# Preface: Life through death—Key role of cellular suicide for colonial and organismal homeostasis

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The term "regulated cell death" (RCD) is commonly employed to indicate a form of cell death that is controlled by a dedicated molecular machinery, and hence can be modulated (at least to some degree) with specific pharmacological or genetic interventions (Galluzzi et al., 2015, 2018a). RCD can occur in the context of two diametrically opposed scenarios. On the one hand, RCD can represent the ultimate response of cells to microenvironmental perturbations that are excessively intense or prolonged for cells to adapt and recover homeostasis (Spetz et al., 2019). On the other hand, RCD can contribute to purely physiological programs of development and adult tissue homeostasis (Bock and Tait, 2020). The expression "programmed cell death" (PCD) is often used to refer to these latter variants of RCD that occur at a predetermined point in time, irrespective of potentially cytotoxic alterations of the intracellular or extracellular microenvironment (Fuchs and Steller, 2011, 2015).

For multicellular organisms, the advantages provided by genetically encoded programs for cell death are obvious. On the one hand, PCD can be harnessed as a morphogenetic mechanism that shapes first (and maintains then) tissue and organ architecture (Tuzlak et al., 2016). On the other hand, stress-driven RCD constitutes a robust mechanism for the elimination first (and replacement then) of postmitotic cells that are damaged beyond recovery, and hence functionless and/or prone to constitute a threat for the entire organism (e.g., prone to malignant transformation) (Cao and Tait, 2018). Less obvious are the advantages provided by RCD to unicellular organisms, such as bacteria and yeast. However, both prokaryotes and unicellular

eukaryotes have rudimentary RCD machineries that allow individual cells to suicide (Carmona-Gutierrez et al., 2018). This happens, as an example, when nutrients for the entire colony are limiting, and the demise of old cells increases the chances of younger, fitter cells to survive dwindling nutrient levels and ultimately reconstitute the colony (Fabrizio et al., 2004; Herker et al., 2004).

In higher eukaryotes, the molecular machinery for RCD has considerably diversified (Galluzzi et al., 2017a; Stockwell et al., 2017; Vanden Berghe et al., 2014; Weinlich et al., 2017) to enable variants of RCD that (1) occur according to diverse kinetics (Buque et al., 2019; Grootjans et al., 2016) and (2) are accompanied by the emission of specific signals that engage or suppress immune reactions (Galluzzi et al., 2017b; Rodriguez-Ruiz et al., 2019; Vanpouille-Box et al., 2018). Thus, dying mammalian cells can deliver signals in the form of damage-associated molecular patterns (DAMPs) or cytokines that are responsible for immune modulation at sites of active RCD (Galluzzi et al., 2018b; Green et al., 2009; Krysko et al., 2012). Many of the enzymes that have long been considered as pure RCD regulators, such as apoptotic caspases, have now been shown to mediate multipronged immunomodulatory functions (Galluzzi et al., 2016; Rodriguez-Ruiz et al., 2019; Rongvaux et al., 2014; White et al., 2014), and to support tissue regeneration, at least in some settings (Cheng et al., 2019; Huang et al., 2011; Ichim and Tait, 2016).

Given the key role of RCD in the maintenance of organismal homeostasis and the control of immune responses against dying cells, it is not surprising that deregulated RCD contributes to the pathology of a variety of human disorders. On the one hand, uncontrolled RCD associated with inflammatory reactions is involved in the pathogenesis of ischemic, cardiac, renal and neurodegenerative conditions, among others (Del Re et al., 2019; Fang et al., 2019; Hetz and Saxena, 2017; Kers et al., 2016; Quinlan et al., 2017). On the other hand, insufficient RCD (as such or in the context of immunosuppressive signaling) is etiologically linked to autoimmunity, proliferative syndromes, and cancer (Cao and Tait, 2018; Czabotar et al., 2014; Khan and Ghazanfar, 2018; Nagata and Tanaka, 2017; Singh et al., 2019; Spetz et al., 2019). In summary, RCD in its various forms stands out as a key mechanism for the preservation of colonial and organismal homeostasis, thus constituting an attractive target for the development of pharmacological interventions against a plethora of human disorders for more than 2 decades (Degterev et al., 2019; Huang and Ichikawa, 2008; Naderer and Fulcher, 2018; Valentin et al., 2018). As of today, however, very few drugs that target

the molecular machinery for RCD have successfully entered clinical development, including the BCL2 inhibitor venetoclax (currently approved for the therapy of some hematological tumors) (Jain et al., 2019), and the pan-caspase inhibitor emricasan (which was recently granted fast track status by the US Food and Drug Administration for the therapy of cirrhosis) (Mehta et al., 2018; Shiffman et al., 2019). It is tempting to speculate, yet remains to be formally demonstrated, that translating RCD modulation from the bench to the bedside has been difficult because RCD has been often investigated (especially when the molecular machinery for RCD has begun to emerge) irrespective of its immunological context.

In *Cell Death Regulation in Health and Disease* (a special issue of the *International Review of Cell and Molecular Biology* series) a group of world-renowned experts in the field gathered to discuss mechanistic features and physiopathological implications of RCD in a variety of model organisms. Each of the chapters of *Cell Death Regulation in Health and Disease* addresses a specific aspect of cell death biology, ranging from RCD control in prokaryotes and lower eukaryotes to the contribution of cell death deregulation to various human disorders. The book (which comes in three separate volumes, i.e., parts A, B, and C) is equally addressed to experienced investigators who may want to acquire in-depth insights into a specific aspect of cell death biology, as well as to students or neophytes who are moving their first steps in this broad field of research.

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## References

Bock, F.J., Tait, S.W.G., 2020. Mitochondria as multifaceted regulators of cell death. Nat. Rev. Mol. Cell Biol. 21, 85–100.

Buque, A., et al., 2019. Apoptotic caspases cut down the immunogenicity of radiation. Onco. Targets. Ther. 8 (11), e1655364.

Cao, K., Tait, S.W.G., 2018. Apoptosis and cancer: force awakens, phantom menace, or both? Int. Rev. Cell Mol. Biol. 337, 135–152.

Carmona-Gutierrez, D., et al., 2018. Guidelines and recommendations on yeast cell death nomenclature. Microb. Cell 5 (1), 4–31.

Cheng, J., et al., 2019. The caspase-3/PKCdelta/Akt/VEGF-A signaling pathway mediates tumor repopulation during radiotherapy. Clin. Cancer Res. 25 (12), 3732–3743.

Czabotar, P.E., et al., 2014. Control of apoptosis by the BCL-2 protein family: implications for physiology and therapy. Nat. Rev. Mol. Cell Biol. 15 (1), 49–63.

Degterev, A., et al., 2019. Targeting RIPK1 for the treatment of human diseases. Proc. Natl. Acad. Sci. U. S. A. 116 (20), 9714–9722.

Del Re, D.P., et al., 2019. Fundamental mechanisms of regulated cell death and implications for heart disease. Physiol. Rev. 99 (4), 1765–1817.

Fabrizio, P., et al., 2004. Superoxide is a mediator of an altruistic aging program in Saccharomyces cerevisiae. J. Cell Biol. 166 (7), 1055–1067.

Fang, X., et al., 2019. Ferroptosis as a target for protection against cardiomyopathy. Proc. Natl. Acad. Sci. U. S. A. 116 (7), 2672–2680.

Fuchs, Y., Steller, H., 2011. Programmed cell death in animal development and disease. Cell 147 (4), 742–758.

Fuchs, Y., Steller, H., 2015. Live to die another way: modes of programmed cell death and the signals emanating from dying cells. Nat. Rev. Mol. Cell Biol. 16 (6), 329–344.

Galluzzi, L., et al., 2015. Essential versus accessory aspects of cell death: recommendations of the NCCD 2015. Cell Death Differ. 22 (1), 58–73.

Galluzzi, L., et al., 2016. Caspases connect cell-death signaling to organismal homeostasis. Immunity 44 (2), 221–231.

Galluzzi, L., et al., 2017a. Necroptosis: mechanisms and relevance to disease. Annu. Rev. Pathol. 12, 103–130.

Galluzzi, L., et al., 2017b. Immunogenic cell death in cancer and infectious disease. Nat. Rev. Immunol. 17 (2), 97–111.

Galluzzi, L., et al., 2018a. Molecular mechanisms of cell death: recommendations of the nomenclature committee on cell death 2018. Cell Death Differ. 25 (3), 486–541.

Galluzzi, L., et al., 2018b. Linking cellular stress responses to systemic homeostasis. Nat. Rev. Mol. Cell Biol. 19 (11), 731–745.

Green, D.R., et al., 2009. Immunogenic and tolerogenic cell death. Nat. Rev. Immunol. 9 (5), 353–363.

Grootjans, S., et al., 2016. A real-time fluorometric method for the simultaneous detection of cell death type and rate. Nat. Protoc. 11 (8), 1444–1454.

Herker, E., et al., 2004. Chronological aging leads to apoptosis in yeast. J. Cell Biol. 164 (4), 501–507.

Hetz, C., Saxena, S., 2017. ER stress and the unfolded protein response in neurodegeneration. Nat. Rev. Neurol. 13 (8), 477–491.

Huang, D., Ichikawa, K., 2008. Drug discovery targeting apoptosis. Nat. Rev. Drug Discov. 7 (12), 1041.

Huang, Q., et al., 2011. Caspase 3-mediated stimulation of tumor cell repopulation during cancer radiotherapy. Nat. Med. 17 (7), 860–866.

Ichim, G., Tait, S.W., 2016. A fate worse than death: apoptosis as an oncogenic process. Nat. Rev. Cancer 16 (8), 539–548.

Jain, N., et al., 2019. Ibrutinib and venetoclax for first-line treatment of CLL. N. Engl. J. Med. 380 (22), 2095–2103.
Kers, J., et al., 2016. An overview of pathways of regulated necrosis in acute kidney injury. Semin. Nephrol. 36 (3), 139–152.
Khan, U., Ghazanfar, H., 2018. T lymphocytes and autoimmunity. Int. Rev. Cell Mol. Biol. 341, 125–168.
Krysko, D.V., et al., 2012. Immunogenic cell death and DAMPs in cancer therapy. Nat. Rev. Cancer 12 (12), 860–875.
Mehta, G., et al., 2018. A placebo-controlled, multicenter, double-blind, phase 2 randomized trial of the pan-caspase inhibitor emricasan in patients with acutely decompensated cirrhosis. J. Clin. Exp. Hepatol. 8 (3), 224–234.
Naderer, T., Fulcher, M.C., 2018. Targeting apoptosis pathways in infections. J. Leukoc. Biol. 103 (2), 275–285.
Nagata, S., Tanaka, M., 2017. Programmed cell death and the immune system. Nat. Rev. Immunol. 17 (5), 333–340.
Quinlan, S., et al., 2017. MicroRNAs in neurodegenerative diseases. Int. Rev. Cell Mol. Biol. 334, 309–343.
Rodriguez-Ruiz, M.E., et al., 2019. Apoptotic caspases inhibit abscopal responses to radiation and identify a new prognostic biomarker for breast cancer patients. Onco. Targets. Ther. 8 (11), e1655964.
Rongvaux, A., et al., 2014. Apoptotic caspases prevent the induction of type I interferons by mitochondrial DNA. Cell 159 (7), 1563–1577.
Shiffman, M., et al., 2019. Randomised clinical trial: emricasan versus placebo significantly decreases ALT and caspase 3/7 activation in subjects with non-alcoholic fatty liver disease. Aliment. Pharmacol. Ther. 49 (1), 64–73.
Singh, R., et al., 2019. Regulation of apoptosis in health and disease: the balancing act of BCL-2 family proteins. Nat. Rev. Mol. Cell Biol. 20 (3), 175–193.
Spetz, J., et al., 2019. T cells and regulated cell death: kill or be killed. Int. Rev. Cell Mol. Biol. 342, 27–71.
Stockwell, B.R., et al., 2017. Ferroptosis: a regulated cell death nexus linking metabolism, redox biology, and disease. Cell 171 (2), 273–285.
Tuzlak, S., et al., 2016. Interrogating the relevance of mitochondrial apoptosis for vertebrate development and postnatal tissue homeostasis. Genes Dev. 30 (19), 2133–2151.
Valentin, R., et al., 2018. The rise of apoptosis: targeting apoptosis in hematologic malignancies. Blood 132 (12), 1248–1264.
Vanden Berghe, T., et al., 2014. Regulated necrosis: the expanding network of non-apoptotic cell death pathways. Nat. Rev. Mol. Cell Biol. 15 (2), 135–147.
Vanpouille-Box, C., et al., 2018. Cytosolic DNA sensing in organismal tumor control. Cancer Cell 34 (3), 361–378.
Weinlich, R., et al., 2017. Necroptosis in development, inflammation and disease. Nat. Rev. Mol. Cell Biol. 18 (2), 127–136.
White, M.J., et al., 2014. Apoptotic caspases suppress mtDNA-induced STING-mediated type I IFN production. Cell 159 (7), 1549–1562.