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Cellular stress management by caspases

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Abstract

Cellular stress plays a pivotal role in the onset of numerous human diseases. Consequently, the removal of dysfunctional cells, which undergo excessive stress-induced damage via various cell death pathways, including apoptosis, is essential for maintaining organ integrity and function. The evolutionarily conserved family of cysteine-aspartic-proteases, known as caspases, has been a key player in orchestrating apoptosis. However, recent research has unveiled the capability of these enzymes to govern fundamental cellular processes without triggering cell death. Remarkably, some of these non-lethal functions of caspases may contribute to restoring cellular equilibrium in stressed cells. This manuscript discusses how caspases can function as cellular stress managers and their potential impact on human health and disease. Additionally, it sheds light on the limitations of caspase-based therapies, given our still incomplete understanding of the biology of these enzymes, particularly in non-apoptotic contexts.

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General background

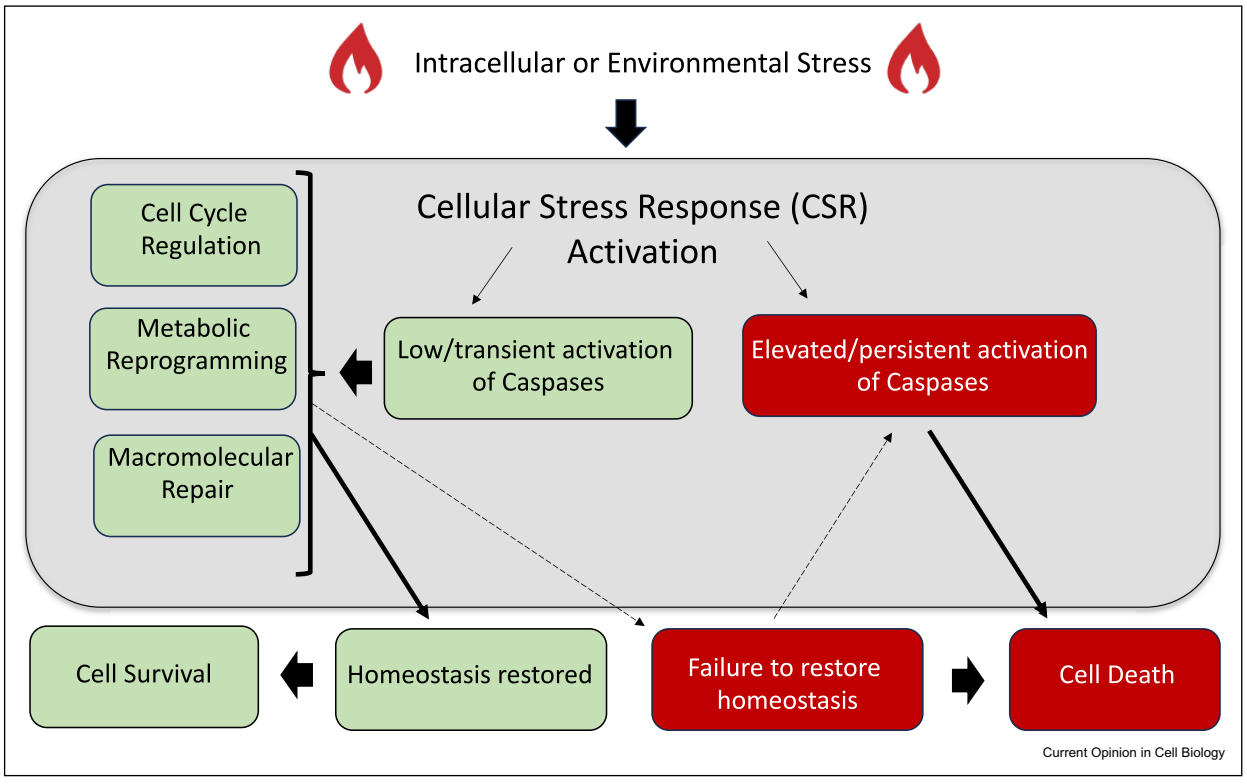
The intuitive correlation between physiological stress and various human diseases (e.g., heart failure, diabetes, neurological diseases, and cancer) is ingrained in the collective mind. However, the intricate molecular underpinnings behind this correlation are not yet fully understood. Cells are exposed to a constant barrage of intra- and extracellular challenges that lead to macromolecular damage, metabolic imbalances, aberrant gene expression, protein malfunction, and changes in lipid composition, all of which can alter cellular homeostasis [1,2]. To counteract the burden of these cellular defects and reinstate equilibrium, cells have evolved numerous stress response strategies [1,2]. The cornerstones that uphold the cellular stress response (CSR) are cell proliferation arrest, metabolic reprogramming, macromolecular repair, and on/off activation of cell death pathways [1] (Figure 1).

The evolutionarily conserved family of cysteine-aspartases known as caspases is renowned for facilitating the elimination of cells via apoptosis and modulating the inflammatory response [3,4]. Therefore, the caspase-dependent elimination of damaged cells is key to ensure functional organ integrity and development [3,4]. However, recent research indicates the involvement of caspases in the regulation of numerous cellular functions without causing cell death [5–7]. Here we will focus on portraying caspases as pivotal modulators of CSR and how caspase-related deregulation of CSR might contribute to the development of human diseases.

Salient features of caspase activation

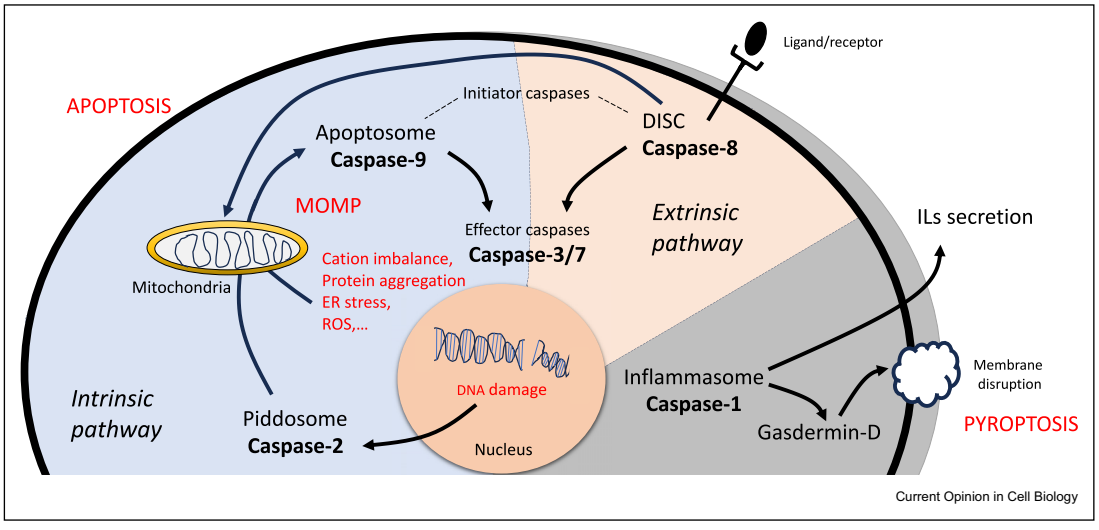
Ever since the identification of Interleukin-1β as the inaugural substrate of caspase-1 [8–13], subsequent investigations have illuminated the proficiency of caspases in cleaving a multitude of proteins in both apoptotic and non-apoptotic contexts [5–7]. Consequently, catalytic activity has emerged as the defining hallmark of caspases and even coined the name of the protein family (**c**ysteine-**asp**artic prote**ases**; caspases). In humans, caspases have functionally been divided into two main categories: inflammatory (such as caspase-1, -4, -5, -11, 12) and apoptotic caspases (including caspase-2, -3, -6, -7, -8, -9, -10). They have also been subcategorized based on their temporal activation during apoptosis as either upstream initiator (caspase-2, -8, -9) or down-stream effector caspases (caspase-3, -7, -6) [3]. Nevertheless, these classifications do not entirely account for the diverse repertoire of caspase roles and features (Figure 2). For instance, evidence has demonstrated non-apoptotic activation of formerly described as apoptotic caspase members [6], the induction of pyrolytic cell death mediated by caspase-1 [14], and caspase-3 activation in the absence of caspase-9 in specific contexts [15]. Furthermore, some caspase members elude formal inclusion in these categories because they seemingly do not contribute to

Figure 1



Interplay between cellular stress and caspase activation. Various forms of intracellular stress, such as DNA damage, protein accumulation and aggregation, ER stress, metabolic imbalances, changes in membrane lipid composition, mitochondrial dysfunction, and others, along with external environmental stressors like radiation, heat shock, signalling deregulation, and more, initiate the Cellular Stress Response (CSR). This, in turn, prompts caspase activation to maintain cellular homeostasis and support proper organ function.

Figure 2



Schematic Illustration of Intrinsic and Extrinsic Pathways Regulating Caspase Activation. In response to diverse intracellular and environmental cues, cells can initiate the activation of both initiator caspases and effector caspases. Robust and sustained engagement of the caspase pathway culminates in the induction of apoptosis. A crucial event in this process is the permeabilization of the mitochondrial outer membrane (MOMP). Separately, damage-associated- and pathogen-associated-molecular-patterns (DAMPs and PAMPs) prompt inflammasome assembly, leading to the efficient activation of Caspase-1. Active Caspase-1 can cleave Gasdermin-D, which subsequently disrupts the cell membrane, resulting in the lytic form of cell death known as pyroptosis. Caspase-1 activation also facilitates the release of pro-inflammatory molecules (e.g., interleukins, ILs). Importantly, transient and low levels of caspase activation can also modulate the status of numerous proteins relevant to the Cellular Stress Response (CSR) without inducing cell death.

either apoptosis or inflammation regulation (e.g., caspase-14 [16]).

The biological consequences of caspase activation hinge significantly on the activation process itself. If the level of caspase activation becomes excessive and prolonged throughout cells, it disrupts vital cellular tasks, ultimately resulting in apoptotic cell demise [17]. Among the best-investigated series of consecutive molecular events are those that lead to apoptosis, involving initiator caspases followed by the action of effector caspases. This has been fairly well-documented for a variety of biological scenarios in both physiological and pathological conditions.

Traditionally, intracellular stress signals, such as DNA damage, reactive oxygen species accumulation, ER stress facilitate the permeabilisation of the outer membrane of the mitochondria (MOMP) and the potent activation of the intrinsic apoptotic caspase pathway. The activation of initiator caspases (e.g., Caspase-9 or -2) during apoptosis in response to intracellular cues is strongly linked to the formation of multiprotein platform complexes, such as the apoptosome or piddosome, which subsequently boost the activation of effector caspases (e.g., Caspase-3 and -7) in all of the subcellular compartments [18] (Figure 2). In parallel to the intrinsic pathway, cells have developed mechanisms based on ligand−receptor interactions to activate the caspase pathway in response to extracellular signals (extrinsic caspase activation mechanism) [18] (Figure 2). For instance, ligands such as TNF-alpha and Trail bind to their respective receptors and ultimately facilitate the formation and subsequent activation of Caspase-8 in the death-inducing signalling complex (DISC) [18]. Then Caspase-8 mediates the cleavage of effector caspases and consolidates the apoptotic fate [18]. Dysregulated induction of the intrinsic or extrinsic apoptotic caspase pathway contributes to numerous human diseases, either due to the accumulation of malfunctioning cells (including those exposed to prolonged cellular stress) or due to excessive cell death (e.g.; neurological disorders, developmental defects, autoimmune diseases, sensitivity to infection, and other) [19].

In stark contrast to apoptosis, the molecular mechanisms governing caspase activation in non-apoptotic scenarios are largely unknown, mainly due to the dearth of caspase regulators and substrates identified in such situations [6]. However, the experimental evidence suggests that non-apoptotic caspase functions are intricately linked to transient and/or low thresholds of caspase activation [20−22]. For example, transient activation of Dronc (Drosophila ortholog of Caspase-2/9 in mammals) is required in intestinal precursors to hold the premature differentiation into enterocytes [23]. Furthermore, this activation appears to be confined within specific subcellular regions [24−28], possibly due to transient interactions between caspases and specific regulators and/or substrates. For instance, research has revealed the necessity of Dronc activation for the individualization of sperm in fruit flies [27]. However, this non-apoptotic role can be compromised by reducing the expression of the de-ubiquitylating enzyme DUBA, which physically interacts with and modulates the activity of Dronc in the sperm [29].

Caspases as key managers of cellular stress response

The elimination of undesired cells could be considered the ultimate mechanism to reinstate tissue homeostasis in stress conditions. Accordingly, the malfunction of caspases as regulators of apoptosis is at the origin of numerous human diseases [19]. Beyond apoptosis, non-lethal caspase activation could be highly effective in modulating the distinctive features of CSR (Figure 1). In the following lines, we provide specific examples indicating how caspases can either slow down or accelerate the cell cycle, control the repartitioning of energy within cells, and modulate the dynamics of macromolecular structures and proteins to restore cellular equilibrium.

Intersection of caspases with the cell cycle

Caspases take on a pivotal role in the governance of cell proliferation [30]. This regulation predominantly derives from their enzymatic activity, which enables them to exercise direct control over the functionality of cell cycle regulators, including but not limited to the retinoblastoma factor [31], p21 [32−36], cyclins and specific cyclin-dependent kinases (CDKs) [30,37−40] (Figure 3). Caspases can also influence signalling pathways with profound regulatory implications for the cell cycle such as the Hippo [41−43], MAPK [44−47], and insulin cascade [48] (Figure 3). Moreover, caspases are accountable for the regulated release of either secreted molecules or enclosed in membrane-bound extracellular vesicles with the ability to modulate cell proliferation [49]. For instance, the caspase dependent release of the mature form of IL-1β [50] triggers signalling events that promote the phosphorylation of different components of the MAPK pathway, ultimately stimulating the cell proliferation of HELA cells [51]. In a distinct experimental setting, Gupta and colleagues described the caspase-dependent release of apoptotic compensatory proliferation signalling vesicles (ACPSVs) containing the Chicken tumour virus10 regulator kinase, CrkI [52]. Notably, CrkI induced the distant proliferation of recipient cells upon the activation of the JNK pathway [52]. Consequently, the activation of the caspase cascade in response to physiological stress can either temporarily halt or stimulate cell proliferation, thus facilitating biological processes such as cell differentiation [53], reorganisation of macromolecular complexes [5,54], and defence

Figure 3

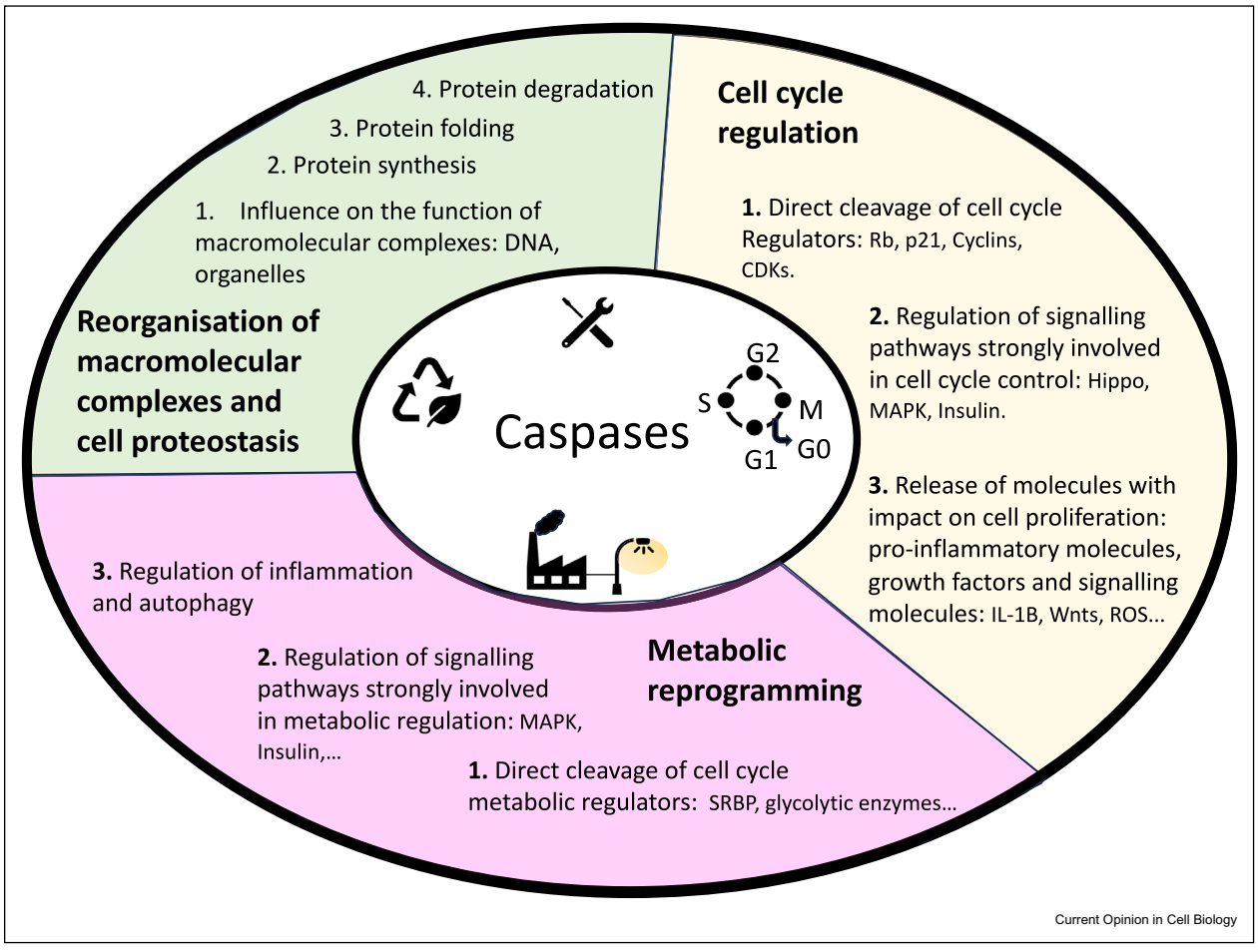


Diagram summarising the impact of caspases on the cornerstones of the CSR.

mechanism against pathogens [55] (Figure 3). Moreover, the interplay of caspases with the cell cycle is pivotal for finely tuning cell proliferation in healthy cells juxtaposing damaged tissues [49,50,56–59]. Unfortunately, our current limited understanding of the interplay of caspases and the cell cycle significantly hinders our ability to predict the outcomes of their interaction. However, we speculate that the result hinges heavily upon the presence of specific caspase regulators/substrates and the levels of caspase activation within distinct cellular contexts. While further research is essential to validate this hypothesis, it is conceivable that persistent cellular stress coupled with sustained caspase activation might contribute to the occurrence of diverse developmental anomalies, regeneration defects, and heightened susceptibility to cancer and infectious diseases.

Caspases and metabolic reprogramming

Metabolic perturbations are among the primary cellular alterations caused by cellular stress. Consequently, cells have evolved a diverse range of compensatory mechanisms to restore equilibrium. Depending on the source and intensity of cellular stress, various signalling adaptations (e.g., activation of the AKT pathway, biosynthesis of lipids, ATP generation) and biological processes (e.g., autophagy and mitochondrial reprogramming) come into play to counteract energy deficits, shortages in essential cellular metabolites, and aberrant intracellular signalling [60].

Caspases have been shown to cleave key metabolic proteins like sterol-regulatory binding proteins (SREBPs) [61,62] and AMPK [63], the peroxisome proliferator-activated receptor gamma [64], and glycolytic enzymes [65], significantly impacting the metabolic state of cells in physiological and stress conditions (Figure 3). Furthermore, it has been observed that caspases are essential for the timely initiation and/or termination of key signalling events controlling the metabolic reprogramming in response to stress. For instance, activated caspase-3 can cleave a RasGAP-

activating protein responsible for the regulation of the AKT signalling pathway, which, in turn, limits the apoptotic potential of caspase-3 upon cleveage, thereby ensuring cell survival [66,67]. Caspase activation in normal and transformed cells can also prevent the sustained activation of stress-related pathways like the JNK [68,69] and P38-MAPK signalling cascades [47,70], which can shorten lifespan and induce the release of growth factors with oncogenic potential [47,68,70]. Separately, a vast amount of literature out of the scope of this manuscript describes the ability of caspases to modulate the inflammatory response by controlling the secretion of pro-inflammatory molecules and cytokines, which have powerful effects in the activity of metabolic organs such as the adipose tissue and liver [71,72] (Figure 3).

Finally, a complex and reciprocal regulation exists between caspase activation and the process of autophagy. Autophagy is a lysosomal-dependent degradation mechanism that promotes the breakdown of obsolete organelles and large protein complexes confined within vesicles upon fusion with lysosomes [73,74]. This process is accompanied by the recycling of essential structural components (e.g., essential amino acids) and ATP generation. Autophagy prevents the accumulation of intracellular debris, supports organelle repair, and compensates energy deficits during periods of cellular starvation [73]. Additionally, it often targets cell death related proteins for lysosomal degradation [74,75]. Together, these factors usually confer a pro-survival role to autophagy; however, in excess, autophagy can also lead to cell death by exhausting key intracellular resources. Although caspases usually abrogate autophagy by excising key autophagy-activating proteins (e.g. Beclin and Atg8) [76–78], they can also induce its activation in specific situations through mechanisms not always fully understood [22,79–81]. Importantly, the complex crosstalk between caspases and the autophagy machinery seems to be evolutionarily conserved [82,83], and is crucial to modulate the metabolic status of cells and basic cellular functions such as cell proliferation, differentiation and cell survival [22,83,84]. All of these effects reinforce the hypothesis that precise control of the interactions between caspases and metabolic regulatory pathways could play a crucial role in preventing the onset of various metabolic disorders, including insulin resistance, non-alcoholic steatohepatitis (NASH), and liver degeneration [71].[a]

[a] During the revision process of this manuscript was published novel data indicating that the fatty acid synthase (FASN) has a conserved caspase cleaveage site in humans and C. elegans. Importantly, caspase dependent cleveage of FASN seems to broadly limit and control stress responses. Wei, H., Weaver, Y.M., Yang, C. et al. Proteolytic activation of fatty acid synthase signals pan-stress resolution. Nat Metab (2024). https://doi.org/10.1038/s42255-023-00939-z

Caspase-dependent modulation of macromolecular repair and cell proteostasis

Caspases are closely associated with degradative processes, including DNA fragmentation, proteolytic cleavage of pro-survival factors, and essential mitochondrial proteins, typically occurring before apoptosis. In addition, the precise modulation of non-apoptotic caspase activity on macromolecular complexes and proteins can also play a role in restoring cellular homeostasis and, consequently, promoting cell survival. As expected, the consequences of apoptotic and non-apoptotic caspase activation in this context can either amplify or constrain the mechanisms involved in disease progression.

For instance, DNA fragmentation is one of the caspase-mediated hallmark events of apoptosis, caused by the Caspase-activated DNAse (CAD) upon caspase-3-dependent release from its inhibitor (inhibitor of CAD; ICAD) [85,86]. However, these events can also be instrumental in promoting cell differentiation through the activation of specific genetic programs in both physiological and pathological conditions [87,88]. Along these lines, caspase-2 maintains the ploidy while inducing cellular senescence in stressed cells, thus acting as a tumor suppressor without necessarily causing apoptosis [54]. Conversely, caspase-dependent DNA damage can cause aneuploidy [89] and fuel malignancy by reprogramming the genetic profile of transformed cells [90] and/or conferring metastatic behaviour [91,92]. Beyond reorganising large macromolecular structures such as the DNA, the caspase-dependent modulation of autophagy and proteostasis can influence the functionality of entire organelles such as the mitochondria that, in turn, control diverse cellular processes [93].

Protein production and turnover, collectively referred to as cellular proteostasis, require precise regulation to prevent the development of numerous human diseases, ranging from Alzheimer's to cancer [94,95]. The stress-dependent accumulation of misfolded or truncated proteins induces different cell death programmes including apoptosis. Conversely, caspase activation has been demonstrated to influence cellular proteostasis from yeast [96] to humans [93].

Caspases can regulate protein synthesis and protein levels by influencing every step involved in gene expression. Notably, caspase-driven reorganisation of DNA can yield global alterations in the gene expression profiles of cells [90]. A large number of transcriptional (e.g., Nanog [97]) and translation factors (e.g., EIF3g [98]) contain demonstrated or predicted cleavage sites, and therefore its caspase-dependent modulation affects the levels of numerous proteins [37]. Similarly, microRNA processing factors involved in gene regulation, such as Drosha, DGCR8, Dicer, and TRBP2, appear to be caspase targets under stress conditions [99].

Regarding protein folding, ER/Golgi resident components and cytosolic factors such as the heat shock proteins play a crucial role in ensuring proper protein folding [94,95]. Accumulation of misfolded proteins can trigger the unfolded protein response (UPR) stress response pathways, which secondarily trigger caspase activation and apoptotic cell death [100]. However, caspases can also cleave key components of the UPR machinery (e.g., IRE1) without necessarily causing cell death, thus regulating the protein quality control and the degradation mechanisms [78]. Separately, caspases can also exert an influence on the protein degradation rate acting on the autophagy process (see above) and the proteasome activity. Along these lines, caspases seem to maintain proteostasis through multiple interactions with the ubiquitin system without causing cell death [82]. Additionally, caspases have been observed to induce the proteasomal-dependent degradation of specific ubiquitin ligases (e.g, Nedd4 [101]), inhibitors of apoptosis (e.g., DIAPs [102]) and key regulatory subunits of the proteasome (e.g., Rpt5, Rpn2, Rpn10) [103]. The action of caspases on these proteins may play a dynamic role in controlling protein levels regardless of the apoptotic or non-apoptotic purpose of their activation.

Paradoxically, the molecular systems responsible for controlling cell proteostasis often protect cells from excessive caspase activation. For example, it has been shown that specific IRE1 peptides released as a result of caspase-dependent cleavage can function as buffers for caspase activation [78]. The formation of stress granules can sequester effector caspases, thus limiting caspase activity [104]. Heat shock proteins, such as Hsp-70, can interact with inducers of apoptosis like Apaf-1 and AIF, limiting their apoptotic capacity [105]. Moreover, the levels of caspase activation within cells are continuously regulated by heat shock proteins [106] and ubiquitin ligases that can associate them with the proteasome [107].

The intertwined interplay between caspases and proteostasis networks makes it challenging to elucidate the precise role of caspases in human disease. For instance, data is accumulating linking caspase activity with the origin of several neuropathologies, including Alzheimer's disease, frontotemporal dementia, and Huntington's disease. Supporting this hypothesis, Caspase-2 and Caspase-3-dependent cleavage of Tau might reduce the amounts of full-length Tau protein, thus alleviating Tau accumulation and aggregation. However, the caspase-dependent generation of small Tau peptides, prone to aggregate, seems to inhibit the excitatory postsynaptic transmission in dendritic spines ([108,109] and lead to synapse degeneration [110]. In another example, it has been demonstrated that different effector caspases can cleave Huntingtin (HTT) at specific residues, resulting in opposing outcomes. Caspase-3-mediated cleavage of HTT at D552 enhances its myristoylation at G553 and subsequent autophagic degradation, thus effectively preventing HTT accumulation. Conversely, pathogenic variants of HTT with a newly generated Caspase-6/-8 at residue D586 hampered the Caspase-3-mediated effects, worsening Huntington's disease manifestations [111].

These examples not only illustrate the intersection of caspases with the proteostasis network in physiological and stress conditions but also underscore the challenges in interpreting their biological contributions. Adding an additional layer of complexity, it is important to note that for certain proteins, caspase-cleavage sites might be concealed within specific structural stretches of the protein or shielded by regulatory interactors, making them conditionally accessible.

Caspase-related therapies: potential and realisation

The enzymatic nature of caspases makes them attractive targets from a therapeutic perspective, as they are theoretically targetable by using small molecules. This chemical accessibility and their functional versatility have potently trapped the attention of pharmaceutical companies. Specifically, substantial efforts have been made to activate the caspase pathway in transformed cells to eliminate them [112]. Combination therapies that include agonists of cell death receptors, such as TRAIL, along with antagonists of apoptosis (e.g., antagonists of IAPs and BCL2 proteins), have shown promising preclinical efficacy [113]. However, tumour cells often develop diverse molecular adaptations, such as transcriptional downregulation of caspases or enhanced protein stability of IAPs, which confer resistance to apoptosis in cells treated with single therapeutic molecules [114–116]. To address this challenge, a recent approach has explored the efficacy of using a sequential combination of two pro-drugs acting on the same target through independent routes. One of these routes facilitates the transcriptional activation of Caspase-3, while the other stabilises the activated form of the protein [117]. Counterintuitively, caspase pathway inhibition could be also effective for the treatment of transformed cells. For instance, the caspase inhibitor Z-VAD-FMK can enhance the radio-sensitisation of MDA-MB-231 breast and H460 lung cancer cells by diverting them to die through autophagy [118].

Beyond cancer, caspase modulation is frequently employed to either protect cells against apoptosis or to limit the inflammatory response. As a result, numerous caspase modulators are undergoing experimental phase or clinical trials for the treatment of inflammatory, neurological, and metabolic diseases [119] (e.g., Table 1).

Table 1

Summary of caspase-based interventions under investigation. The table provides a summary of the performance of a subset of small molecules available in the Drugbank database (https://go.drugbank.com/) that specifically target and influence the activity of caspase family members. It's important to note that there are additional small molecules that can indirectly lead to caspase activation, but they are not featured in this table.

Drugbank ID	Drug name	Target	Activity	Status	Disease categories	Disease	References
DB04875	Pralnacasan	Caspase-1	Inhibitor	Investigational	Inflammatory	Rheumatoid arthritis (RA), osteoarthritis (OA)	(Pavelka K 2002, Rudolphi, Gerwin et al., 2003)
DB05301	LAX-101	Caspase-1	Inhibitor	Investigational	Neurological	Depression and huntington's disease	Drugbank website
DB05408	IDN-6556/ Emricasan	Caspase-1, 3, 7	Inhibitor	Investigational	Metabolic Inflammatory	Hepatitis (viral, C), liver diseases, and transplantation	(Pockros, Schiff et al., 2007)
DB05507	VX-765	Caspase-1	Inhibitor	Phase II Completed	Inflammatory	Partial Epilepsy, Psoriasis, Epilepsies	(Wannamaker, Davies et al., 2007)
DB11752	Bryostatin 1	Caspase-8	Inhibitor	Phase II Completed	Neurological Cancer	Alzheimer's Disease, Breast cancer, colorectal cancer, Cervical cancer	(Gomez-Angelats, Bortner et al., 2000)
DB00282	Pamidronic acid	Caspase-3, 9	Activator	Phase IV Completed	Cancer Metabolic	Breast cancer, prostate cancer, Metabolic Bone Disorder, Osteopenia	(Ullen, Schwarz et al., 2009)

However, the realization of caspase-related therapies has proven to be challenging due to issues like partial efficacy, poor specificity, or adverse side effects. These problems are primarily rooted in our limited understanding of caspase regulation and function, especially in non-apoptotic scenarios, and their diverse tissue-dependent roles. For example, while caspase-3 inhibition might be beneficial in the early stages of stroke to limit apoptosis [120], it could be detrimental in the long term, as caspase-3 activity promotes cell proliferation during the regeneration phase [48]. In another instance, caspase activators can sensitize transformed cells to undergo apoptosis but may also confer cell motility, potentially facilitating metastatic events [91,92]. These complexities do not diminish the therapeutic value of caspase modulation, but they underscore the need to enhance our understanding of the molecular interactions between caspases and their substrates/regulators in various biological contexts, as well as the biological function of new peptides generated due to caspase cleavage [63,78]. Instead of concentrating solely on adjusting caspase activation levels, targeting specific caspase–substrate interactions could be a more promising approach for the development of safer and more effective targeted therapeutic interventions.

Conclusion

In addition to their extensively researched roles in apoptosis and inflammation, emerging evidence accentuates the involvement of caspases in governing alternative biological processes. It is noteworthy that the intersection of caspases with these additional cellular functions does not invariably result in cell death; rather, it frequently contributes to reinstating cellular equilibrium in response to stress. Caspases appear to facilitate this restoration of balance by exerting influence on the cell cycle machinery, metabolic regulation, cellular signalling, clearance of misfolded proteins, and reorganisation of macromolecular structures. While these mechanisms remain subjects of intense investigation, they collectively underscore the capacity of caspases to coordinate cellular responses against stress across multiple tiers. Obtaining deeper insights into the mechanisms governing caspase activation and the specificity of their functions in relation to the substrates is of critical importance. This knowledge could pave the way to develop caspase-based therapies for a variety of diseases, including cancer, inflammation, and neurodegenerative disorders.

Contributions

L.A.B-L., L.W., and F.W. conceptualized the content together; L.A.B-L. wrote the original draft and prepared the figures; L.W. prepared Table 1; all authors reviewed, edited, and add comments to the text.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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