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Review

Cell death in disease: from 2010 onwards

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The strong interest in cell death, and the shift in emphasis from basic mechanisms to translational aspects fostered the launch last year of the new sister journal of *Cell Death and Differentiation*, named *Cell Death and Disease*, to reflect its stronger focus towards clinical applications. Here, we review that first year of activity, which reflects an enthusiastic response by the scientific community. On the basis of this, we now launch two novel initiatives, the start of a new section dedicated to cancer metabolism and the opening of a new editorial office in Shanghai.

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It is impossible to overstate the relevance of cell death research to human pathology. Compromised cell death pathways clearly contribute to proliferative diseases, and overactive death mechanisms are implicated in degenerative disease. In addition, cell death results from ischaemic episodes, and reducing ischaemic death correspondingly reduces the structural and functional deficits that follow, for example, myocardial and cerebral infarction. It is also likely that manipulation of the form of cell death that follows injuries such as ischaemia may also influence disease outcome. Thus, converting cell loss from a necrotic to an apoptotic phenotype will reduce the associated inflammation, resulting in a smaller final lesion and fewer clinical consequences.

In 1991, a mouse strain was serendipitously discovered for its resemblance to patients with the disease Systemic Lupus Erythematosus, that is, the mice showed a tendency to develop enlarged lymph nodes and spleens along with autoimmune diseases such as immune complex glomerulonephritis.[1] The mice, named *lpr* and *gld*, had mutations in CD95 (Fas, Apo-1) and CD95 L (FasL, Apo-1L), respectively. The lymphocytes from these mice proliferated normally in response to antigenic challenges, but they failed to be eliminated at the end of the immune response because of the mutation in the death receptor and its ligand (CD95 and CD95L) that impaired the ability to undergo apoptosis, resulting in an abnormal T-cell accumulation in the lymphoid tissues. Some of the lymphocytic clones triggered autoimmune diseases. Furthermore, the normal development of T cells was defective in these mice, with drastically reduced double positive mature T cells, which should normally express either CD4 or CD8 markers along with CD3 receptors for antigen. This was the first clear evidence of defects in the cell death machinery leading to immunological disease, both in mice and human. The molecular mechanisms regulating the activation of death receptors have now been analysed in detail, with their ubiquitylation[2–4] regulating cell fate.[5] In addition to elucidating the role of death receptors in inflammation and immunity, the improved understanding of these pathways opens novel therapeutic perspectives, which are only now beginning to be exploited in the clinic.

Cell death is crucial also for the development of malignancies. Here, the list of defective genes linked to the cell death machinery is long and well established, see, for example, the role of p53. This transcription factor regulates cell cycle as well as cell death.[6] Humans with defects in p53 (Li–Fraumeni syndrome) are cancer-prone. Loss of p53 function by gene mutation or other mechanisms of inactivation has been shown to be a characteristic of a large majority of human tumours, and many tumours also have lost genes whose products stabilize p53, such as ataxia telangiectasia mutated.[7–9]

DNA damage is normally detected in the nucleus by specific protein complexes, which then can induce cell cycle arrest and/or classic apoptosis via p53, or via its family members p73 or p63,[10,11] (Figure 1) and deregulation of these pathways leads to cancer progression. The stability of proteins of the p53 family is regulated by specific ubiquitin E3 ligases[12] and, correspondingly, inhibition of these E3 enzymes would stabilize the protein with enhancement of its activity. Thus, pharmacological methods for stabilizing the p53 family of transcription factors would seem to offer a potential therapeutic window (Figures 1b and c). Interestingly, in addition to classic apoptosis, the p53 family members are able to interact with components of the kinetochore complex such as BubR1,[13,14] affecting mitosis and leading to mitotic catastrophe. Of course, the p53 family, like other transcription factors, does not act in isolation at enhancer elements, but

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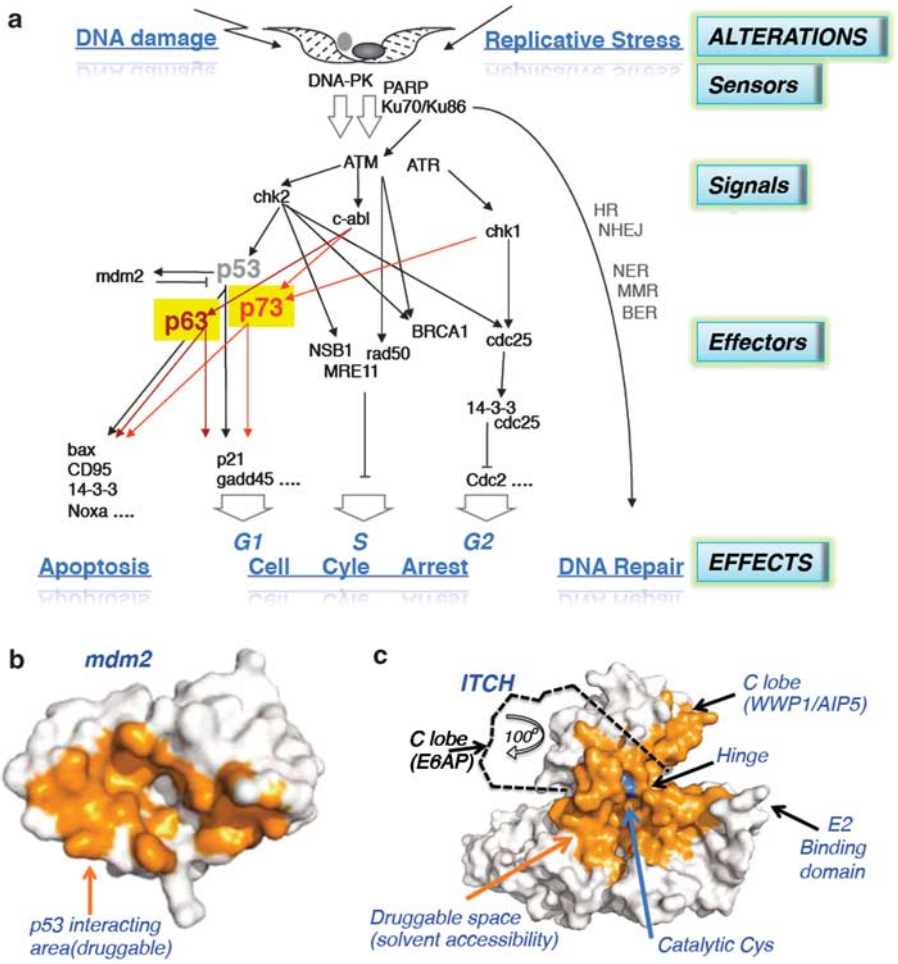

Figure 1 The p53 family in the DNA damage response and cell death regulation. (**a**) DNA damage and replicative stress can trigger a DNA damage response that involves the function of p53 to regulate cell cycle arrest or apoptosis. During the absence or functional inactivation of p53, the two p53 family members p63 and p73 can at least partially substitute this role through distinct upstream regulators, but with the same biological effect. (**b**) The protein stability of p53 is mainly regulated by mdm2, whose interaction with p53 can be inhibited by specific low molecular compounds, currently in clinical trials, leading to restoration of p53 steady state protein levels and function. (**c**) Similarly, the degradation of p63 and p73 is mainly regulated by the ubiquitin E3 ligase ITCH, which offers also a novel therapeutic target. ITCH, in mediating its activity, undergoes a conformational modification in the C-terminal portion (WWP1/AIP5 *versus* E6AP) in a specific hinge region

as a complex with other factors that may increase or reduce their transcriptional activity on specific targets. Unlike the vast literature devoted to p53 and its siblings, however, comparatively little attention has been focused on these cofactors, and a better understanding of how specific cofactors may act to enhance the apoptotic activity of p73 in cancers where p53 is inactive may provide other therapeutic opportunities.

Intrinsic cell death pathways exist in a state of dynamic equilibrium between pro- and anti-apoptotic elements. Death receptor signalling, for example, is inhibited by cFLIP, and activation of procaspase-9 within the apoptosome is restrained by X-IAP until Smac/DIABLO is released from damaged mitochondria. This inherent balance provides an opportunity for influencing death decisions both to enhance and to reduce cell death. In addition to these intrinsic factors, other extrinsic intracellular factors, such as the urocortins, can also powerfully influence the outcome of cell death stimuli.

So far, we have concentrated on the manipulation of apoptosis as a means of influencing pathology – what of necrotic death? It remains unclear how much of the necrosis that occurs, for example, in myocardial infarction, is a catastrophic and irreversible event, and how much occurs as programmed necrosis. The former would probably not be possible to target therapeutically, but the latter mechanism, once its molecular details are better understood, may provide potential therapeutic windows. Finally, in the panoply of cell death modalities, what is the contribution of autophagy to death pathologies – is it protective, and should we therefore promote it, or does it contribute to cell loss? Some evidence suggests that it is the severity and duration of the stimulus that determines this, and short stimuli, such as brief ischaemia, result in an autophagic process, which is protective by providing an intracellular source of nutrients. This, if not resulting in cell salvage, may allow less harmful apoptotic death to proceed instead of necrosis. Since we have hung up our Gilsons much more recently than when we began to help patients, we tend to compartmentalize cell death modes into neat academic entities, but in the real world of patients with cell death pathologies, it is likely these pathways overlap and

interact. As such, effective therapies will need to address all cell death subroutines.

Clearly, the study of cell death is pivotal to understand and manipulate disease processes,[15,16] and this was the scientific basis for launching last year a translational sister journal of *Cell Death and Differentiation* (CDD).

Cell Death and Disease, CDDIS, was launched in January 2010 as the first peer-reviewed open access online journal by Nature Publishing Group that publishes full-length papers, reviews and commentaries describing original research in the field of translational cell death. It seeks to promote diverse and integrated areas of Experimental and Internal Medicine in specialties such as cancer, immunity and neuroscience.

CDD is now in its eighteenth volume and, given the conventional 20-year time lag for the journey from bench to bedside, 2010 seemed an appropriate time to launch CDDIS. This reflects the fact that the academic Cell Death field has now become mature enough to contribute to the physiology and pathology field, a fact reflected in the growing interest in cell death by pharmacists and clinicians. Thus, a significant proportion of papers are focused on translational and therapeutic aspects, and therefore CDDIS seeks to encompass the breadth of translational implications of cell death, and topics of particular concentration will include, but are not limited to, the subspecialities highlighted above.

The original plan was to publish 30 papers in the first year. Instead the response by the scientific community was so positive that CDDIS has published over 100 papers in its first year of life. More important, this success has encouraged NPG to launch more new open access journals, and so now we are witnessing the birth of a number of scientific journals, all based on this novel experimental business model.

Data from Medline show that in 2010, a total of 23 611 papers have been published (compared with 5458 in 1995 or 2219 in 1990) in the area of cell death. By inputting the keywords 'cell death' and 'medicine', the search yields 5990 (25.4%) papers, while 'cell death' with 'cancer' yields 9306 (39.4%) papers, with 'neuron' 2313 (9.8%) papers, with 'heart' 1238 (5.2%) papers and with 'immunity' 1091 (4.6%) papers. See Table 1 for more details. In order to compare with a more basic interest, the total number of papers on 'cell death + caspases' reduced from 14.9% (2741 out of 18 517) to 12.0% (2838 out of 23 611), in 2005 and 2010, respectively. These numbers indicate both that the number of translational papers and those of a more general interest in cell death remains extremely high, and suggests that we are witnessing a shift in interest from basic molecular mechanisms to the manipulation of cell death in pathology.

Table 2 shows that CDDIS has followed this translational trend, publishing a significant number of papers equally distributed in the different sections.

How can we make CDDIS evolve in the right direction? Here, we propose two novel initiatives that we hope will be positive for CDDIS.

During the same time frame used above, 1995 *versus* 2010, matching 'cell death' with 'metabolism' shows a rise from 3012 to 17 284 (73.5%) papers. See also Table 1. More generally, the number of scientific papers on 'cancer metabolism' has increased from 16 924 in 1995 to the respectable number of 44 769 in 2010. For this reason, CDDIS has decided to immediately launch a new section of CDDIS dedicated to Cancer Metabolism. Christina Munoz-Pinedo will help us to achieve this aim.

An interesting new trend in recent years is the rise of high quality science in China and, indeed, several leading scientists have moved back from the United States and Europe to mainland China encouraged by the huge financial investment that has been put in place in China. Accordingly, in

Table 1 Number of papers published in the field of 'Cell Death'

Year	1990	1995	2000	2005	2010
CD+cancer	593	1668	4161	6846	9306
CD+medicine	486	1197	3260	4897	5990
CD+neuron	221	684	1566	2108	2313
CD+heart	161	211	555	875	1238
CD+immunity	67	305	601	898	1091
CD+metabolism	690	2583	8157	13 556	17 394
CD	2219	5458	12 513	18 517	23 611
Autophagy	29	29	70	261	1823

Abbreviation: CD, cell death Data from Medline/Pubmed

Table 2 Sections in CDDIS

	References
Experimental medicine	
Micro-RNA	17–21
HIV, coxackie	22,23
Leishmania, malaria	24,25
Diabetes	26
Eye, glaucoma	27,28
Mammary development	29
Stemness	18,30,31,32
Cancer	
Autophagy	33–42
P53 family	43–49
Bcl2 family	31,50–53
Melanoma	33,54
Nasopharyngeal carcinoma, mesothelioma	17,55,56
Leukaemia	57–60
Prostate cancer	20, 34,61
Glioma	62,63
Tumour markers/treatment	64–70
Histone deacetylase	71
Immunity	
Death receptors	72–76
Caspases	56,77,78
NF-kB/JNK	79–84
T cells	85,86
Autoimmunity	51
Cytokines	87,88
Mast cells, macrophages	87,89
Internal medicine	
Steatosis	90
Ear nose throat	91
Autism	92
Cardiac defects	93
Infertility	21
Skin	45,46,48,49
Aging, senescence	94–101
Neuroscience	
Neurodegeneration	19,43,98,102–119
Mitochondrial dysfunctions	36,42,105,120,121
Nitric oxide, NMDA	122,123
Hypoxia-ischaemia	36,90,124

May of this year CDDIS organized a scientific meeting in Shanghai in the presence of several members of the Editorial board, including Andreas Strasser, Tak W Mak, Martin Bushell, Xin Lu, Doug R Green, Yufang Shi and both of us. To reflect the increase in high quality scientific output from China, and the global influence this will have in the future, we are opening a new Editorial Office in Shanghai, headed by Yufang Shi.

We hope that these novel initiatives will help us to build on a successful first 18 months and to reach a wider international audience. Our goal, as always, is to provide a satisfying and stimulating forum of knowledge exchange, particularly for those seeking to exploit basic cell death research in the clinic as well as for those more interested in how cell death modalities relate to disease rather than in the molecular complexities of the pathways involved.

Conflict of Interest

The authors declare no conflict of interest.

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