitro increases inflammasome activity (Faustin et al. 2007). Notably, human NLRP1 can also bind to caspase-5 and thereby contribute to the processing of pro-IL-1β and pro-IL-18 (Tschopp et al. 2003). In contrast, the mouse NLRP1 orthologues do not contain a functional PyD domain, and consequently NLRP1-associated caspase-1 activation in mouse macrophages is not dependent on ASC (Hsu et al. 2008).

Aim2 Inflammasome. Absent in melanoma 2 (AIM2) is a member of the pyrin and HIN domain-containing protein (PYHIN) family (Ludlow et al. 2005). AIM2 interacts with ASC through PyD–PyD interactions (Fernandes-Alnemri et al. 2009) to form an inflammasome that recruits and activates procaspase-1 in response to cytosolic double-stranded DNA (dsDNA) (Fernandes-Alnemri et al. 2009; Hornung et al. 2009). AIM2 senses cytosolic DNA

through its carboxy-terminal HIN-200 domain, which contains two oligonucleotide/oligosaccharide-binding folds (Fernandes-Alnemri et al. 2010). Because AIM2 does not contain a central oligomerization domain equivalent to the NACHT domain in NLRs, it is believed that the dsDNA ligand itself, which can bind to multiple AIM2 molecules, mediates AIM2 oligomerization in the inflammasome (Fernandes-Alnemri et al. 2009). Studies of gene-targeted Aim2-deficient mice have shown that, in addition to dsDNA, AIM2 detects the cytosolic bacterial pathogen *Francisella tularensis* (live vaccine strain) as well as DNA viruses such as vaccinia and mouse cytomegalovirus (mCMV) (Fernandes-Alnemri et al. 2010; Rathinam et al. 2010). Because it recognizes dsDNA, the AIM2 inflammasome may also play a role in the autoimmune responses to dsDNA characteristic of systemic lupus erythematosis (SLE) and related diseases (Fernandes-Alnemri et al. 2010; Rathinam et al. 2010).

Caspase-1 and Cell Death

Although caspase-1 activation most often contributes to inflammation, excessive caspase-1 activity can cause pyroptosis, a nonapoptotic type of programmed cell death that is characterized by plasma membrane rupture and the release of proinflammatory intracellular contents (Cookson and Brennan 2001; Fink and Cookson 2006). Pyroptosis does not involve classical apoptotic caspases like caspase-3 and -8. Instead, activated caspase-1 activates caspase-7 and an unidentified nuclease that induces DNA cleavage and nuclear condensation without compromising nuclear integrity (Molofsky et al. 2006; Bergsbaken and Cookson 2007). Because caspase-1 activation is required for cell death in a variety of experimental settings, including in the immune system (Shi et al. 1996), the cardiovascular system (Kolodgie et al. 2000; Frantz et al. 2003), and the central nervous system (Liu et al. 1999; Yang et al. 1999; Zhang et al. 2003), pyroptosis has been thought to have an important physiological role. However, casp1$^{-/-}$ mice develop normally, implying that this protease is redundant in vivo during development (Kuida et al. 1995; Li et al. 1995). Additional reports suggest that caspase-1 is also capable of cleaving and activating BID and thereby engaging the mitochondrial pathway of apoptosis (Guegan et al. 2002; Zhang et al. 2003).

Recently it has been shown that caspase-1-deficient mice show enhanced tumor formation in an azoxymethane and dextran sodium sulfate colitis-associated colorectal cancer model. Interestingly the mechanism of caspase-1 tumor formation in this model was not through regulation of inflammation, but rather owing to increased colonic epithelial cell proliferation in the early stages of tumor formation and reduced apoptosis in advanced tumors in the caspase-1-deficient mice (Hu et al. 2010).

It should be noted that the interpretation of past data generated using caspase-1-deficient animals may need to be revisited in light of several new pieces of evidence. It has recently been shown that caspase-1-deficient mice generated from strain 129 embryonic stem cells also harbor a mutation in the caspase-11 locus, and so are de facto caspase-1/caspase-11 double-knockout mice (Kayagaki et al. 2011). Kayagaki et al. addressed this issue in their study by rescuing caspase-11 activity in their caspase-1-deficient mice via transgenic expression of a caspase-11 bacterial artificial chromosome. The in vivo data then generated indicate that caspase-11 rather than caspase-1 may be the critical effector caspase responsible for the inflammatory response, making human caspases-4 and -5 potential interesting targets for intervention in patients with sepsis (Kayagaki et al. 2011).

Caspase-12 and Anti-Inflammation

In mice, caspase-12 appears to abrogate the inflammatory response largely owing to an inhibitory effect on caspase-1 (Scott and Saleh 2007). Consequently, casp12$^{-/-}$ mice show enhanced bacterial clearance and resistance to sepsis (Saleh et al. 2006). Interestingly, the enzymatic function of caspase-12 is not required for caspase-1 inhibition (Saleh et al. 2006), suggesting that caspase-12 is more likely a protease regulator rather than a protease itself.

In most humans from Eurasia and a significant proportion of individuals from African populations, there exists a frameshift mutation in the caspase-12 gene (CASP12) that generates a premature stop codon and prevents expression of full-length caspase-12 leading to a shortened caspase-12 protein (caspase-12S) (Fischer et al. 2002). However, in about 20% of individuals of sub-Saharan African descent, a single nucleotide polymorphism (SNP) changes this stop codon to an arginine residue, resulting in successful readthrough and the synthesis of the full-length caspase-12 protein (caspase-12L) (Saleh et al. 2004). Individuals expressing the readthrough polymorphism show reduced inflammatory and innate responses to endotoxins and thus an increased risk of developing severe sepsis (Saleh et al. 2004). It has been suggested that the rise in infectious disease that accompanied the increased population density developing in Europe over time favored the survival of individuals expressing the truncated caspase-12 variant (Xue et al. 2006).

Caspases in Proliferation

Although caspases are most often associated with apoptosis, there has been persistent evidence that some of these enzymes can also influence proliferation. One of the earliest observations was that treatment of T cells with caspase inhibitors led to a surprising suppression of CD3-induced T-cell expansion (Alam et al. 1999; Kennedy et al. 1999). This growth-promoting caspase function was later attributed to caspase-8, because c-FLIP, a caspase-8 inhibitor, was shown to modulate T-cell proliferation (Lens et al. 2002). Similarly, caspase-8 and -6 can positively regulate B-cell proliferation (Olson et al. 2003; Beisner et al. 2005).

However, caspase-3 may have the opposite effect, as B cells lacking caspase-3 showed increased proliferation in vivo and hyperproliferation after mitogenic stimulation in vitro (Woo et al. 2003). This hyperproliferative B-cell phenotype was rescued in double-knockout mice lacking both caspase-3 and the cyclin-dependent kinase inhibitor p21 (encoded by *Cdkn1a*), which is a caspase-3 substrate (Woo et al. 2003).

As mentioned earlier, recent work has now provided convincing evidence that the suppression of RIPK signaling by caspase-8 and FADD accounts for the nonapoptotic roles of these proteins (Kaiser et al. 2011; Oberst and Green 2011; Oberst et al. 2011; Zhang et al. 2011). Another important question, namely, how is it possible that the proteolytic function of caspase-8, which normally leads to apoptosis, can suppress RIPK signaling without causing apoptotic cell death, can also now be explained. C-FLIP has a greater affinity for procaspase-8 than this proenzyme has for itself, which permits C-FLIP to inhibit the activation of apoptosis by caspase-8 while allowing caspase-8 to retain its catalytic activity (Boatright et al. 2004; Oberst and Green 2011).

Less Well-Categorized Caspases

Caspase-2

Caspase-2 is evolutionarily ancient, the most highly conserved caspase among animals, and one of the earliest caspases discovered (Kumar et al. 1994; Wang et al. 1994); its function resembles a more rudimentary type caspase similar to *Caenorhabditis elegans* in which it needs to fulfill multiple, sometimes opposing roles, that later during evolution have been taken over by other members of the caspase family.

The mammalian caspase-2 protein has a long prodomain containing a CARD sequence. In response to apoptotic stimuli such as DNA damage, cytoskeletal disruption, metabolic perturbation, or heat shock (Harvey et al. 1997), inactive procaspase-2 monomers are induced to oligomerize and are activated by induced proximity. The ensuing autocatalytic cleavage stabilizes the mature caspase-2 enzyme and enhances its activity (Baliga et al. 2004; Krumschnabel et al. 2009).

Procaspase-2 oligomerization is mediated by the adapter protein Rip-associated protein with a death domain (RAIDD), which binds to procaspase-2 via CARD–CARD interaction (Harvey et al. 1997; Baliga et al. 2004; Krumschnabel et al. 2009). Procaspase-2-bound RAIDD molecules form a complex via additional

adapter molecules such as p53-induced protein with a DD (PIDD), which binds to RAIDD via DD–DD interaction. This PIDD–RAIDD–procaspase-2 complex has been termed the PIDDosome (Tinel and Tschopp 2004). Resolution of the crystal structure of the PIDDosome has revealed the presence of multiple PIDD and RAIDD subunits (Park and Wu 2006; Park et al. 2007) in a structure resembling the CD95–FADD complex involved in procaspase-8 activation.

Caspase-2 can also be activated by a mechanism that involves p53-dependent CD95 up-regulation and the recruitment of caspase-8 to the DISC complex. BID is cleaved by this coordination of caspase-2 and -8 and mitochondrial apoptosis is activated (Sidi et al. 2008; Olsson et al. 2009). However, caspase-2 is also involved in seemingly opposing functions such as protection against DNA damage (Shi et al. 2009) or cancer development (Ho et al. 2009). Caspase-2 is also important for programmed oocyte death during mouse development (Bergeron et al. 1998).

Caspase-10

Human caspase-10 is highly homologous to caspase-8 and is recruited to the DISC on DR engagement (Sprick et al. 2002). However, the role of caspase-10 in the extrinsic apoptotic cascade is still not clear. Reports have conflicted on the requirement for caspase-10 in CD95-mediated apoptosis in the absence of caspase-8 (Kischkel et al. 2001; Sprick et al. 2002). Although some recent findings suggest that caspase-10 acts in an atypical CD95-induced cell death pathway (Lafont et al. 2010), other evidence points to a role for caspase-10 in intrinsic apoptosis that is triggered by cytotoxic drugs in a fashion that is FADD-dependent but DR-independent (Park et al. 2004; Filomenko et al. 2006; Lee et al. 2007). To date, no mouse caspase-10 homolog has been reported.

Caspase-14

Caspase-14 is unique because it is found only in terrestrial mammals and does not seem to have evolved from orthologues in insects or nematodes like the apoptotic caspases (Lamkanfi et al. 2002). Furthermore, caspase-14 expression is restricted to cornifying epithelial cells, such as occur in the skin, and plays a role in terminal keratinocyte differentiation (Denecker et al. 2008). Studies of casp14$^{-/-}$ mice have shown that caspase-14 is responsible for both the correct processing of profilaggrin during cornification and the protection of mice against UVB irradiation (Denecker et al. 2007). However, caspase-14 is dispensable for keratinocyte apoptosis (Denecker et al. 2008).

CASPASES IN HUMAN DISEASE

Caspase activity is a double-edged sword. Although defective caspase activation and the inadequate cell death that results can promote tumorigenesis, extreme caspase activation and the excessive cell death that ensues can promote neurodegenerative conditions. Furthermore, insufficient activation of caspases involved in inflammation can lead to an increased susceptibility to infection, whereas hyperactivation of these caspases can promote inflammatory conditions.

Caspases and Cancer

Our bodies use several sophisticated mechanisms to safeguard against cancer development. These mechanisms recognize DNA mutations, and induce either the repair of the faulty DNA, or the death of the affected cell before it can become oncogenic. Because caspases are crucial for apoptosis, it is not surprising that deregulation of these enzymes and the pathways in which they are involved can aid in the persistence of mutated cells and promote tumorigenesis. However, although caspases are key players in the best documented mechanism of cancer cell death, unlike mutation of p53 or elements of the PI3K pathway, mutation of CASP genes is not frequent in human tumor cells. Genetic and inhibitor studies have shown that the inactivation of individual caspases is not usually sufficient to either prevent continuation of the caspase cascade, or to derail alternative nonapoptotic cell death mechanisms. Instead,

malignant cells appear to more frequently gain a survival advantage by inactivating signaling mediators upstream of caspase activation.

Despite the above, the reduced expression of proapoptotic caspases has been reported in a variety of cancers (Philchenkov et al. 2004), and specific inactivating mutations have been linked to various tumor types and stages of transformation (discussed below). Moreover, although inherited mutations in the CASP genes are relatively rare, certain caspase polymorphisms thought to affect caspase abundance or activity have been associated with variable effects on tumorigenesis.

Caspase-8

Inactivating CASP8 mutations have been reported in various cancers, including childhood neuroblastoma. Wild-type caspase-8 acts as a tumor suppressor in neuroblastomas with amplification of N-myc (Teitz et al. 2000), thus mutations leading to loss of caspase-8 function render neuroblastoma cell lines resistant to DR-induced apoptosis (Hopkins-Donaldson et al. 2000; Teitz et al. 2000; Eggert et al. 2001; Yang et al. 2003). Furthermore, in an experimental neuroblastoma cell line model, caspase-8 deletion enhanced the metastatic potential of neuroblastoma cells in chick embryos (Stupack et al. 2006).

In a study of 180 human colorectal tumors (98 invasive carcinomas and 82 adenomas), somatic CASP8 mutations were detected in 5% of invasive carcinomas but in no adenomas. At least three of the mutations were confirmed to decrease caspase-8-mediated apoptosis by acting in a dominant–negative fashion (Kim et al. 2003). In a similar study of 69 hepatocellular carcinomas (HCCs), a single somatic CASP8 mutation was detected in nine cases (13.0%). This frameshift mutation resulted in a two base-pair deletion (1225_1226delTG) that caused premature termination of translation and loss of caspase-8 function (Soung et al. 2005b). In another study of 162 gastric carcinomas (40 early and 122 advanced cancers), 185 non-small-cell lung cancers, 93 breast carcinomas, and 88 acute leukemias, CASP8 mutations were detected only in advanced gastric cancers (10.7%) (Soung et al. 2005a). Again, these mutations led to markedly decreased caspase-8-dependent cell death in vitro (Soung et al. 2005b).

An interesting linkage between CASP8 and cancer occurs for inheritance of the D302H polymorphism in CASP8 (rs1045485), which substitutes histidine for aspartic acid and is associated with reduced breast cancer risk (MacPherson et al. 2004; Frank et al. 2005). An analysis of 16,423 cases and 17,109 controls from 14 studies conducted by the Breast Cancer Association Consortium (BCAC) has confirmed the dose-dependent protective effect of this allele [P trend $= 1.1 \times 10^{-7}$, per allele odds ratio (OR) $= 0.88$, with a 95% confidence interval (CI) of 0.84–0.92] (Cox et al. 2007). Another well-studied inherited CASP8 polymorphism is a six-nucleotide deletion (-652 6N del; 6N del, rs3834129) in the promoter region. A recent meta-analysis of 23 publications covering 55,174 cancer cases and 59,336 controls from 55 individual studies concluded that the D302H variant and the -652 6N del polymorphism were associated with a significantly reduced overall risk of cancer (Yin et al. 2010). It is assumed that these alterations to the mutated caspase-8 protein enhance its proapoptotic effects and prevent tumor cell persistence, although such a relationship has yet to be shown in vivo.

Caspase-9

Germline variation in the CASP9 gene has been linked to non-Hodgkin's lymphoma (NHL) (Kelly et al. 2010). In a study of 36 apoptosis pathway genes, alterations of CASP9 at both the gene and SNP levels were associated with NHL risk (Kelly et al. 2010). In another study of the impact on lymphomagenesis of genetic variation in 12 caspases, examination of 1946 NHL cases and 1808 controls showed significant associations for alterations of CASP8, CASP9, or CASP1 with NHL (Lan et al. 2009). An earlier smaller study of 461 NHL cases and 535 controls also showed a significant association between certain variants of CASP3 and CASP9 and NHL risk (Lan et al. 2007). In both studies, the caspase-9 SNPs associated with NHL

showed decreased risk of NHL, whereas the other caspases showed increased NHL risk.

In an analysis of polymorphisms in the CASP9 promoter in 432 lung cancer patients and 432 matched controls, the −1263 GG genotype was linked to a significantly decreased risk of lung cancer compared with the −1263 AA genotype or the −1263 AA + AG genotype (Park et al. 2006). It was proposed that this protective effect might be owing to increased promoter activity of the G-C haplotype compared with the −1263G/−712T and −1263A/−712C haplotypes that enhances caspase-9 expression (Park et al. 2006).

Caspase-3

Many studies have analyzed whether alterations to the CASP3 gene encoding the crucial executioner caspase-3 might promote human tumorigenesis. One study examined the caspase-3 coding region in 944 tumors of 14 different types compared with healthy adjacent tissue. However, only 14 tumors (1.48%) showed somatic CASP3 mutations (Soung et al. 2004). In another study analyzing 930 squamous cell carcinomas of the head and neck (SCCHN) and 993 controls, the CASP3 rs4647601:TT variant was associated with an increased risk of SCCHN compared with the GG genotype (Chen et al. 2008a). This finding was most evident in certain subgroups, including younger ($\leq$56 yr) subjects, males, and never smokers. Conversely, in an analysis of 582 lung cancer patients and 582 controls, individuals bearing at least one allele with a −928A > G, 77G > A, or 17532A > C polymorphism had a significantly decreased risk for lung cancer compared with individuals who were homozygous for the wild-type CASP3 allele (Jang et al. 2008).

An important study of 128 multiple myeloma cases and 516 controls analyzed five SNPs in various CASP genes. Compared with individuals with the TT genotype of CASP3 Ex8 + 567 T > C, subjects with the CC genotype had a fivefold lower risk of multiple myeloma (Hosgood et al. 2008). Multiple myeloma risk was also reduced in individuals with the AG and AA genotypes of CASP9 Ex5 + 32 G > A (Hosgood et al. 2008). An earlier study by the same group found a similar association between decreased risk of NHL and certain CASP3 variants (Lan et al. 2007). Finally, a study of 1028 endometrial cancer patients and 1003 healthy controls examined potential links between caspase-3, -7, and -8 variant alleles and risk of endometrial cancer. Compared with the CC genotype, the GG genotype of rs2705901 in CASP3 was significantly associated with increased cancer risk (Xu et al. 2009). Taken together, these results suggest that CASP3 polymorphisms and their haplotypes help to define an individual's genetic susceptibility to cancer development.

Caspase-7

In one analysis of multiple cancer types, somatic mutations in CASP7 were detected in two of 98 colon carcinomas (2.0%), one of 50 esophageal carcinomas (2.0%), and one of 33 head/neck carcinomas (3.0%), but not in stomach, urinary bladder, or lung cancers (Soung et al. 2003). When these tumor-derived caspase-7 mutants were overexpressed in 293T human kidney cells, the cells showed reduced apoptosis (Soung et al. 2003). In a different study of 720 lung cancer patients and 720 controls, certain CASP7 polymorphisms were found to promote susceptibility to lung cancer (Lee et al. 2009b). As mentioned earlier, a study of 1028 endometrial cancer patients and 1003 healthy controls examined potential links between caspase-3, -7, and -8 variant alleles and risk of endometrial cancer. Of 35 selected SNPs, four in CASP7 were in high linkage disequilibrium and associated with increased risk of endometrial cancer; two CASP7 SNPs were associated with reduced risk; and two CASP7 SNPs were associated with increased risk compared with individuals homozygous for the major CASP7 alleles. These findings suggest that mutations altering the executioner function of caspase-7 affect the pathogenesis of some human solid cancers.

Caspase-1, -4, -5

An evaluation of mutations in the inflammatory caspases-1, -4, and -5 in 337 samples of

various types of human cancers showed that CASP1 mutations were present in two malignancies (0.6%), CASP4 mutations in two (0.6%), and CASP5 mutations in 15 (4.4%) (Soung et al. 2008). The highest prevalence of CASP5 mutations was in microsatellite instability (MSI)-positive gastric carcinomas, suggesting that caspase-5 activity may be important in the etiology of these tumors.

In a mouse model of colorectal cancer based on colitis induced by azoxymethane and dextran sodium sulfate treatment, casp1$^{-/-}$ mutants showed enhanced tumor formation owing to alterations to two different caspase functions. In early-stage tumors, the proliferation of colonic epithelial cells was increased in the absence of caspase-1, whereas in advanced tumors, apoptosis was reduced (Hu et al. 2010). Interestingly, despite the association of caspase-1 with inflammation, in neither early nor late colorectal tumors was defective regulation of inflammation observed.

Caspase-6

CASP6 mutations have been found in 2% of 150 human cancers of colonic or gastric origin (Lee et al. 2006). Furthermore, expression of caspase-6 in gastric cancer samples is decreased, suggesting that loss of caspase-6 expression might be involved in the mechanism of gastric cancer development (Yoo et al. 2004).

Caspase-10

An analysis of 117 NHL samples revealed that 17 (14.5%) contained inactivating CASP10 mutations (Shin et al. 2002). When overexpressed in 293T cells, these mutations suppressed apoptosis. Rare CASP10 mutations have also been detected in cases of T-cell acute lymphoblastic leukemia and multiple myeloma (Kim et al. 2009), as well as in colon, breast, lung, and hepatocellular carcinomas (Oh et al. 2010) and gastric cancers (Park et al. 2002).

Caspase-1 in Inflammatory Diseases

The production of IL-1, and thus caspase-1 activation, has been implicated in a wide variety of inflammatory and autoimmune diseases (Gabay et al. 2010). Researchers have frequently sought to confirm the involvement of caspase-1 in these conditions through the use of agents that attempt to modulate IL-1 production by blocking caspase-1, IL-1 functions, or IL-1 receptors. However, human trials of agents targeting IL-1 in rheumatoid arthritis (RA) (Drevlow et al. 1996; Bresnihan et al. 1998; Jiang et al. 2000; Cohen et al. 2002; Genovese et al. 2004; Alten et al. 2008), as well as in other rheumatic diseases such as SLE, psoriatic arthritis, and osteoarthritis (Finckh and Gabay 2008), have shown only modest efficacy or no improvement. Nevertheless, these drugs have improved the health of patients with several other hereditary and acquired conditions linked to elevated IL-1β levels, as outlined below.

Gout

Gout is a common autoinflammatory disorder characterized by chronic elevated blood uric acid levels (hyperuricemia) and the deposition of monosodium urate (MSU) crystals in joints. Patients experience severe pain and joint inflammation. The pathogenesis of this disease, as well as that of pseudogout (deposition of calcium pyrophosphate dihydrate crystals) and pulmonary silicosis, have been linked to inflammatory responses activated by the deposited crystals and mediated by the NLRP3 inflammasome (Cronstein and Terkeltaub 2006; Martinon et al. 2006; Hornung et al. 2008).

Cryopyrin-Associated Periodic Syndromes

Mutations in NLRP3 cause three rare inherited autoinflammatory diseases known collectively as cryopyrin-associated periodic syndromes (CAPS) (Hoffman et al. 2001; Aksentijevich et al. 2002; Feldmann et al. 2002). These disorders are, in order of increasing severity, familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and neonatal-onset multisystem inflammatory disease (NOMID), which is also referred to as chronic infantile neurologic cutaneous articular (CINCA) syndrome. Gene-targeted mice harboring Nlrp3

mutations equivalent to those found in FCAS and MWS patients have hyperactive NLRP3 inflammasome activity and elevated IL-1β levels (Brydges et al. 2009; Meng et al. 2009).

Type 2 Diabetes

Type 2 diabetes (T2D) occurs when insulin production by pancreatic islet β cells fails to compensate for insulin resistance. Elevated IL-1β levels are a risk factor for T2D development (Spranger et al. 2003) and contribute to insulin resistance (Maedler et al. 2009). Excessive caspase-1 activity has thus been implicated in T2D etiology.

Familial Mediterranean Fever

Familial Mediterranean fever (FMF) is an autoinflammatory disease caused by mutations in the Mediterranean fever gene (MEFV) that encodes the pyrin protein (Chae et al. 2008). The most severe form of FMF arises from missense mutations affecting the carboxy-terminal B30.2/SPRY domain of pyrin, which is important for its interaction with procaspase-1 (Chae et al. 2006; Papin et al. 2007). However, there is conflicting evidence on whether pyrin mutations affect IL-1β production (Chae et al. 2003, 2006; Yu et al. 2006; Seshadri et al. 2007). Treatment with an IL-1 targeting agent (see below) has induced symptom regression in FMF patients, implying a causative role for IL-1β in this disease (Roldan et al. 2008).

Pyogenic Sterile Arthritis, Pyoderma Gangrenosum, and Acne Syndrome

Pyogenic sterile arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome is a rare autosomal-dominant genetic disorder caused by mutations in the CD2-binding protein 1 (CD2BP1) gene. Patients suffer from severe, juvenile-onset arthritis, pyoderma gangrenosum, and acne. These mutations disrupt the binding of (CD2BP1) to protein tyrosine phosphatase, nonreceptor type 12 (PTPN 12) (Wise et al. 2002), thereby increasing CD2BP1 binding to pyrin. Association with CD2BP1 reduces pyrin's ability to inhibit inappropriate inflammasome activation (Shoham et al. 2003).

Hyperimmunoglobulinemia D with Periodic Fever Syndrome

Hyperimmunoglobulinemia D with periodic fever syndrome (HIDS) is a rare autosomal-recessive disorder (van der Meer et al. 1984) that is thought to be caused by mutations in the gene encoding mevalonate kinase (Drenth et al. 1999; Houten et al. 1999). HIDS patients show increased blood levels of IL-1β and IgD. Mevalonate kinase deficiency (MKD), an autosomal-recessive disorder characterized by recurring episodes of inflammation, leads to decreased production of nonsterol isoprenoid end products, in particular, geranylgeranyl groups (Mandey et al. 2006). Isoprenoid deficiency can induce PI3K pathway-dependent procaspase-1 activation, leading to increased IL-1β production (Kuijk et al. 2008).

Systemic-Onset Juvenile Idiopathic Arthritis

The pathophysiology of systemic-onset juvenile idiopathic arthritis (sJIA), which affects an estimated 250,000 children in the United States alone, and which presents itself with initial systemic symptoms such as fever, anemia, leukocytosis, and elevated erythrocyte sedimentation rate (ESR), has been linked to elevated levels of IL-1β (Pascual et al. 2005).

Caspases in Other Diseases

Alzheimer's Disease

Neuronal death in a variety of neurodegenerative diseases, including Alzheimer's disease (AD), has been associated with deregulated caspase activation (Rohn and Head 2009). However, several lines of evidence suggest that the role of caspases in AD may involve more than just action as cellular executioners driven by upstream disease processes. Caspase-mediated cleavage of β-amyloid precursor protein (APP) has been reported (Rohn et al. 2001), as has caspase activation by amyloid-β peptide (O'Brien and Wong 2011). In

one murine AD model, caspase activation associated with disease onset occurred earlier than the induction of neuronal apoptosis (D'Amelio et al. 2011). Similarly, caspase activation has been noted before the development of neurofibrillary tangles of Tau in the brain of tau transgenic mice (de Calignon et al. 2010).

Kawasaki Disease

Kawasaki disease (KD) is an acute vasculitis syndrome that predominantly affects arteries in young children (Kawasaki 1967; Burns 2002). In one study, a G to A substitution in a particular SNP located in the 5′ untranslated region of CASP3 abolished the binding of the nuclear factor of activated T cells (NFAT) transcription factor to the DNA sequence surrounding the SNP, suggesting that altered CASP3 expression in immune effector cells can influence KD susceptibility (Onouchi et al. 2010). However, another study of 341 KD patients and 751 controls found an association of only borderline significance between this CASP3 polymorphism and KD ($P = 0.0535$ under the dominant model; $P = 0.0575$ under the allelic model) (Kuo et al. 2011).

Autoimmune Lymphoproliferative Syndrome

Autoimmune lymphoproliferative syndrome (ALPS) causes lymphoadenopathy, splenomegaly, autoimmune hemolytic anemia, thrombocytopenia, and hypergammaglobinemia in children (Lenardo et al. 1999; Straus et al. 1999). The majority of ALPS patients have dominant mutations in CD95, CD95L, or CASP10 (Lenardo et al. 1999; Straus et al. 1999; Wang et al. 1999). It is thought that ALPS may be caused by insufficient apoptosis of autoreactive T cells during negative thymic selection (Fleisher 2008).

CASPASES IN DISEASE THERAPY

Activating Caspases to Promote Cell Death

Cancer

Several attempts have been made within the last decade to develop molecules capable of directly activating caspase-3 for use in cancer therapy. A particular target suggested for intervention has been the "safety catch" sequence present in inactive procaspase-3 (Roy et al. 2001). This sequence is a triplet of aspartic acid residues that maintains the intramolecular electrostatic interactions that keep procaspase-3 in an inactive state in resting cells (Roy et al. 2001). High-throughput screening (HTS) projects have identified a series of molecules, including α-(trichloromethyl)-4-pyridineethanol (PETCM), gambonic acid, and the gambonic acid derivative MX-2060, that efficiently activate caspase-3 in vitro (Jiang et al. 2003; Zhang et al. 2004; Fischer and Schulze-Osthoff 2005). This series has shown promise in inducing the apoptosis of cancer cell lines, but no clinical development of these agents has been reported. Another promising caspase-3 activator identified by HTS is first procaspase-activating compound (PAC-1), which contains a zinc-chelating motif (Putt et al. 2006). This motif is critical to PAC-1's ability to activate caspase-3 (Peterson et al. 2009). Recent in vivo canine studies using a "next-generation" compound (S-PAC-1) have been efficacious, and treatments induced partial tumor regression (Peterson et al. 2010). However, the mechanism of PAC-1-mediated caspase activation is controversial because another group was unable to confirm the results obtained by Putt et al. (Putt et al. 2006). Denault et al. (2007) have suggested instead that PAC-1 cannot directly activate executioner caspases but rather uses an indirect and therefore blunted and less effective activation mechanism.

Another area of active research concentrates on compounds that activate caspases indirectly. Some of these agents block endogenous caspase inhibitors such as the Bcl-2 and IAP proteins (Vogler et al. 2009), whereas others are analogs of the endogenous IAP inhibitor Smac (Chen and Huerta 2009). Still others are activators and antibodies that engage DRs (Ying Lu 2011). Several of these compounds are currently under examination in clinical trials.

It should be noted that the use of apoptosis-inducing compounds for cancer treatment is not new, and most of these agents are subject to the same limitations of delivery and specificity as traditional chemotherapeutics. However,

certain caspase activators, such as those that inhibit antiapoptotic molecules like Bcl-2, appear to have an enhanced therapeutic index when used to treat cancer cells that rely mainly on antiapoptotic proteins to stave off cell death (Certo et al. 2006).

Graft versus Host Disease

Another situation in which induction of cell death might be advantageous is the elimination of autoreactive lymphocytes in graft versus host disease (GVHD). Patients are currently being recruited for a phase I/II clinical trial of a modified version of caspase-9. This inducible caspase-9 "safety switch" agent consists of a truncated caspase-9 protein that lacks the CARD domain and is fused to a forkhead protein binding sequence. In the presence of a particular small molecule, the caspase-9 safety switch protein dimerizes and activates the hydrolytic function of the enzyme, triggering apoptosis (Straathof et al. 2005). When used as a therapy, the caspase-9 safety switch is virally transduced into allodepleted T cells, which are then administered to patients who have received a T-cell-depleted stem cell transplant (Tey et al. 2007). Should GVHD occur following the transplant, the small molecule is administered to the patient to induce caspase-9 activation and quickly eliminate autoreactive T cells via apoptosis.

Inhibiting Caspases to Prevent Cell Death

In general, the inhibition of caspase activity has had less striking therapeutic effects than has caspase activation. Nevertheless, there are several instances in which, regardless of whether caspases have been definitively implicated in the etiology or pathological consequences of a disease, caspase inhibition has ameliorated the symptoms of several conditions caused by inappropriate apoptotic cell death. For example, because chronic hepatitis virus C infection is accompanied by detrimental hepatocyte apoptosis, a recent clinical trial examined the therapeutic potential of a caspase inhibitor (Manns 2010). Similarly, the severity of ischemia reperfusion injury resulting from cell death that often follows a stroke (Renolleau et al. 2007), traumatic brain injury (Knoblach et al. 2004), or organ transplant (Baskin-Bey et al. 2007) can be reduced by caspase inhibition. Last, because the neuronal death characteristic of AD and other neurodegenerative diseases, as well as possibly other aspects of disease progression, are associated with caspase activation (see above), caspase inhibitors are under investigation in mouse models of AD and have already shown promising results (O'Brien and Wong 2011).

IL-1β Antagonism

A key component of many inflammatory disorders appears to be the activation of caspase-1 leading to the generation of active IL-1β. Accordingly, agents that can antagonize either the generation or function of IL-1β or its receptor (IL-1R) have been developed for patient treatment. An early such agent was Anakinra, a small molecule antagonist of IL-1R. Newer agents include monoclonal antibodies (mAbs) directed against IL-1β (canakinumab) (Alten et al. 2008; Church and McDermott 2009; Lachmann et al. 2009a), and IL-1Trap, a decoy receptor with high affinity for IL-1 (Kalliolias and Liossis 2008).

Clinical trials are currently under way to assess the efficacy of the above inhibitors and related molecules as treatment for several of the inflammatory diseases discussed above. For example, patients with gout, pseudogout, or pulmonary silicosis have shown great improvement after treatment with an IL-1β antagonist (McGonagle et al. 2007, 2008; So et al. 2007; Terkeltaub et al. 2009). CAPS patients also respond well to IL-1β antagonists (Hawkins et al. 2003, 2004a,b; Hoffman et al. 2004, 2008; Goldbach-Mansky et al. 2006, 2008; Hoffman 2009; Lachmann et al. 2009b), although the disease is also ameliorated by caspase-1 inhibition (Stack et al. 2005). IL-1β antagonists have also shown efficacy in clinical trials for the treatment of T2D (Larsen et al. 2007, 2009), confirming the important role of the NLRP3 inflammasome containing caspase-1 as a sensor of metabolic stress (Schroder and Tschopp 2010). Lastly, IL-1β antagonists have induced symptom regression in

FMF patients (Roldan et al. 2008), HIDS patients (Cailliez et al. 2006), and sJIA patients (Pascual et al. 2005; Kelly and Ramanan 2008; Lequerre et al. 2008).

CONCLUSION

In conclusion, caspase family members are at the nexus of critical regulatory networks controlling cell death and inflammation. We know that although caspase activity is critical for homeostasis of organisms, cells must take steps to protect themselves against unintended caspase activation through complex systems required to turn inactive caspase zymogens into functional proteases. The long list of diseases associated with caspases tells us that the inappropriate activation of caspases and dysregulation of the cell death and inflammatory pathways they control has dire consequences for human health. A growing body of research is providing us with ever increasing clarity about how these exciting proteases operate and how we might fight disease by manipulating their functions.

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