On the pervasiveness of dualistic thought in the cell death field: awareness and limitations

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Dichotomies are ubiquitous in all spheres of knowledge:
in and out, left and right, light and dark, whole and part, nature and culture, sacred and profane, software and hardware, absolute and relative,…

Life sciences are no exception to this rule with their antonymous concepts:
mind and body, normal and pathological, self and non-self, innate and acquired, soma and germline, structure and function,…

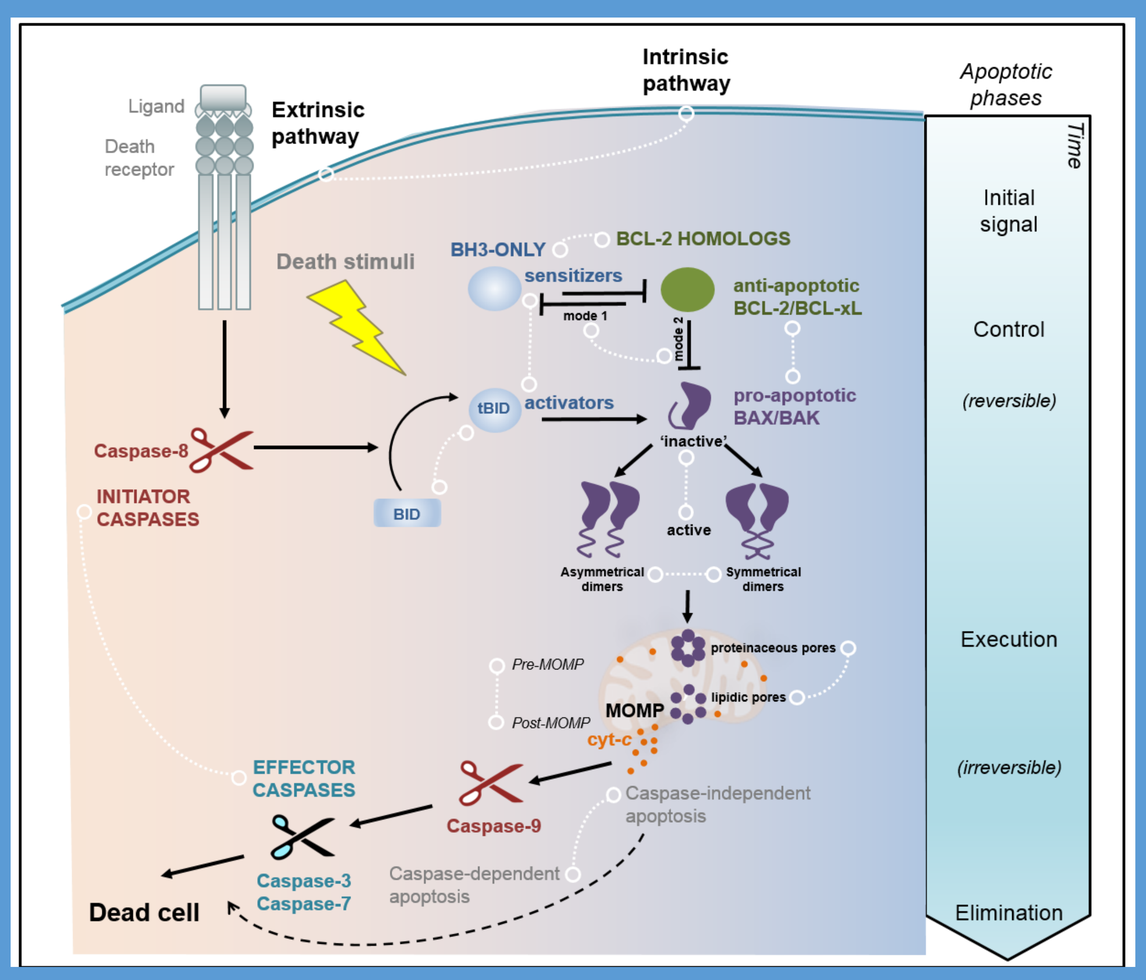
Scientific thinking often involves antithetical couples - G. Holton's Themata:
constancy and change, complexity and simplicity, reductionism and holism,…

Plato' d*iaeresis* (dichotomization) : a method for providing a full account of truth and reality.

However, most of the time, dualistic conceptions are a reflection of a fundamental feature of the psyche prompting us to think in **pairs of opposites, contraries and reverses.**

The epistemology of cell death, and particularly mitochondria-mediated apoptosis, arose from binary systems in the image of the primary life versus death opposition.

Instances of dualistic conceptions in the cell death field



Dichotomies in the representation of the main apoptosis pathways

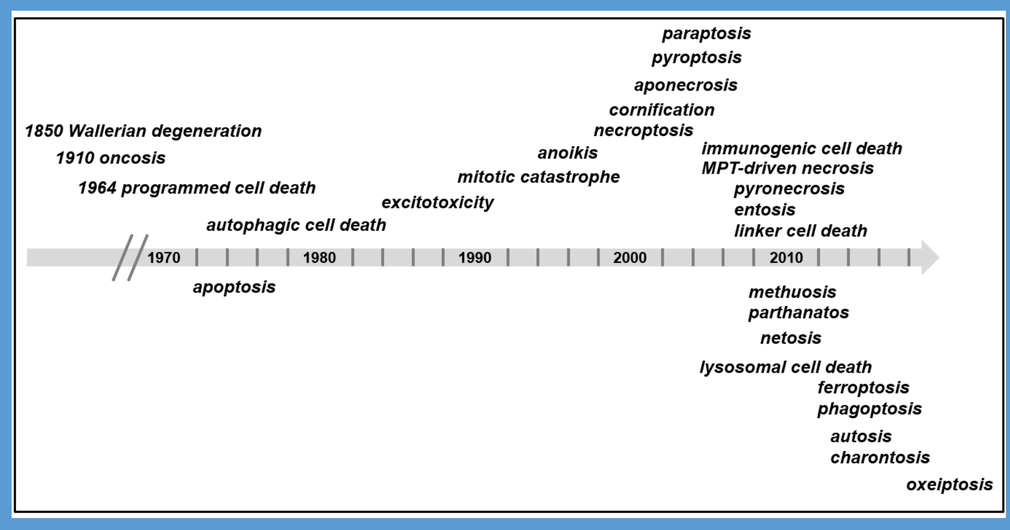
Dichotomies (A versus B)		Non-binary framework
Life (concept)	Death (concept)	Ambivalence of living, which integrates the fact of dying.
Cell survival	Cell death	Cell death as a vital process (i.e., occurring in living cells and crucial for organismal development, homeostasis, health, fitness and life span).
Developmental programmed cell death	Stress-induced cell death	Similar death effectors can be activated by both processes.
Apoptosis (active cell death, inside out)	Necrosis (passive cell death, outside in)	Apoptosis can be elicited by extracellular clues. Existence of intracellular machineries mediating programmed necrosis (necroptosis, pyroptosis, ferroptosis).
Proliferation	Cell death	Proliferative signals can be emitted by apoptotic cells (compensatory proliferation). Hyperproliferative cells (tumoral cells) are 'primed' for death.
Intrinsic (mitochondrial) apoptosis pathway / Type II cells	Extrinsic (death receptor) apoptosis pathway / Type I cells	Extrinsic and intrinsic apoptosis pathways can crosstalk through caspase-8-mediated cleavage of BID.
Reversible stage of apoptotic cell death	Irreversible stage of apoptotic cell death	Reversibility of apoptosis in various cancer cell lines and with different apoptotic stimuli.
Find-me signals	Eat-me signals	PS exposure occurs not only on the surface of apoptotic cells, but also on the surface of engulfing cells and cells undergoing other forms of cell death or fusion events.
Caspase-dependent	Caspase-independent	The notion of caspase-independent apoptosis (now falling into disuse) was probably linked to features associated with the merge of apoptotic and non-apoptotic death processes.
Pre-MOMP stage (temporal) / mitochondrial integrity (spatial)	Post-MOMP stage (temporal) / mitochondrial permeabilization (spatial)	Caspase activation and cell death can be inhibited after MOMP.
Mitochondrial fission	Mitochondrial fusion	Mitochondrial dynamics comprises not only fission, fusion but also mitophagy, mitochondrial biogenesis, mitochondrial movement and changes in the mitochondrial network.
Initiator caspases	Effector caspases	Initiator caspases (e.g. caspase-8) can act as effectors for several substrates.
Apoptotic caspases	Non-apoptotic caspases	Non-apoptotic roles of apoptotic caspases and non-apoptotic caspases may contribute to apoptosis.
Mitochondria as vital organelles / cytochrome c in energy production	Mitochondria as deadly organelles / cytochrome c in apoptosome formation	The death-related role of mitochondria is just one of many roles exerted by this organelle. Components of the mitochondrial apoptosis pathway have additional roles, other than regulating MOMP. Emerging role of ER-mitochondria contact sites.
Anti-apoptotic BCL-2 family members	Pro-apoptotic BCL-2 family members	Both anti- and pro-apoptotic BCL-2 family members phylogenetically derive from a same ancestral protein. Functional antagonism can be blurred as a result of proteolytic cleavage, binding to other partners, post-translational modifications, alternate splicing and according to cell type and context. Existence of non-apoptotic roles ('day-jobs') for BCL-2 homologous proteins and BH3-only / BH3-containing molecules
Multi-BH BCL-2 family proteins (with a globular helical bundle fold)	BH3-only proteins (intrinsically disordered)	BID is a bona fide BH3-only protein structurally homologous to BCL-2 and BAX. BH3 motifs can be found in proteins adopting a defined structural fold, different from the BCL-2 fold. Several BH3-containing proteins (e.g. ATR, TCTP) were reported to act as apoptosis inhibitors
Activator BH3-only proteins	Sensitizer BH3-only proteins	Activator BH3-only proteins are sensitizer BH3-only proteins able to bind BAX/BAK. Originally described as sensitizers, PUMA and NOXA were also shown to be activator BH3-only proteins. Most of the non-canonical BH3-containing proteins (n>40) are not included in the activator/sensitizer classification. BH3 motifs are inherently variable in sequence. Presence of membranes as well as regions outside the BH3 motif may change binding affinities. Need for quantitative measurements of the relative affinities in solution and in membrane environments.
Canonical BH3-binding groove	Non-canonical BH3-binding groove	Existence of multiple docking sites for BH3 motifs on globular proteins (including BCL-2-like and non-BCL-2-like proteins).
Direct models of BAX activation during apoptosis	Indirect models of BAX activation during apoptosis	Integrated models were proposed (unified, embedded together and hierarchical).
Mode 1 of action by BCL-2 proteins	Mode 2 of action by BCL-2 proteins	Mode 0 (BAX retro-translocation by pro-survival BCL-2 proteins at the mitochondrial surface). Mode 3 (degradation of the pro-apoptotic factor BOK). Existence of interactions with protein partners outside of the BCL-2 group.
'Inactive' BAX monomers	Membrane-active BAX oligomers	Non-apoptotic functions of BAX ('day-jobs').
BAX core (or piercing) domain / "BH3 in groove" model (BAX/BAK symmetric dimer)	BAX latch (or dimerization) domain / "Head-to-tail" model (asymmetrical assembly)	Enigmatic nature of the combined dimers and oligomers between BAX and BAK. Presence of lipids or additional proteins is currently unknown. Other models were proposed for the topology of active BAX dimers at the MOM (for instance the 'clamp-model').
BAX proteinaceous channel (barrel-stave model)	BAX proteolipidic pore (toroidal lipidic model)	Recent research converges on the idea that the BAX pore is of proteolipidic nature.
Life-specific structural determinants (or residues), e.g. the 'anti-apoptotic' BH4 motif, or K128 of BAX	Death-specific structural determinants (or residues), e.g. the BH3 'death' motif	Based on bioinformatics, BH4 and BH3 motif sequence signatures of pro- and anti-apoptotic BCL-2 proteins are not distinguishable. BCL-2 homologous proteins present individual specificities despite their similar fold. Impact of amino acid substitutions in mutated proteins do not necessarily reflect the biological role of the residue in the wild-type protein.

Binary opposites encountered in the field and counterexamples

But there have been numerous findings in the last decades that do not fit neatly into any simplistic dualist framework. **Three layers of complexity** can be uncovered.

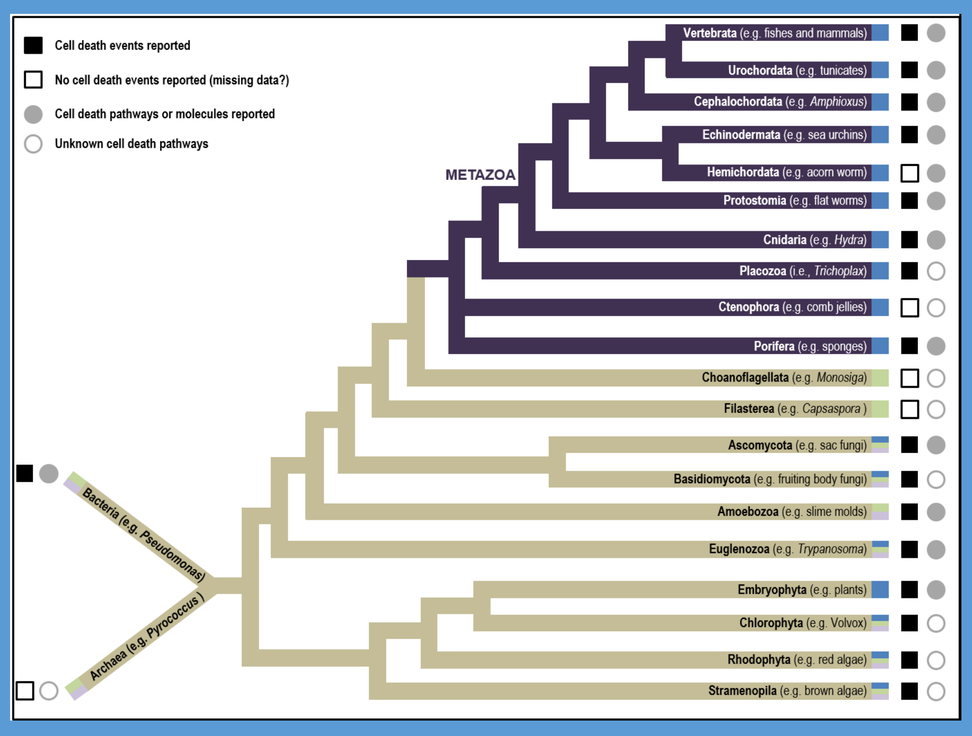
The limitations of dualistic conceptions of cell death

1. Multiple cell death mechanisms

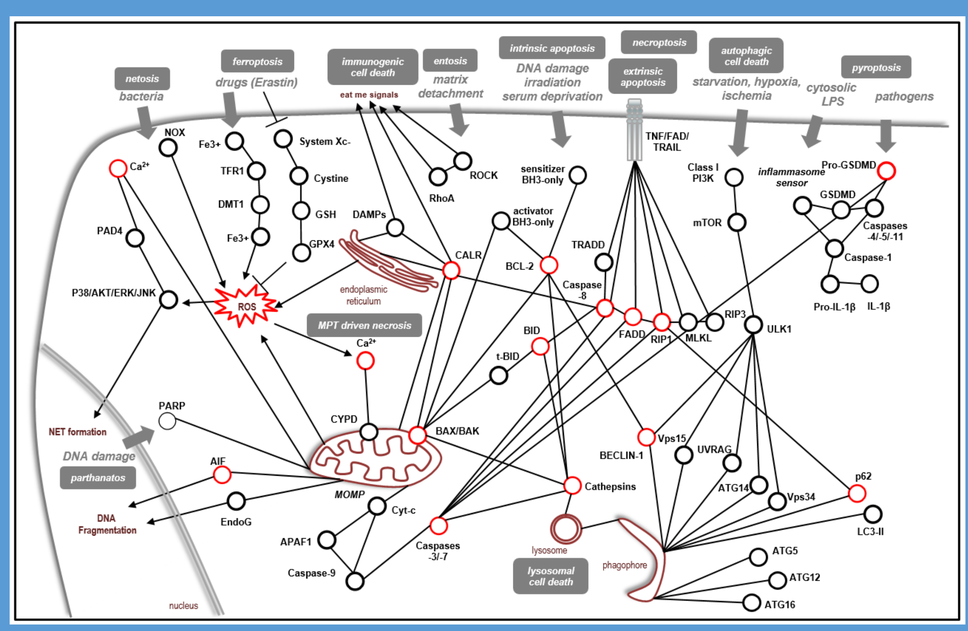


Timeline of different cell death modes in history of cell death research

2. Diversity of cell death-related factors

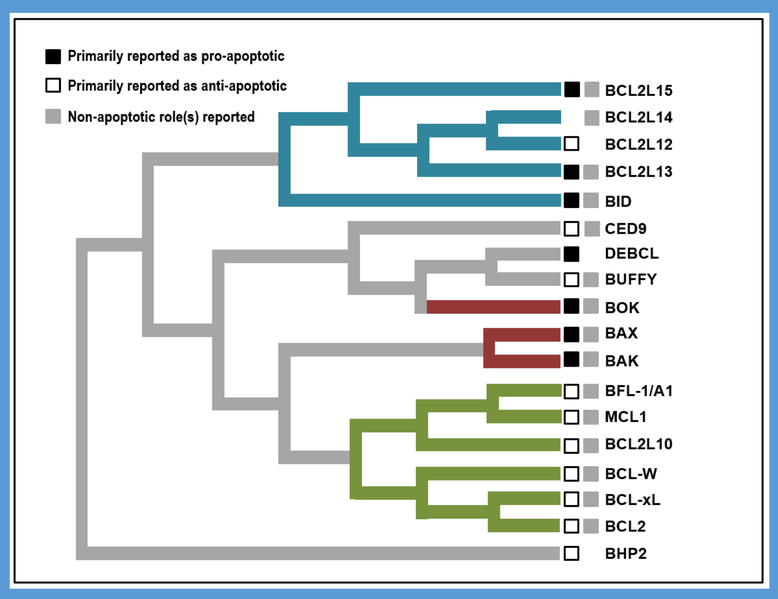


Cell death across the tree of life (phylogenetic diversity)



Diversity of molecular players implicated in cell death

3. Polyfunctional nature of the molecular players (pleiotropy)



Representative members of the BCL-2 family of homologs and their functions

Kerr and colleagues "*propose[d] [their] concept of apoptosis as a vital biological phenomenon*". This recognition of the ambivalence of living, which integrates the fact of dying, corresponds to a dialectical means to overcome the primary life-death dichotomy. The second and more important approach to overcome dual vision is to recognize the notion of multiplicity / diversity, passing this time not from 'two' to 'one', but from 'two' to 'three', then to 'four', etc., which amounts to opening a series. This form of 'metabiology of complexity' can be useful for articulating the relationships between structure and function of death-related proteins, between alternative cell death forms and between each cell death pathway and its own unique evolutionary history.