

Defective Apoptosis and Efficient Autophagy: Two Ways to Protect Cancer Cells from Death

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Editorial

Cancer cells often display resistance to conventional therapies, possibly mediated by an inefficient ability to undergo apoptosis [1,2]; in fact, apoptotic pathways may be significantly altered in cancer cells [3]. Thus, a major objective in cancer research is to succeed in reactivating the apoptotic machinery [4], exploiting the defects in this pathway for the development of new strategies to overcome uncontrolled cancer cell proliferation and migration [5].

Caspases, for example, the key players in protein and DNA degradation during the apoptotic program, are often inactivated in cancer cells [6], thus representing a good target for anticancer therapies. Caspases are present within the cell as pro-caspases, regulated by upstream endogenous factors, i.e. IAPs (Inhibitors of Apoptosis Proteins), which are in charge for keeping caspases inactive unless required. IAP overexpression/overactivation occurs in cancer cells, possibly being responsible for contrasting apoptosis [7]; for this reason, their inhibition could represent a goal for the treatment of cancer [8-10]. This strategy has been already applied to the IAP survivin, which is not expressed in normal cells and is overexpressed in the majority of human cancers [11], thus being attractive to selectively increase the susceptibility of cancer cells to apoptosis-based approaches preserving the viability of non-neoplastic tissues [12,13]. Different approaches have been used to downregulate survivin, including molecular antagonists, hammerhead ribozymes, anti-sense oligonucleotides, small interfering RNAs and gene therapy [11,14]. Some survivin inhibitors entered phase I-II clinical trials (<http://clinicaltrials.gov/ct2/results?term=survivin>). However, despite the promising effects of survivin inhibitors in reducing tumor growth, increasing apoptotic response and sensitizing cancer cells to therapy without heavy side effects, a more careful characterization of its functions other than caspase inhibition is desirable [11].

An active involvement of autophagy in protecting cancer cells from death has been recently reported [15]. Basically, autophagy has a protective function in many cellular stress conditions, being able to counteract nutrient deprivation by recycling energy through macromolecule degradation [16]. The so-called autophagy paradox is based on the opposite role in i) homeostasis control under stress conditions; ii) protection of cancer cell dynamics by eliminating DNA and organelles damaged by anti-cancer therapy, thus ensuring cancer cell survival [17]. In the latter context, autophagy has a very dangerous function, so its inhibition could block the fuel necessary for sustaining uncontrolled proliferation and possibly re-sensitize cancer cells to apoptogenic stimuli driven by chemo/radiotherapy [18]. As for the possible modulation of autophagy, the best target is mTOR, a serine/threonine protein kinase belonging to the PI3K/Akt family acting as upstream autophagy regulator; a strategy based on rapalogs, which includes the mTOR inhibitor rapamycin and its analogues, has been developed [19] and currently applied in a number of clinical trials (<http://clinicaltrials.gov/ct2/results?term=autophagy>). Nevertheless, it could be deleterious to block autophagy, because of the effects on the contribution of autophagy to the correct metabolism of normal cells [20].

The paper from Boya et al. [21], showing that autophagy may be cytoprotective in nutrient-depleted cells, and that autophagy inhibition triggers apoptosis, stimulated the work of many groups. Accumulating evidence supports the existence of cross talk between autophagy and apoptosis [22,23], which is so intricate that it requires an accurate deciphering of the key signals. As a cautionary note, it has to be reminded that the final outcome of the autophagic process is not univocal, depending on the cell type, the stimulus a cell has to face and the ability to evade or not apoptosis in response to drug treatment. In fact, it has been shown that apoptosis-resistant cancer cells can be killed through enforced autophagy, which acts in this case as Programmed Cell Death type II [17,20,24] either by cooperating with other cell death mechanisms or murdering cells by itself [24].

On the whole, the above described approaches represent the new challenge in cancer research, aiming at beating cancer through the identification of molecular targets playing a crucial role in drug resistance. The canonical idea of stimulating silent apoptosis is now paralleled by the innovative concept that modulation of autophagy could be beneficial to sensitize cancer cells to the therapy. Several still unanswered questions need further work to identify the complex interconnection between these processes.

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