Cell Death and Differentiation (2016) 23, 913–914

www.nature.com/cdd

Editorial

Dying cell recognition shapes the pathophysiology of cell death

G Kroemer*,[1,2,3,4,5,6,7]

Cell Death and Differentiation (2016) **23,** 913–914; doi:10.1038/cdd.2016.30

A vast majority of the cell death research community has been focusing over decades on the mechanisms through which cells die, thereby providing profound insights into the biochemical pathways of distinct modalities of cellular demise. It is only relatively recent that a sizeable portion of the community realizes that perhaps the most important question of the area concerns the functional consequences of cell death.[1–3]

What are these possible consequences of cell death as they occur in tissues?

The first and perhaps the most trivial one is silent efferocytosis, meaning that the dying or dead cell (which mostly succumbed to an apoptotic program) is engulfed by its healthy neighbors or by professional phagocytes, allowing for removal of corpse without any inflammatory or immunological consequence. Thus, the tissue is cleared from potentially dangerous debris that might elicit unwarranted inflammatory and even autoimmune reactions.

The second possibility (which is nonexclusive with the first) is that the stressed and dying cell emits signals that stimulate its replacement. Such a mechanism of compensatory proliferation may be fundamental for tissue homeostasis. Would not it be a tragedy if a dying epithelial cell in the gut failed to be replaced, thus creating a breach in barrier function with consequent microbial invasion? At a low level, tissue repair induced by mitotic signals from stressed and dying cells occurs in an imperceptible manner, especially if cell death occurs in a scattered rather than in a focused manner.

As a third possibility, when cell death is massive or affects a large group of cells simultaneously at the same spot, it is accompanied by the release of danger-associated molecular patterns (DAMPs) that, beyond a certain concentration threshold, induce an inflammatory reaction, which usually resolves without any major deleterious consequences, leading to *restitutio ad integrum* (complete restoration to the original condition), but possibly also causes fibrosis (scars) or other types of chronic tissue damage due to smoldering or overt inflammation.

As a fourth option, cell death occurring in the context of neoantigens may stimulate immune responses. Such antigens may be introduced into the cells by infectious microorganism, reactivation of endogenous retroviruses, aberrant reexpression of genes that usually should be silenced or by mutation of coding sequences, as this often occurs in oncogenesis. Immune responses against dead-cell antigen result from a combination of antigenicity and adjuvanticity provided by DAMPs.[4–6]

As an overarching leitmotif, cell death hence has major consequences for normal tissue homeostasis, stress responses, inflammation and antimicrobial as well as anticancer immune responses, as this is clearly illustrated in this special issue of *Cell Death & Differentiation*. How can we link cell death then to pathophysiology? One possible answer to this question is to postulate a sort of combinational code (Figure 1) that determines the functional sequels of cell death.[1]

At a first level, it is important at which intensity (low/high?) and with which spatial distribution (scattered/focal?) cell death events occur. Moreover, the history of prior stress before death may be determinant for the functional outcome because stress can change the properties of the plasma membrane (for instance, due to endoplasmic stress-related exposure of calreticulin, CALR) or induce the production of chemoattractants (such as chemokines and prostaglandins) and interferons.[4,7–10] In this context, it is certainly important which cell type with its unique properties with regard to antigenicity, chemokine production patterns and adjuvanticity is concerned by the lethal event. The exact cell death mortality (apoptosis, necrosis, necroptosis etc.) certainly influences the recognition of corpses by phagocytes.[5] Nonetheless, the simple equation that apoptosis would be an anti-inflammatory and nonimmunogenic event, contrasting with necrosis that would be proinflammatory and potentially immunogenic, constitutes a hitherto inadmissible oversimplification.[6,11,12]

At a second level, the surface exposure and release of a vast collection of cell danger-associated molecular patterns (CDAMPs) shape the response to stressed, dying and dead cells. Such CDAMPs include an ever-expanding list of 'find-me' signals (also called chemotactic signals) that attract specific leukocyte populations,[13] 'keep-out' signals (also

[1]Equipe 11 labellisée Ligue contre le Cancer, Centre de Recherche des Cordeliers, Paris 75006, France; [2]INSERM U1138, Paris 75006, France; [3]Université Paris Descartes/Paris V, Sorbonne Paris Cité, Paris 75006, France; [4]Université Pierre et Marie Curie/Paris VI, Paris 75006, France; [5]Metabolomics and Cell Biology Platforms, Gustave Roussy Comprehensive Cancer Institute, Villejuif 94805, France; [6]Pôle de Biologie, Hôpital Européen Georges Pompidou, AP-HP, Paris 75015, France and [7]Department of Women's and Children's Health, Karolinska Institute, Karolinska University Hospital, Stockholm 17176, Sweden
*Corresponding author: G Kroemer, INSERM U1138, Centre de Recherche des Cordeliers, 15 Rue de l'École de Médecine, Paris F-75006, France. Tel: +33 1442 77667; Fax: +33 1442 77674; E-mail: kroemer@orange.fr

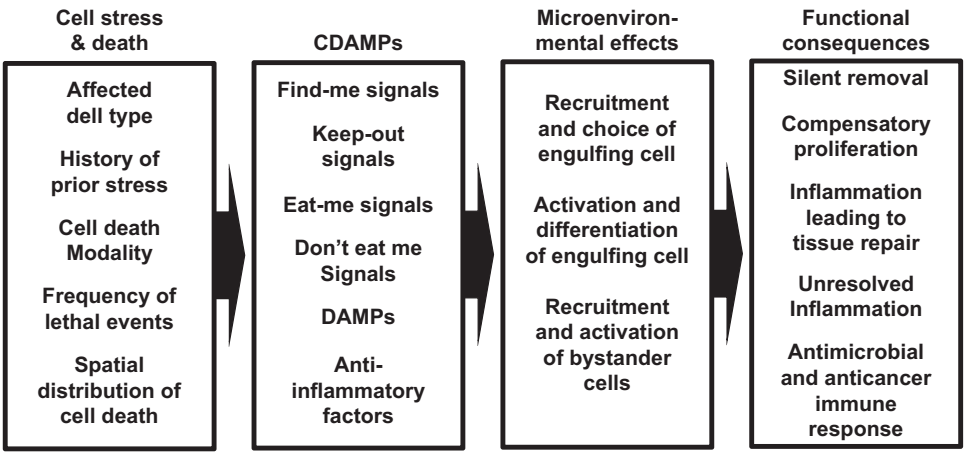

Figure 1 A combinational code linking cell death occurring in tissue to its functional outcome. For explanations, see text. CDAMP, cell danger-associated molecular pattern

called chemorepellents) that repel other leukocyte types, 'eat-me' signals that stimulate phagocytosis in different ways,[14,15] 'don't eat me' signals that avoid phagocytosis[15] and a collection of DAMPs that are often proteins or nucleic acids, which can only be fully released if the plasma membrane bursts,[6,11,12] as well as anti-inflammatory factors that mitigate local tissue reactions.[1,15] In a way, agonizing cells 'choose' by which phagocyte they will be engulfed, in which way their clearance will occur and what the consequences on the microenvironment will be.

Hence, at a third level, leukocytes come into play. Depending on the combinatory code of 'find-me' and 'keep-out' signals, either macrophages or dendritic cells (the latter likely with superior antigen presentation capacity, although this has been contested)[16] approach the dying or dead cell.[1,15] Depending on the properties of the plasma membrane of the dying cell (intact or not, with high or low lateral diffusibility of proteins, with changes in the glycocalyx and local ion gradients) and the combinatory code of 'eat-me' and 'don't eat me' signals, cells or portions thereof may then be taken through molecularly different pathways (phagocytosis, macropinocytosis etc.). Moreover, the DAMPs exposed on or released from dying cells determine the activation and differentiation of the engulfing cells (including M1/M2 polarity or maturation of dendritic cell precursors)[15–17] and the possible activation of bystander cells that participate to inflammatory and immunological reactions.[5,6]

Viewed in this manner (Figure 1), it is easily comprehensible that multiple distinct molecular pathways must contribute to normal organismal maintenance and the reestablishment of an equilibrium state after local or generalized tissue damage. Hence, mutations or alterations in the expression level of genes that affect cell death signaling cascades, as well as the optimal function of clearance systems (which likely involve many genes/proteins involved in autophagy as well),[18] may have deleterious consequences by causing overshooting responses (and hence autoinflammatory and autoimmune disease)[19] or their functional failure. In this way, deficient immunosurveillance leading to cancer[4,10] or persistent infection[20] may be attributed to suboptimal recognition of stressed and dying cells. However, the perplexing intricacy of the processes linking cell death to health and disease constitutes an ongoing challenge for the community of cell death researchers.

Conflict of Interest

The author declares no conflict of interest.

Acknowledgements. GK is supported by the Ligue contre le Cancer (équipe labelisée); Agence National de la Recherche (ANR) – Projets blancs; ANR under the frame of E-Rare-2, the ERA-Net for Research on Rare Diseases; Association pour la recherche sur le cancer (ARC); Cancéropôle Ile-de-France; Institut National du Cancer (INCa); Fondation Bettencourt-Schueller; Fondation de France; Fondation pour la Recherche Médicale (FRM); the European Commission (ArtForce); the European Research Council (ERC); the LabEx Immuno-Oncology; the SIRIC Stratified Oncology Cell DNA Repair and Tumor Immune Elimination (SOCRATE); the SIRIC Cancer Research and Personalized Medicine (CARPEM); and the Paris Alliance of Cancer Research Institutes (PACRI).

1. Zitvogel L, Kepp O, Kroemer G. *Cell* 2010; **140**: 798–804.
2. Galluzzi L *et al. Cell Death Differ* 2015; **22**: 58–73.
3. Arandjelovic S, Ravichandran KS. *Nat Immunol* 2015; **16**: 907–917.
4. Galluzzi L *et al. Cancer Cell* 2015; **28**: 690–714.
5. Green DR *et al. Nat Rev Immunol* 2009; **9**: 353–363.
6. Garg AD. *Cell Death Differ* 2016; in press (this issue).
7. Krysko DV. *Nat Rev Cancer* 2012; **12**: 860–875.
8. Kepp O *et al. Oncoimmunology* 2014; **3**: e955691.
9. Pol J. *Oncoimmunology* 2015; **4**: e1008866.
10. Garg AD. *Front Immunol* 2015; **6**: 588.
11. Maueröder C. *Cell Death Differ* 2016; in press (this issue).
12. Yamazaki T. *Cell Death Differ* 2016; in press (this issue).
13. Medina CB, Ravichandran KS. *Cell Death Differ* 2016; in press (this issue).
14. Nagata S. *Cell Death Differ* 2016; in press (this issue).
15. Birge RB. *Cell Death Differ* 2016; in press (this issue).
16. Larson S. *Cell Death Differ* 2016; in press (this issue).
17. Chen S. *Cell Death Differ* 2016; in press (this issue).
18. Green DR, Qguin TH, Martinez J. *Cell Death Differ* 2016; in press (this issue).
19. Scioriati C. *Cell Death Differ* 2016; in press (this issue).
20. Ucker DS. *Cell Death Differ* 2016; in press (this issue).