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REVIEW

An Old Death with a New Twist: The Roles of Intrinsically Disordered Proteins and Phase Separation in Cellular Suicide

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Abstract—Programmed cell death (PCD) is a set of tightly controlled biological pathways that eliminate obsolete or damaged cells to preserve tissue homeostasis and support development. Despite their mechanistic variations, all PCD pathways share three fundamental characteristics: a genetic basis, stringent regulation, and an active requirement for energy to drive cellular self-destruction. While PCD signaling pathways are heavily studied, their precise spatial and temporal organization remains elusive. Intrinsically disordered proteins (IDPs), liquid–liquid phase separation (LLPS), and membraneless organelles (MLOs) have emerged as fundamental principles for cellular organization, enabling rapid stress adaptation and signal integration. This review provides a brief overview of the complexity of PCD pathways and summarizes the roles of IDPs, LLPS, and MLOs in PCD regulation and execution. This biophysical perspective challenges the view of cell death as a fatalistic, binary outcome, reimagining cellular suicide not as something 'written in stone', but as a highly regulated continuum of decreasing vitality.

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MANY WAYS TO DIE YOUNG: MULTIPLICITY OF THE PROGRAMMED CELL DEATH MECHANISMS

Death is an inevitable and universal process of irreversible cessation of biological functions that sustain life marking the permanent end of the physical existence of all living things. Biologically, this process represents a necessary mechanism that maintains ecological balance and allows for the continuity of species. It drives the recycling of organic matter, controls overpopulation, prevents ecosystem collapse, and enables constant adaptation, evolution, and continuous biological diversification. Being the foundational units of life, cells face death through two primary pathways: accidental destruction or deliberate, programmed, and tightly controlled self-destruction [1]. Accidental cell death (ACD also known as necrosis) is an unregulated process that originates from sudden, severe external injury, such as chemical or physical disruption of the plasma membrane. This uncontrolled form of cell death, being described for the first time by Rudolf Virchow (1821-1902) in 1858 [2], results in the rupture of the cell membrane and spilling the cellular contents into surroundings. On the contrary, controlled cell death, also known as programmed cell death (PCD), being caused by various intrinsic signals, represents a multitude of highly regulated processes that trigger "cellular suicide" leading to the elimination of damaged, potentially dangerous, or redundant cells to maintain organismal health [1]. Importantly, PCD represents an innate cellular suicide mechanism not limited to multicellular life, and even single-celled organisms, such as bacteria, yeast, and algae, utilize PCD as an altruistic strategy, sacrificing a fraction of their population to ensure the survival

of a colony under extreme environmental stress [3-5]. Some of the illustrative examples of such rather counterintuitive self-destruction of single-celled organisms include kin selection (self-sacrifice of damaged or infected cells releases resources or prevent the spread of toxins) [6], viral defense [7], stress response [6, 8], and biofilm formation [9, 10].

For a long time, PCD was synonymous with apoptosis, a term proposed in 1972 by Kerr, Wyllie, and Currie to define the distinct morphological features of controlled cell death in different contexts via a genetically controlled, active mechanism "complementary to mitosis in the regulation of animal cell populations" [11]. It is recognized now that apoptosis is one of many PCD forms, and cells have numerous distinct, genetically regulated ways to commit suicide allowing the multicellular organisms to precisely manage development, maintain tissue health, and fight off diverse pathogens [12-15]. In fact, there are at least 26 distinct mechanisms of PCD, which are intrinsic and extrinsic apoptosis, mitochondrial permeability transition (MPT)-driven necrosis, necroptosis, ferroptosis, pyroptosis, parthanatos, entotic cell death, NETotic cell death, lysosome-dependent cell death, autophagy-dependent cell death, immunogenic cell death, cellular senescence, and mitotic catastrophe described in the Recommendations of the Nomenclature Committee on Cell Death (2018) [12], as well as oncosis [16], paraptosis [17], methuosis [18], autosis [19] and more recently discovered oxeiptosis [20], alkaliptosis [21], PANoptosis (inflammatory programmed cell death pathway that incorporates elements of Pyroptosis, Apoptosis, and Necroptosis) [22], lysozincrosis [23], cuproptosis [24], erebosis [25], disulfidptosis [26], and mitoxyperilysis [27].

Despite their differences, all PCD pathways share three core traits: they are genetically encoded, tightly regulated, and energy-consuming mechanisms of cellular self-destruction. And, of course, they all lead to the untimely demise of the affected cells. The "multiplicity of ways to die young"; i.e., the existence of multiple, overlapping death programs, ensures that an organism can adaptively respond to various internal and external threats. Because cell death is the ultimate biological safeguard, nature employs a redundant system of overlapping pathways. This redundancy ensures that if one pathway is blocked, alternative routes guarantee the targeted destruction of compromised (damaged, mutated, or infected) cells that constantly evolve ways to block cell death to survive.

PROTEINS BEYOND LOCK-AND-KEY AND INDUCED FIT

There are no doubts that the "lock-and-key" model proposed by Hermann Emil Fischer (1852-1919) in 1894, suggesting that the active site of an enzyme has a rigid, predefined shape perfectly complementary to its specific substrate, was a revolutionary milestone in biochemistry [28, 29]. Although it explained the exquisite specificity of some enzyme and also laid the foundational framework for molecular recognition, it failed to explain how certain enzymes can catalyze multiple similar substrates, or how proteins stabilize transition states during reactions. To address these inconsistencies, an "induce fit" model was proposed by Daniel Edward Koshland Jr. (1920-2007) in 1958, where the initial contact with the substrate was suggested to induce dynamic structural changes in a flexible enzyme, allowing an active site to "mold" itself tightly around the substrate (like a glove) for a precise fit [30]. This allows for a much tighter, highly specific fit, properly placing catalytic amino acid residues in optimal positions and stabilizing the high-energy transition state to accelerate the reaction. Despite differences in nuances, both models relied on the established structure-function paradigm assuming that a fixed amino acid sequence dictates a single, unique 3D structure responsible for unique biological function of a protein. These ideas were extremely fruitful and formed the roots for vast majority of knowledge accumulated in protein science by the end of the last century.

Departure from the long-held dogma that a protein must possess a stable, rigid 3D structure to be functional happened at the turn of the 21st century due to the discovery of intrinsically disordered proteins (IDPs) and proteins containing intrinsic ally disordered regions (IDRs) proving that flexibility, rather than rigidity, is essential for many cellular functions [31-41]. It is now established that IDPs and IDRs exist in all living organisms and become more abundant as biological complexity increases [42-45]. With up to 30% of eukaryotic proteins predicted as unstructured [42] and with over 70% of signaling proteins containing extended IDRs [39], intrinsic disorder is now recognized as a fundamental principle of modern biology rather than an exception. This also led to the recognition that proteins are characterized by spatiotemporal heterogeneity, possessing complex mosaic structures comprised of regions with varying degrees of order and disorder. Here, protein structure represents a complex mixture of independently foldable units (foldons), regions that fold upon partner binding (inducible foldons), regions adopting different conformations based on the partner (inducible morphing foldons), permanently non-foldable regions (non-foldons), permanently semi-folded regions (semi-foldons), and ordered regions requiring an order-to-disorder transition for function (unfoldons) [46, 47]. Importantly, this mosaic structural organization makes proteins inherently multifunctional,

as differently (dis)ordered regions have different specific functions, and all of them coexist and are stitched together within a single protein [48]. These factors form the basis of a protein structure-function continuum model, which posits that the functionality of a protein is determined by a dynamic blend of its ordered, differently disordered, and continuously shape-shifting modules [48-56].

IDPs/IDRs are highly adaptable, multi-tasking binding specialists [57-67]. They regulate complex signaling pathways [33, 38, 40, 68-71], acting as a flexible counterpart to rigid, structured proteins that rely on traditional "lock and key" or "induced fit" models. This structural flexibility provides unique functional advantages, allowing for diverse regulatory mechanisms [46, 57, 68, 70], such as post-translational modifications (PTMs) [72, 73], and enabling the formation of both highly stable and highly transient protein complexes [57, 67]. Due to their ability to become engaged in weak multivalent interactions, many IDPs/IDRs can undergo liquid–liquid phase separation (LLPS) and form various membrane-less organelles (MLOs) and biomolecular condensates (see below) [48, 74, 75].

Finally, the malfunction of IDPs/IDRs, which are essential regulators of diverse biological processes, is linked to the pathogenesis of several human pathologies, such as amyloidosis, cancer, cardiovascular disease, diabetes, and neurodegenerative disorders [76, 77]. Furthermore, IDRs are prevalent in many viral pathogens [44, 45, 78, 79], while host organisms rely on IDPs/IDRs to facilitate innate antiviral immunity [80].

MEMBRANE-LESS ORGANELLES: STATES WITHOUT BORDERS

Mentioning "eukaryotic cell" brings iconic image, where the membrane-enclosed cell body contains a set of membrane-bound organelles (nucleus, mitochondria, endoplasmic reticulum (ER), Golgi apparatus, lysosome, peroxisomes, and, in plant and some algae, chloroplasts). These highly organized structures segregate distinct biochemical environments and, by compartmentalizing different cellular functions, allows for the simultaneous and efficient management of complex, physically and chemically incompatible, biological processes, such as energy conversion, protein synthesis, and waste degradation. Highly stable and enclosed by a lipid bilayer, these organelles protect their internal components from the fluctuating cellular environment over extended periods. Their structural integrity remains intact even after extraction from the host cell. Consequently, scientists long believed that membrane-bound compartments were the sole method of organizing intracellular space [81].

However, biology is full of surprises, and various membrane-less "cellular bodies" have long been observed alongside traditional, membrane-bound compartments. The most famous of these MLOs is the nucleolus, a well-studied subcellular structure initially identified approximately two centuries ago (reviewed in [82]). In fact, although the nucleolus was officially described as early as in the 1830s [83, 84]; Felice Fontana (1730-1805) discovered nucleolus in 1774 as a cellular compartment that becomes visible under the microscope during the interphase of the eukaryotic cell division (reviewed in [82]). Expanding far beyond their original nuclear discoveries, nearly 100 distinct types of MLOs are now mapped across bacteria and eukaryote [85]. Many MLOs are structurally inhomogeneous, representing complex, multi-layered, phase-in-phase systems, where one distinct phase exists inside another [86-88], much like a Russian nesting doll "matryoshka".

For decades, cell biologists studied them independently, often giving the same organelle multiple names while focusing strictly on cataloging their individual structures and cellular functions. Consequently, only recently, in the mid-2010s, it was realized that these functionally diverse compartments share common properties and a uniform formation mechanism, reversible LLPS that yields a marked increase in the localized concentration of biopolymers, such as proteins and nucleic acids, relative to the surrounding cytoplasmic environment [89-93]. MLOs are commonly found in cytoplasm, nucleus, and mitochondria of various eukaryotic cells, in chloroplasts of plant cells, as well as in bacterial cells, where they play a number of crucial roles in the organization of various intracellular processes, operating as molecular microreactors, storage hubs, and central regulators for cellular signaling pathways [94]. The discovery of MLOs has revolutionized our understanding of cellular organization, revealing that in addition to lipid membranes, cells systematically use LLPS to compartmentalize vital biochemical processes [95-103].

The complexity of these systems is further illustrated by the fact that MLOs can be formed in three, two, or one dimension (3D, 2D, and 1D, respectively), depending on their cellular location [101]. Here, the best known and most common form is given by the "3D MLOs", which are the phase-separated, liquid-like droplets. Protein clusters on membrane surfaces constitute "2D MLOs" originating from the dynamic interactions between multivalent transmembrane protein tails/loops and their multivalent binding partners [104, 105]. Such "2D MLOs" are involved in regulation and control of multiple cellular signaling pathways [104, 106-113]. The "1D MLOs" are the chromatin-

associated subcompartments [101, 114] formed via the LLPS [115-118], with DNA functioning as a 1D entity [101, 114] due to its long, string-like nature, extending 2 to 8 cm in human chromosomes [119]. The "1D MLOs" can also be formed on cytoskeletal filaments [120], giving another illustration of a "droplet on a stick" model.

Finally, since LLPS and MLOs are critical to cellular health, their deregulation is directly linked to severe human pathologies [121-123]. Typically, many functional MLOs operate within a tightly regulated "safe existence" window defined by specific times, locations, and physiological conditions. Outside this window, the highly concentrated environment inside an MLO can transition from a functional liquid to a pathological solid [124], serving as a potential source of the insoluble protein aggregates [125]. This shift is driven by the misfolding and aggregation of resident proteins, and can be promoted by the elevated levels of the proteins undergoing LLPS, their aberrant PTMs, pathological mutations, or chromosomal translocations [126]. Furthermore, the biogenesis and dynamics of PMLOs can be altered by inclusion of pathology-related proteins [127].

LIQUIDITY OF LIQUIDS: INTRINSIC DISORDER IN MEMBRANELESS ORGANELLES

Since MLOs or biomolecular condensates are highly concentrated dynamic compartments within cells characterized by liquid-like properties, such as fusion and fission, dynamic assembly/disassembly, rapid continuous material exchange with the surrounding cytosol or nucleoplasm via partitioning in and out, and intrinsic density and viscosity comparable to those of the surrounding cytoplasm or nucleoplasm [128, 129], they represent a very special case of highly dynamic protein-based assemblages [130]. Being formed via LLPS, they contrast sharply with classical, membrane-bound organelles by acting as highly responsive, dynamic reaction hubs rather than static structures. It was indicated that assembly, properties, and functions of MLOs are shaped by site-specific (i.e., precise interactions at specific sites driven by partially or fully structured interfaces) and chemically specific interactions (i.e., interactions without the requirement for a persistent bound-state structure) [131].

Furthermore, the aforementioned capability of IDPs/IDRs to be involved in weak multivalent interactions plays a crucial role in driving LLPS and MLO biogenesis [48, 74, 75, 132], making biomolecular condensates a special form of the disorder-based protein complexes [74, 132, 133]. In fact, IDPs/IDRs are the biological "edge of chaos" systems capable of emergent behavior and self-organization resulting in the unanticipated appearance of novel structures, patterns, and properties [46, 121, 134, 135]. The formation of MLOs and biomolecular condensates driven by LLPS serves a prime example of disorder-driven emergent behavior [74, 75, 91, 96, 100, 130, 136-147]. MLOs organize key intracellular processes and are found across various cell types, often acting as a transient "fifth level" of protein structure; i.e., quinary structure complementing the well-known primary, secondary, tertiary, and quaternary structures of a protein molecule [148-152]. Typically, these palpation-like interactions are not accompanied by noticeable structural changes in proteins undergoing LLPS [74, 75, 147, 153-157]. Concluding, the liquidity of liquid MLOs and biomolecular condensates is determined by the highly dynamic nature of IDPs/IDRs undergoing LLPS. In fact, IDPs/IDRs contain scattered, low-affinity interaction motifs (e.g., aromatic residues, such as tyrosine, or charged residues, such as arginine) known as "stickers," which act as cross-linking points that facilitate transient, weak, multivalent interactions. On the other hand, the regions between stickers act as flexible "spacers" that provide conformational elasticity, allowing condensates to remain fluid, coalesce, and easily deform [131, 158, 159].

INTRINSICALLY DISORDERED PROTEINS AND LIQUID–LIQUID PHASE SEPARATION IN PROGRAMMED CELL DEATH: FLUIDITY WRITTEN IN STONES

Historically, PCD was viewed as a strict, linear cascade of structured enzymatic reactions, primarily characterized by the caspase (cysteine-aspartic proteases) cascade in apoptosis, where the caspase activation leads to substrate cleavage and, ultimately, cell death (reviewed in [160]). Besides caspases, several other distinct classes of enzymes act as crucial regulators and executioners across diverse PVD forms [161]. These enzymes drive both caspase-independent pathways and alternative cell death modalities, such as necroptosis, ferroptosis, parthanatos, and plant-specific PCD. For instance, some non-caspase proteases were shown to dismantle cellular components or activate pro-death proteins [162, 163]. A key example of a PCD-related protease is the calpain family. These calcium-dependent cysteine proteases live in the cytosol. When calcium floods the cell, calpains break down cytoskeletal proteins, rupture the plasma membrane, and activate caspases or cathepsins during necrosis and apoptosis-like PCD [163-165]. Another example is given by cathepsins (e.g., cysteine cathepsins (B, L) and aspartic cathepsins (D, E)),

which are the lysosomal enzymes that after the lysosomal membrane permeabilization, leak into the cytosol and drive Lysosome-Dependent Cell Death (LDCD) [163, 166, 167]. Granzymes A and B are serine proteases injected into target cells by natural killer (NK) cells and cytotoxic T lymphocytes (CTLs). Granzyme B triggers cell death directly by cleaving executioner caspases, whereas granzyme A bypasses caspases entirely, causing cell death by degrading specific nuclear targets [163, 168, 169]. Cysteine proteases, vacuolar processing enzymes (VPEs) [170] and metacaspases [171] are involved in plant-specific PCD and autophagy. Furthermore, several kinases act as the primary signaling molecular switches that initiate regulated lytic and inflammatory cell death. For example, when caspases are blocked, cells can still undergo programmed death through alternative, caspase-independent pathways (CICD) [172], as illustrated by necroptosis, which relies on specific kinases, such as receptor-interacting protein kinase 1 (RIPK1) [172] and the mixed lineage kinase domain-like protein (MLKL) serving as the ultimate executioner of the pathway [173]. There are also oxidative enzymes (e.g., lipoxygenases (LOXs) and NADPH oxidases (NOXs)) that drive death by modifying cellular lipids or generating lethal levels of reactive oxygen species [174, 175], and nucleases and DNA-modifying enzymes (endonucleases, such as endonuclease G (EndoG), apoptosis-inducing factor (AIF), and caspase-activated DNase (CAD)) that break down genetic material at the final stages of PCD [176, 177].

Importantly, it is recognized now that IDPs/IDRs play crucial roles in regulation and execution of PCD [178-181]. Their conformational plasticity, structural heterogeneity, and ability to act as versatile interaction hubs allow them to tightly manage PCD modules, such as apoptosis, autophagy, necroptosis [178, 179], and ferroptosis [180]. A recent comprehensive bioinformatics analysis of human proteins associated with 14 PCD pathways, such as apoptosis, autophagy-dependent cell death, cellular senescence, mitotic catastrophe, entotic cell death, ferroptosis, cuproptosis, immunogenic cell death, lysosome-dependent cell death, mitochondrial permeability transition-driven necrosis, necroptosis, neutrophil extracellular trap formation-related cell death (NETosis), parthanatos, and pyroptosis, revealed the presence of numerous previously unrecognized cross-pathway interactions and regulatory nodes, where IDPs/IDRs played multiple crucial roles [181]. This broad involvement of IDPs/IDRs in PCD is determined by specific features of these structure-less proteins. Their lack of a fixed 3D structure provides them with the possibility structure to undergo disorder-to-order transitions upon interacting with target molecules. This allows them to bind to multiple structurally unrelated partners with high specificity but low affinity, which is essential for rapidly initiating or halting cell death pathways. IDPs/IDRs are highly accessible to modifying enzymes (such as kinases). This provides unique means for fast and highly controllable functional regulation, where PTMs are used to instantly turn a pro-survival IDP into a pro-death signal, acting as rapid "on/off" switches for cell suicide. A few illustrative examples of PCD-related IDPs are briefly presented below.

Discussion of the roles of intrinsic disorder in PCD would be incomplete without mentioning the master regulator of PCD, transcription factor p53 that has a central role in DNA double-strand break (DSB)-related cell cycle regulation [182]. Being one of the most studied proteins, p53 is recognized as a polyfunctional multibinder, whose molecular functional mechanisms starkly contrast with the classical "lock-and-key" protein mode. Long N- and C-terminal IDRs are targets for multiple PTMs and act as central hubs for numerous protein–protein interactions, allowing p53 to physically bind to and coordinate an enormous array of cell-death and stress-response pathways [53]. By operating outside the lock-and-key mechanism, the intrinsic disorder of p53 allows it to act as an adaptable master regulator, integrating multiple upstream signals to dictate cell survival or PCD. In fact, depending on the severity and duration of the upstream signals, the structurally adaptive p53 shifts the cell fate between survival/repair, if damage is mild, to PCD, if damage is severe and irreparable [183]. Furthermore, p53 was shown to undergo LLPS induced by multivalent electrostatic interactions between its two intrinsically disordered domains leading to the formation of p53 biomolecular condensates in the nucleus to regulate target genes [184, 185]. Importantly, oncogenic mutations in the tetramerization or DNA-binding domains of p53 impair its ability to undergo normal phase separation [185] and promote misfolding and partially rigidify the p53 condensates [186]. Due to its inability to form properly functional condensates, the potential of mutant p53 to activate PCD target genes drops significantly, promoting tumor survival and cancer progression [186].

Members of the BCL2 (B-cell lymphoma 2) family are evolutionarily related proteins that govern mitochondrial outer membrane permeabilization (MOMP), are broadly involved in regulation of PCD, and have pro- or anti-apoptotic activities, with their dysregulation being widely implicated in various cancers and autoimmune diseases [187]. Based on their structure and relation to PCD, they are grouped into three functional subfamilies. Here, BCL2, BCL-X_L, myeloid cell leukemia-1 (MCL1), and BCL-w form a group of anti-apoptotic proteins [188] containing long IDRs [179]. BAX and BAK are mostly ordered, multidomain, pro-apoptotic proteins containing BH1, BH2

and BH3 domains [189] and short IDRs [179]. Finally, BH3-only proteins, such as BAD, BIM, BID, and PUMA, are largely disordered in solution, but adopt specific α-helical conformations only when binding to pro-survival partners, triggering the intrinsic (mitochondrial) apoptosis pathway [190]. These BH3-only proteins are involved in multiple PCD pathways.

Promyelocytic leukemia protein (PML) is a tumor suppressor known to exist in multiple proteoforms generated by alternative splicing [191, 192]. There are six nuclear PML isoforms designated PMLI to PMLVI and one cytoplasmic isoform, PMLVIIb (also defined as PMLVII in some publications) [191]. Although these isoforms mostly differ in size and amino acid sequence of the C-terminal domain, they were shown to have different functional roles [193]. PML protein is widely recognized as the primary scaffold and driving force behind the assembly of PML-nuclear bodies (PML-NBs), which are polyfunctional dynamic protein organelles located in the nucleus of most cell types and serve as regulatory hubs for multiple cellular processes [194-196]. It was shown that all seven PML isoforms are capable of LLPS [197, 198]. PML-NBs are also implicated in leukemia and cancer pathogenesis [199, 200]. PML-NBs are structural hubs tied to the nuclear matrix that gather a remarkably diverse and disconnected set of proteins [200]. Curiously, a bioinformatics analysis of 205 proteins found in PML-NBs revealed that 85% of these proteins were predicted as moderately or highly disordered, and more than half of the proteins in the analyzed PML-NBome were capable of spontaneous LLPS [201].

It is difficult to underestimate the roles of LLPS in PCD, as phase separation acts as a crucial biophysical organizer, rapidly assembling and concentrating death-signaling molecules, transcription factors, and stress response proteins to execute precise cell fate decisions [202]. It seems that the formation of biomolecular condensates driven by LLPS represents a central, unifying mechanism across essentially all forms of PCD. This biophysical process orchestrates precise cell death signaling, as evidenced by related observations in the following pathways and systems: autophagy [203-205], ferroptosis [206-209], apoptosis [210-213], pyroptosis [214-216], necroptosis [217], parthanatos [218], NETosis [219, 220], cellular senescence [221-223], mitotic catastrophe [224], cuproptosis [225, 226], immunogenic cell death [227], lysosome-dependent cell death (LDCD) [228, 229], and PANoptosis [230].

CONCLUSION

It is clear that the focused analysis of IDPs, LLPS, and MLOs is critical to uncovering how cells orchestrate diverse forms of PCD. By deviating from traditional structure–function paradigms, IDPs and their phase-separated assemblies act as highly dynamic, responsive hubs that fine-tune cell survival and demise. In regulatory networks, LLPS directly modulates protein degradation and chaperone protection, either sequestering key factors to prevent premature death [202, 231-235] or concentrating them to accelerate killing cascades [202, 236, 237]. During the execution phase of PCD, these non-membrane-bound compartments physically compartmentalize and accelerate critical biochemical events [202, 238], including the mitochondrial outer membrane permeabilization (MOMP) cascade [227, 239, 240] and downstream caspase-mediated proteolytic cleavage [241-243]. Furthermore, MLOs act as spatial sensors that respond to environmental stressors [231], such as lipid peroxidation mechanics [244, 245], while also driving pattern recognition receptor (PRR) activation during immunogenic cell death [246-248]. Finally, the fluid, adaptable nature of these macromolecular condensates plays a vital role in autophagic vacuolization, serving as the organizational scaffolds required for cargo sorting and degrading damaged cellular components [203, 249-251]. Ultimately, decoding the biophysical principles of IDPs, LLPS, and MLOs provides a unified framework to understand how chaotic molecular signals are transformed into organized, definitive cell death decisions.

Broad involvement of IDPs, LLPS, and MLOs in PCD defines important paradigm, where the fluidity and dynamics strictly dictate the irreversible fate of the dying cell. In other words, it underscores important “fluidity written in stones” concept, where the rigid and unbreakable finality of cell death (i.e., “written in stones”, fixed, irreversible, and inevitable outcome) is governed by the “fluidity” (macromolecular dynamics) of IDPs, LLPS, and MLOs acting as the biophysical engines of cell death. Therefore, this concept reframes cell death from a rigid, fatalistic, binary “on/off switch” into a dynamic, highly regulated biochemical continuum of decreasing vitality.

Abbreviations

IDP	intrinsically disordered protein
IDR	intrinsically disordered regions
LLPS	liquid–liquid phase separation
MLO	membrane-less organelle
PCD	programmed cell death
PTM	posttranslational modification

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Ethics approval and consent to participate

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Conflict of interest

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