

Cell death and the well of the organism

Gustavo P. Amarante-Mendes

Received: 20 January 2010 / Accepted: 20 January 2010 / Published online: 12 March 2010
© Springer Basel AG 2010

“People always say what we are looking for is a meaning for life...I don’t think that’s what we’re looking for. I think what we’re looking for is the experience of being alive.” Joseph Campbell.

In most cultures around the world, the concept of “Death” comes along with two other unpleasant words: “Disease” and “Sorrow”. Developmental biologists seem to view death in their own way: at the microscopic realm of multicellular organisms, the death of an individual or even a group of cells can be not only beneficial but often required for their proper development and then for the maintenance of the homeostasis during young and adult life. It is estimated that 50–70 billion cells die every day in a healthy adult human being due to constant cellular renewal that occurs in certain tissues, such as skin, intestine, and the hematopoietic system [1]. These numbers are so impressive that they may represent a total body weight of an individual every year, or the accumulation of 2 tons of bone marrow and lymph nodes and 16 km of intestine in an 80-year-old human being [2].

The physiologic form of cell death that we generally observed during development was first called “programmed cell death” (PCD) [3] and then “apoptosis” [4]. With time, PCD was proven to be controlled by an evolutionarily conserved molecular program. The discovery of the specific genes involved in the regulation of organ

development and programmed cell death in the nematode *C. elegans* awarded Sydney Brenner, John E. Sulston, and H. Robert Horvitz the Nobel Prize in Physiology or Medicine in 2002. Nowadays, we recognize many forms of cell death and fairly understand the central molecular mechanism that regulates them. Importantly, to avoid confusion in the literature, the Nomenclature Committee on Cell Death (NCCD) recently developed a guideline directed to authors, reviewers, and editors with recommendations for the use of terms related to the field of cell death [5]. The NCCD also proposed new criteria for the definition of the types of cell death.

In this issue of Cellular and Molecular Life Sciences, review articles will cover the classic and unconventional aspects of molecular pathways that control apoptosis, as well as other forms of cell death such as necrosis, pyroptosis, and death by autophagy. Vandenabeele and collaborators use the TNFR signaling to reveal the molecular switches involved in the control of survival, apoptosis, or necrosis. They highlight the interplay between RIP1, NF- κ B, and caspase activation to the outcome of TNFR signaling. Fimia and Piacentini focus their review on the molecular control of autophagy and discuss the implication of this process to either the preservation of cell viability or to the induction of cell death, in particular in the scenario of tumor cells. Ricci and collaborators explored the role of mitochondria in cell death and carefully review the control of mitochondrial outer membrane permeabilization (MOMP) by Bcl-2 family members. They underscore the importance of mitochondria in inducing (caspase-dependent) apoptosis and point out that mitochondria also have a role in what they call caspase-independent cell death (CICD). Autret and Martin, on the other hand, draw attention to another aspect of the mitochondrial physiology—the process of dynamic remodeling

G. P. Amarante-Mendes (✉)
Departamento de Imunologia, Instituto de Ciências Biomédicas,
Universidade de São Paulo, Av. Prof. Lineu Prestes, 1730,
Cidade Universitária, São Paulo, SP 05508-900, Brazil
e-mail: gpam@usp.br

G. P. Amarante-Mendes
Instituto de Investigação em Imunologia, Instituto Nacional de
Ciência e Tecnologia (INCT), São Paulo, Brazil

of their shape and number by fission and/or fusion and the consequence to survival and cell death. Borner and collaborators provide us with a comprehensive review on proteases involved in cell death and challenge us with their idea that non-caspase proteases are perhaps evolutionarily designed to amplify caspase-dependent apoptosis. Brumatti et al. explored the intersection between cytokine signaling and apoptosis and emphasize the role of growth factors in the homeostasis of hematopoietic cells. Weinlich et al. summarize the current knowledge of the posttranslational regulation of FasL, TNF- α , and TRAIL, and argue for a particular role of distribution, storage, and release of these death receptor ligands to the control of their activity. Bortoluci and Medzhitov call our attention to an important aspect of the host–parasite relationship—the control of infections by mechanisms of host cell death, in particular, pyroptosis and autophagy. They highlight the importance of compartmentalization of innate immune sensors such as the Toll-like and NOD-like receptors to the proper host response to parasites. Finally, Wanderley and Barcinski discuss the importance of programmed cell death in unicellular organisms and the role of what they call “apoptotic mimicry” to pathogen evasion of the host immune system.

In his philosophical view, Joseph Campbell said that we are not looking for a *meaning* for life but rather the *experience* of being alive. So, I ask myself: are we, as experimental biologists, constantly in search of knowledge about (human) nature, or is what we are doing in fact chasing the experience of *being* humans? In any case, together, this series of review articles provides an updated, profound, and broad knowledge of the molecular control of

cell death. I am confident that the reader will also find in between the lines enough material to experience the unique nature of the field of cell death.

References

1. Reed JC (1999) Dysregulation of apoptosis in cancer. *J Clin Oncol* 17:2941–2953
2. Hotchkiss RS, Strasser A, McDunn JE, Swanson PE (2009) Cell death. *N Eng J Med* 361:1570–1583
3. Lockshin RA, Williams CM (1964) Programmed cell death-II. Endocrine potentiation of the breakdown of the intersegmental muscles of silkworms. *J Insect Phys* 10:643–649
4. Kerr JF, Wyllie AH, Currie AR (1972) Apoptosis: a basic biological phenomenon with wide-ranging implications in tissue kinetics. *Br J Cancer* 26:239–257
5. Galluzzi L, Aaronson SA, Abrams J, Alnemri ES, Andrews DW, Baehrecke EH, Bazan NG, Blagosklonny MV, Blomgren K, Borner C, Bredesen DE, Brenner C, Castedo M, Cidlowski JA, Ciechanover A, Cohen GM, De Laurenzi V, De Maria R, Deshmukh M, Dynlacht BD, El-Deiry WS, Flavell RA, Fulda S, Garrido C, Golstein P, Gougeon ML, Green DR, Gronemeyer H, Hajnóczky G, Hardwick JM, Hengartner MO, Ichijo H, Jäättelä M, Kepp O, Kimchi A, Klionsky DJ, Knight RA, Kornbluth S, Kumar S, Levine B, Lipton SA, Lugli E, Madeo F, Malomi W, Marine JC, Martin SJ, Medema JP, Mehlen P, Melino G, Moll UM, Morselli E, Nagata S, Nicholson DW, Nicotera P, Nuñez G, Oren M, Penninger J, Pervaiz S, Peter ME, Piacentini M, Prehn JH, Puthalakath H, Rabinovich GA, Rizzuto R, Rodrigues CM, Rubinsztein DC, Rudel T, Scorrano L, Simon HU, Steller H, Tschopp J, Tsujimoto Y, Vandenabeele P, Vitale I, Voutsden KH, Youle RJ, Yuan J, Zhivotovsky B, Kroemer G (2009) Guidelines for the use and interpretation of assays for monitoring cell death in higher eukaryotes. *Cell Death Diff* 16:1093–1107