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Editorial Open Access

An Escalation in the Recognition of Cell Death Pathways

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The research focused on cell death is very fascinating and involves many groups aiming at identifying the multiple factors regulating this "ultimate" process. After the observation of dead cell morphology by the first basic microscopes, the development of more sophisticated techniques allowed to decipher the molecular elements involved in cell death and to manage them in order to impede or enforce this process.

The best characterized type of cell death is apoptosis, which is regulated in a programmed way and occurs through a cascade of biochemical reactions [1]. Apoptosis evasion has been considered for longtime the major determinant of the resistance of cancer cells to chemo/radiotherapy [2]. With this concept in mind, many attempts to restore the apoptotic potential of cancer cells by stimulating the death effectors have been made [3]. However, this strategy was not totally successful, given that cancer cells could develop alternative routes to survive [4].

In this respect, great attention was paid to autophagy, a catabolic process routinely leading to the degradation of damaged organelles and/or misfolded/aggregated proteins under stress or nutrient deprivation conditions [5]. As a consequence of the autophagic reactions, new energetic pools are generated [6], which can provide an unwanted and dangerous fuel to cancer cells, thus promoting cancer cell proliferation and sustaining drug resistance [7,8]. In this view, autophagy manipulation in order to impede energy implementation in cancer cells is desirable [9,10]; however, this approach could cause deleterious effects, given that in some instances (*e.g.* sustained nutrient deprivation or stress) autophagy could act as a real form of death, thus a potential killer of cancer cells [11-13].

The scenario of cell death mechanisms became more and more complicated. Other forms have been described after drug treatment, characterized by some features reminiscent of apoptosis (caspase-independent apoptosis) [14] and/or regulated by mitochondrial factors, including the apoptosis inducing factor AIF (parthanatos) [15].

Although the detailed molecular pathways of these processes have been only partially depicted, it appeared that distinct forms of death are interconnected (see for example the impact of autophagy on other cell death paradigms [16]), being some factors crucial players in more than one form of death [7-9]. Of note, different forms of cell death could share a common feature, that is the synthesis and accumulation of poly(ADP-ribose), which acts (with largely unknown modalities) as a signaling molecule to drive different pathways [17,18].

Moreover, the dogma of the "accidental" nature of necrosis has been recently revisited, providing the evidence that a "programmed" necrosis often mediated by TNF-α and named necroptosis, exists [19]. Once more, this paradigm of cell death shares some features with other death pathways, thus adding a further level of complexity to the elucidation of the effect of a single death subroutine on cell metabolism [20,21].

In addition to the above described, widely recognized types of cell death, other "minor" processes leading to the elimination of cells have been described. Among them, methuosis represents a peculiar mode of cell dismantling, going through cytoplasmic vacuolization and involving essentially macropinosomes [22]. The recently coined term autosis refers to a special form of autophagy where perinuclear swelling is visible [23]. Caspase-1 dependent pyroptosis takes place in response to inflammation coupled with microbial infection [24], while an iron dependent, non-apoptotic cell death has been described as ferroptosis [25]. In general, anoikis designes the process occurring when cancer cells detach from the extracellular matrix and survive, thus being able to migrate, invade tissues and give metastases [26].

For decades, essentially two death types were described, that are apoptosis and necrosis; despite of this apparently simple situation, a Committee on the Nomenclature of Cell Death was set up by the Society of Toxicologic Pathologists in order to making recommendations useful to avoid confusion between the hallmarks of each process [27].

To face the increasing number of terms related to cell death, in 2009 a Nomenclature Committee on Cell Death (NCCD) published ad hoc recommendations with the scope to provide the scientific community with a set of parameters (essentially morphological) distinctive of each form of cell death [28]. During the following few years, a number of pathways leading to cell death were identified, as well as a lot of reports on their regulation were published, making necessary a further revision of nomenclature. In 2012, NCDD focused on the molecular and biochemical features leading to the classification of cell death paradigms [29].

The actual situation is well represented by the chaotic scenario of the Tower of Babel, where the researchers working on cell death modalities confound their language, sometimes impeding to understand the words of the colleagues [30]. A further classification of cell death is now required in order to define specific parameters for each pathway; this approach has been already used for autophagy, which does not occur in a univocal way. In fact, to establish a series of criteria allowing the definition of autophagy, in 2008 the Editor-in-Chief of the Journal Autophagy, Professor Daniel Klionsky (University of Michigan) involved about 240 scientists in editing the "Guidelines for the use and interpretation of assays for monitoring autophagy", a very helpful handbook for the scientific community [31]. The growing interest towards autophagy prompted Professor Klionsky to revise the previous Guidelines in 2012 [32], publishing a paper signed by about 5 times more authors than in 2008, which "has already been cited over 1,900 times in less than 2 years" (Klionsky, personal communication). Now, an update of this paper is incoming.

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In conclusion, from the huge body of literature it appears that cell death is an exciting matter of research!

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