Janus a God with two faces: Death and Survival utilise same mechanisms conserved by evolution

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During the last two decades there has been a growing interest in the mechanisms which regulate cell death. The main conceptual advance, which fostered the progress in researching cell death, has been the understanding that genetically encoded programmes decide upon cell fate {Ellis, 1986 #13}.

True unicellular organisms, however, might have hardly developed specialized death programmes that would lead to their elimination. Nonetheless, the propagation and evolution based on simple cell division required extinction of unfit cells and selection of those endowed with environmental adaptation. For that reason in initial life forms death must have been a simple consequence of environmental injury when cell demise resulted from the inefficiency of survival mechanisms to cope with exogenous stressors. As evolution progressed, either as a result of a vertical selection or as a consequence of horizontal gene transmission {Goldenfeld, 2007 #21; Vetsigian, 2006 #22}, new survival pathways and protective mechanisms developed and therefore a system of potential multiple failures instigated the appearance of several death pathways. As more altruistic functions have developed first in unicellular agglomerates (Ameisen JC Cell Death Differ. 2002 Apr;9(4):367-93.) and ten in multicellular organisms, death and survival programs begun to diverge to assist cell differentiation and accomplish tissue homeostasis. The most obvious example of a primordial death mechanism would be the failure of ion homeostasis (i.e. sodium and calcium) when the harshest environmental conditions applied a tight control of ion compartmentalisation between the intra- and extracellular space. These mechanisms of cell and tissue damage are still operative today from simple organisms (e.g. *C. elegans*) to mammalian cells. In the latter both Ca^{2+} and Na^+ overloads are

one of the major causes of tissue damage upon, for example, stroke and myocardial infarction. As tissue plasticity and remodelling became a fundamental step in evolution of complex organisms, biochemical programmes involving complex cascades leading to cell disassembly have also developed.

It is universally acknowledged that well known death programmes like, for example, apoptosis include biochemical cascades that are triggered by genetically controlled signalling steps. Indeed, the genetic control is probably restricted to the process of asymmetric division, which decides the fate of each and every daughter cell. The actual machinery involved in cell death execution is constitutively expressed in virtually all cells. This implies its conservation from selfish individual cells to altruistic uni- and multicellular organisms. To explain the apparent dichotomy, the death machinery as such, must have been initially conserved because of its survival roles.

Imbalances in Ca^{2+} are the most trivial examples of death routines using physiological signalling systems. Calcium was the first to be recognised as a ubiquitous trigger of cell death in the myocardium {Fleckenstein, 1974 #9}; later the detrimental role of disrupted Ca^{2+} signalling was recognised for many tissues and cell types {Siesjo, 1989 #15; Orrenius, 1994 #14; Trump, 1995 #16;Choi, 1995 #17}. Importantly, deregulation of Ca^{2+} signalling is involved in many types of cell death: it triggers excitotoxicity in neurones and myocytes, it initiates apoptosis in many excitable and non-excitable tissues, and it of course acts as the most important activator and executor of necrotic cell death {Orrenius, 2003 #11}. All these death subroutines use existing molecular systems, which are responsible for physiological Ca^{2+} signalling.

Similarly, several members of the caspase family of protease, which are involved in signallinga and execution of apoptosis, have physiological roles,which involve their proteolytic functions, but also signals mediated through their prodomains {Lamkanfi, 2007 #12}. Phylogenetic analyses, and also studies of substrate specificity, indicate that human caspases can be subdivided into three different groups, one of which (caspases 1, 4 and 5) is not involved in programmed cell death, but in inflammation. This suggested that this family originated for a distinct function. This was finally evident with the identification of para-caspases and meta-caspases in lower organisms, and also by the fact that viruses learned to regulated cell death, for example via CrmA a p35, first identified by Lois Miller in 1991 in baculovirus (*Autographa californica*). For a more detailed evaluation, please see the recent special issue of CDD {Kumar, 2006 #31; Kumar, 2007 #23;Rozan, 2007 #24;Martinon, 2007 #25;Scott, 2007 #26;Lamkanfi, 2007 #27;Bao, 2007 #28;Timmer, 2007 #29;Callus, 2007 #30}. Similar considerations apply to other protease families e.g. calpains, which normally bear a variety of physiological functions, but are also involved in promotion and progression of cell death.

The duality of survival/death signals is well exemplified by the pancreatic acinar cell, a classical model for studies of protein synthesis and secretion. Here frequency encoded signals are essential to differentiate death or survival routines. Short-lasting, repetitive $[Ca^{2+}]_i$ spikes - confined to the apical granular pole - control exocytotic secretion of digestive enzymes and ion channel opening regulating fluid secretion {Petersen, 2005 #18}. On the other hand, prolonged global $[Ca^{2+}]_i$ elevations induced by, for example, bile acids or alcohol metabolites cause intracellular digestive enzyme

activation, vacuole formation and ultimately necrosis giving rise to the often fatal human disease acute pancreatitis in which the pancreas digests itself and its surroundings {Petersen, 2006 #19}.

It is remarkable that the same fundamental dualism in the survival/death signals is also utilised on a tissue and organism level. Indeed many cells, which are essential for the homeostasis of various tissues, employ the same mechanisms to ensure survival or deliver death to unfit partners. For example glial cells, which normally act as wardens and guardians of brain homeostasis, also ensure the removal of redundant neurones. Brain insults trigger reactive gliosis, which is a well conserved defence reaction; stronger insults however turn reactive glia into natural killers of neurones {Giaume, 2007 #20}. By this mechanism glia saves the whole tissue at the expense of its injured part.

The necessity of accommodating tissue differentiation patterns has also led to diversification of death routines: while the most fundamental death mechanisms are equal in all cells some are tissue-specific. Emergence of multiple death pathways is also evolutionary justified as a single and common death mechanism would have been easily hijacked by opportunistic parasitic organisms. It is therefore not surprising that death and life are entwined and the understanding of death mechanisms could lead to fundamental improvement of our knowledge of survival and protection, and therefore on occurrence and prevention of diseases. These guiding concepts have inspired the articles presented in this issue of *Cell Death & Differentiation*. [PLEASE ADD ALL References of this special issue!!!]

This collection of reviews, dealing with mechanisms of cells and tissue damage and repair, is based on the invited lectures given at an international conference on this broad topic. This conference, which was organized jointly by Academia Europaea and The Klaus Tschira Foundation, took place in Heidelberg, Germany in March 2007 (Fig 1).

References

Figure legend - list of participants

Figure 1.
Photo of the participants in the meeting held at the Klaus Tschira Foundation, Heidelberg, Germany, 1st to 3rd of March 2007.
First row: