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Mini Review

Cell death pathology: Cross-talk with autophagy and its clinical implications

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ABSTRACT

Autophagy is a self-digesting mechanism that cells adopt to respond to stressful stimuli. Morphologically, cells dying by autophagy show multiple cytoplasmic double-membraned vacuoles, and, if prolonged, autophagy can lead to cell death, "autophagic cell death". Thus, autophagy can act both as a temporary protective mechanism during a brief stressful episode and be a mode of cell death in its own right. In this mini-review we focus on recent knowledge concerning the connection between autophagy and programmed cell death, evaluating their possible implications for therapy in pathologies like cancer and neurodegeneration.

1. Introduction

Autophagy is a physiological self digestive process which is involved in the degradation of damaged proteins and intracellular organelles [1]. Under specific stress circumstances, however, autophagy contributes to the regulation of proliferation, differentiation and cell death. During autophagy, cytoplasmic proteins, organelles and other cellular components are surrounded by autophagosomes, which form autolysosomes by fusing with lysosomes, resulting in the degradation of these components by resident hydrolases. The link between autophagy and cell death is demonstrated at the molecular level, for example, by the physical interaction between Bcl2 and Beclin-1 [2], however at the functional level it is still somewhat controversial. Autophagy undoubtedly enhances cell survival in response to nutrient deprivation, but dying cells often display accumulation of autophagosomes, and sustained autophagy can lead to cell death.

The molecular basis of autophagy was initially characterised in yeast in which at least 15 autophagy related genes (ATG) have been identified; subsequently their mammalian counterparts have also been characterised (Fig. 1) [3]. While other reviews describe the molecular pathways of autophagy in detail, here we would like to draw attention to the fact that knockout and knockdown of Atg proteins enhances cell death induced by starvation and growth factor withdrawal (Fig. 1), but in other situations inhibition of autophagy maintains cellular viability [4–11]. The finding of vesicular accumulation in dying cells has led to the concept of autophagic cell death (ACD). ACD is defined morphologically as a type of cell death that occurs in the absence of chromatin condensation and with a large degree of vacuolization of the cytoplasm. ACD does not necessarily imply that the cell death occurs by autophagy, but that death occurs concurrently with morphological features of autophagy. Thus, if cell death occurs only in parallel with autophagic features, inhibition of autophagy does not alter cell fate, while when autophagy is the crucial effector mechanism of cell death, its inhibition determines cell fate. Therefore the current definition of ACD has an important limitation in that it fails to establish the necessary role of autophagy in the cell death process, and thus contributes to the confusion in the literature regarding the role of autophagy in cell death and cell survival.

2. Cross-talk between autophagy and cell death

Increasing evidence is now accumulating on the crosstalk between apoptotic and autophagy pathways. A key regulator of autophagy initiation is the mammalian orthologue of the yeast Atg6, Beclin 1 (Bec1), that forms part of the class III phosphatidylinositol 3-kinase (PI3K) complex [12]. The anti-apoptotic protein Bcl-2 was the first to be identified of an increasing number of Bec1-interacting proteins. The dissociation of Bec1 from Bcl-2 is essential for its autophagic activity, and Bcl-2 only inhibits autophagy when it is present in the endoplasmic reticulum (ER) (Fig. 2) [2,13–15]. A similar interaction has also been described for the Bcl-2 homologue, Bcl-XL [16]. Bec1 has also been shown to be one direct caspase substrate among the large number of caspase targets [17,18]. Caspase-mediated cleavage of Bec1 results in the loss of its

Abbreviations: ATGS, autophagy related genes; ACD, autophagic cell death.

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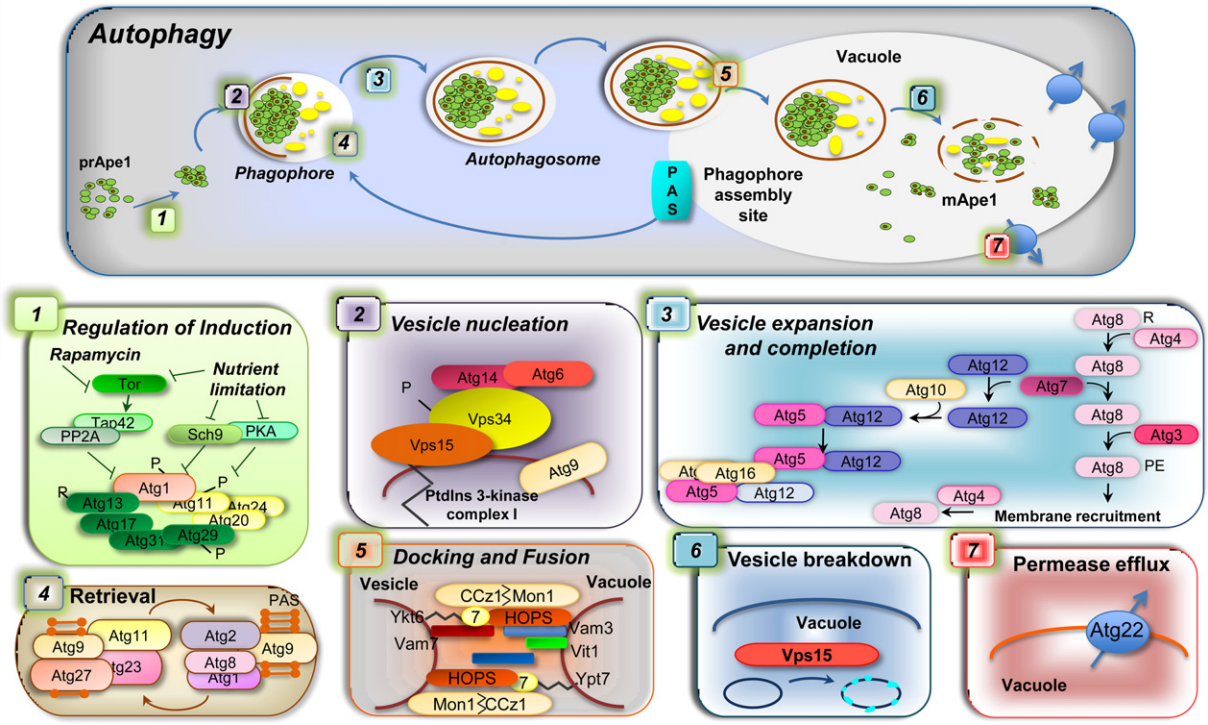

Fig. 1. Schematic overview of autophagy. Autophagy can be divided into seven steps: (1) induction; (2) vesicle nucleation; (3) vesicle expansion and completion; (4) retrieval; (5) fusion; (6) breakdown; (7) efflux. (1) Regulation of induction. Activation of autophagy upon nutrient starvation or growth factor deprivation appears to be mainly mediated by inhibition of the Tor protein kinase. Formation of the Atg1–Atg13 protein kinase complex occurs downstream of Tor inhibition. (2) Vesicle nucleation. Formation of the Atg1–Atg13 complex induces acquisition and processing of membrane material for autophagosome formation. The specific components that act in vesicle nucleation are not completely clear. The PI 3-K complex I, consisting of Vps15, Vps34, Atg6/Vps30 and Atg14, is required for vesicle nucleation in autophagy. (3) Vesicle expansion and completion. Atg8 undergoes proteolytic cleavage of the C-terminal arginine residue (R), by the Atg4 cysteine protease. Atg8 and Atg12 are ubiquitin-like proteins that are activated by the E1-like enzyme Atg7. Atg8 and Atg12 are then transferred to the E2-like enzymes Atg3 and Atg10 and are then conjugated to phosphatidylethanolamine (PE) and Atg5, respectively. Atg8 conjugated to PE acquires the ability to be anchored in the membrane of the PAS (Phagosome Assembly Site) and acts there as a component of the nascent and mature autophagosome. Atg8 is released from the outer membrane of the completed vesicle by a second Atg4-dependent cleavage. (4) Retrieval. Retrieval involves several other Atg proteins. Most Atg proteins are soluble and can easily be released from the membrane surface while Atg9 and Atg27 are integral membrane proteins. The mechanism of targeting and release is unknown. (5) Docking and fusion. Vam3, Vam7, Vti1 and Ykt6, are members of the SNARE family, and, together with Ypt7 and HOPS, they play a role in membrane fusion in a variety of cellular contexts including autophagy. (6 and 7) Breakdown and efflux. The vesicle lysis step depends on the acidic pH of the vacuole lumen and some proteinases. Atg15 has also been implicated in this process. Atg15 has sequence similarity to a family of lipases, and seems likely to function directly in vesicle breakdown. Atg22 is an integral membrane protein located in the limiting membrane. Atg22 is not directly required for the breakdown of autophagic bodies within the lysosome/vacuole, but it acts to mediate the efflux of amino acids resulting from autophagic degradation. This figure was modified from figures previously published by D.J. Klionsky [80,81].

autophagy-inducing capacity, and the release of pro-apoptotic factors due to a direct interaction of a C-terminal fragment, Beclin-1-C, with mitochondria (Fig. 2) [19].

A further link between autophagy and apoptosis is the suppressor effect that the apoptosis inhibitor, cFLIP (Flice inhibitory protein), can exert on autophagy. FLIP competes with the Atg8 orthologue, LC3, for Atg3 binding, thereby preventing Atg3-mediated autophagosome elongation (Fig. 2) [20]. A further point of interconnection is mTOR. The PI3K/Akt/mTOR pathway has been implicated in promoting cell survival in several different tissues [21]. mTOR, along with AMPK, has been shown to phosphorylate the mammalian homologue of Atg1, Ulk1, and thus influence the early stages of autophagic initiation. Therefore regulation of mTOR may represent a crucial point in regulating the balance between cell death and autophagy as reported in different contexts [22–24].

The same cellular stress can in some cases activate both the apoptosis pathway and the autophagic mechanism. As an example, p73 [25–27] is able to both kill via a c-Abl-dependent activation [28] that leads to Puma activation [26,29,30] and also to activate the mTOR pathway [31]. While the former mechanism has been strongly linked to cancer, the latter still awaits a pathological link, and, important for this discussion, the two mechanisms are closely interrelated in cancerogenesis.

These examples highlight the role of factors known to regulate apoptosis in the regulation of autophagy and suggest potential mechanisms how the interrelationship between these processes may be coordinated.

3. Autophagy and cancer therapy

The interaction between apoptosis and autophagy has important implications for cancer therapy. Because one function of autophagy is to act as a survival response to unfavourable conditions, it is reasonable to postulate that it may play a negative role in cancer therapy outcome.

Many factors and mechanisms, implicated at different levels in the regulation of apoptosis, show features which can modulate or predict cytotoxic drug response, such as mitochondrial- and ER-dependent apoptosis pathways [32–34], death receptor pathways [35–37], microRNAs [38–41], and kinases and phosphatases involved in signal transduction [42,43]. Some of these have already been targeted therapeutically while others are potential new pharmacological targets [44,45]. In addition, components of these pathways may be useful as molecular biomarkers [46–48] to monitor and predict cancer therapy outcome.

From what has been discussed above, it is likely that autophagy may act as a protective mechanism to counteract the cellular stress induced by chemotherapy. This may be especially the case, since cells within the tumour core already have low nutrient supplemen-

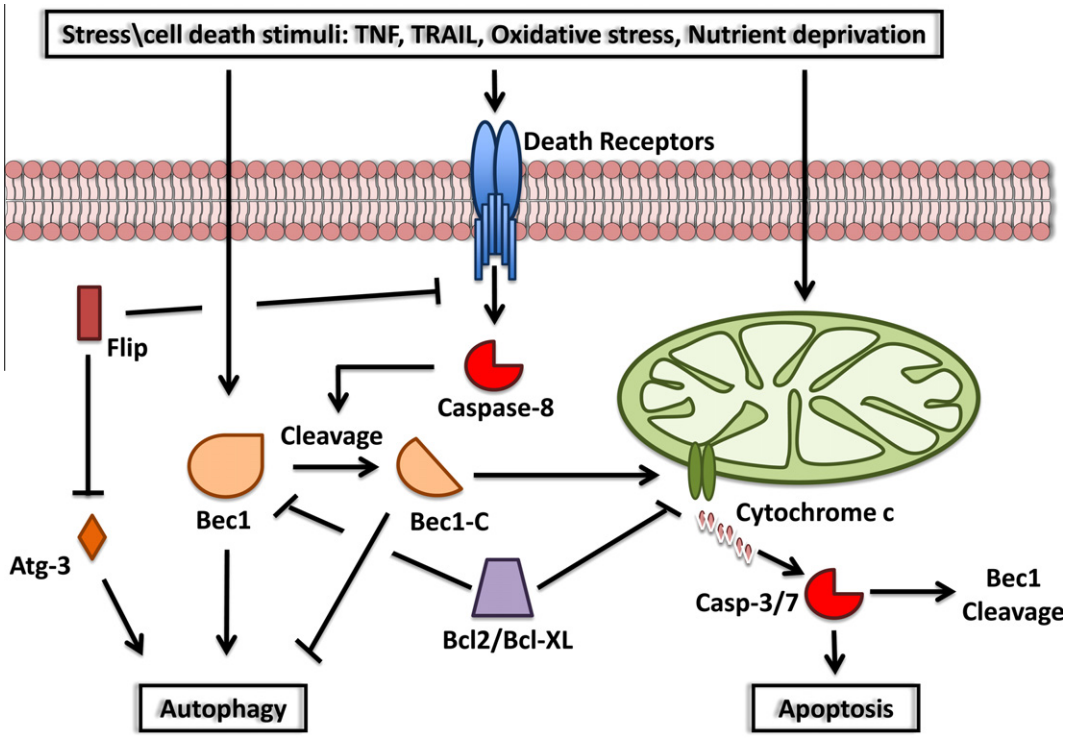

Fig. 2. Schematic representation of molecular interconnections between autophagy and cell death pathways. Beclin1 is a crucial point of interconnection. Caspase-dependent cleavage of Beclin1 represses activation of autophagy and promotes apoptosis via the Bec1-C fragment. Bcl-2/Bcl-XL act as both anti-autophagy and anti-apoptotic factors by specific inhibitory interactions. cFLIP is able to repress the death receptor pathway and counteracts autophagosome elongation.

tation from the reduced microcirculation. Indeed, cancer cells have been shown to utilise autophagy in an attempt to circumvent metabolic stress [49]. The group of Eileen White has, indeed, shown that oncogene addiction requires autophagy to maintain a pool of active mitochondria which sustain oxidative phosphorylation [50]. Thus inhibition of autophagy could be considered as a therapeutic tool in addition to conventional chemotherapy. A relevant role of autophagy is to provide an alternative energy source during nutrient starvation and certain other adverse conditions in order to ensure cell viability. We have recently shown that clomipramine (CMI), and to an even greater extent its active metabolite desmethylclomipramine (DCMI), induces the appearance of autophagy-associated structures in the cytoplasm [51], a process requiring Atg5. In fact, CMI/DCMI alter autophagic flux and, therefore, they could be exploited for novel therapeutic usage to potentiate the effect of chemotherapy. Therefore, as shown for chloroquine, the blockade of the autophagic flux by CMI/DCMI enhances therapy-induced apoptosis [52]. Recent findings support the hypothesis that autophagy regulates conventional chemotherapy, since apoptosis in response to TRAIL agonists is enhanced when autophagy is inhibited [53]. Furthermore, increased autophagy is observed in an erythroleukaemia cell line (TF1) after apigenin treatment and results in a decreased response to vincristine induced-cell death [54]. Consistently, autophagy has also been shown to promote adaptive autophagy after proton pump inhibitor treatment with esomeprazole in melanoma cells with corresponding treatment resistance. Indeed, inhibition of autophagy, by knockdown of Atg5 and Bec1, significantly increased esomeprazole cytotoxicity [55]. Moreover, apart from classical apoptosis, autophagy has been shown to protect cells from caspase-independent cell death following cytochrome *c* release [56].

These and other data have led to a start of pharmacological trials of autophagy inhibitors as sensitizers to anti-cancer therapy [57]. But there is a need for caution here. There is some data suggesting that at least some anti-cancer agents can induce ACD, and thus, autophagic inhibition would result in a reduced therapeutic response (Table 1). Premexetred, and the multikinase inhibitors, such as sorafenib act synergistically to enhance tumour killing via the promotion of a toxic form of autophagy that leads to activation of the intrinsic apoptosis pathway [58]. In a similar manner, the pan-inhibitor of Bcl-2, Obatoclax, currently in clinical development, exerts anti-cancer effects, promoting both apoptosis and

Table 1
Autophagy involvement in cytotoxic drug response.

Cancer type	Treatment	Observation	Ref.
Colon cancer cell line; T leukaemia cell line	TRAIL agonists	Inhibition of autophagy increases TRAIL response	[53]
Erythroleukaemia cell line	Vincristin	Apiegenin-induced autophagy decreases vincristin response	[54]
Melanoma cell line	ESOM	Inhibition of autophagy increases ESOM response	[55]
Different carcinoma cell lines	Premexetred/Sorafenib combination	The combination increases pro-cell death autophagy	[58]
Non-small-cell lung cancer cell line (NSCLC); acute lymphoblastic leukaemia cell line (ALL)	Obatoclax	Treatment induced both cell death and autophagy	[59,60]

autophagy in non-small-cell lung cancer (NSCLC) and acute lymphoblastic leukaemia (ALL) [59,60]. Thus, the overall situation is complex, and the potential benefit of inhibition of autophagy seems likely to vary between individual tumour types and even within the same tumour over time. For example, the androgen receptor (AR), that mediates adaptation to cellular stress in prostate cancer, exerts repressive effects on autophagy and cell death by upregulating the endoplasmic reticulum chaperone glucose-regulated protein 78/BiP (Grp78/Bip) [61], suggesting a contribution of the autophagic pathway to cell death. On the contrary, the estrogen-induced gene, EIG121, implicated in endometrial carcinomas, may protect cells from death by upregulating autophagy under stress conditions, such as starvation and exposure to cytotoxic agents [62].

4. Autophagy and neurodegeneration

Inappropriate activation of cell death pathways has long been implicated in the pathogenesis of neurodegeneration [63–65]. Thus, many reports have correlated molecular activation of cell death pathways with degenerative neurological disease, such as mitochondrial dysfunction in Huntington's [66–68], *14-3-3* proteins in Parkinson's [69], the *NF-KB* pathway activation in ischemic injury [70] microRNAs in SIV/HIV neurological disease [71] and endoplasmic reticulum stress in autism disorder [72]. However, the role of autophagy in these pathologies is mostly poorly understood.

However, there is now good evidence of autophagosome accumulation in neurons [73,74]. Recent findings have shown that autophagy-dependent degradation is able to restrict aggregate accumulation of pathogenic proteins [75], and furthermore pharmacological induction of autophagy has been reported to slow progression of neuronal degeneration by reducing aggregates in Huntington's disease [76]. However other studies report that autophagy may be detrimental when massive accumulation of undegraded autophagic vacuoles occurs, as is observed in many neurodegenerative diseases. Inhibition of autophagosome formation has been reported to decrease neuronal cell death in Alzheimer's disease, frontotemporal dementia and ischemic injury, where low autophagosome clearance produces vesicle accumulation [77,78]. Autophagosome accumulation in neurons can result from an increase in autophagic activation or impaired vesicle clearance, though the relative contribution of these mechanisms is unclear.

Pharmacological compounds able to increase autophagosome clearance are still unavailable for therapy. However, lithium treatment, widely used in bipolar mood disorder, has been reported to exert a neuroprotective effect in models of brain ischemia by repressing autophagy [79]. Therefore, as with the implications in cancer chemotherapy, the promotion or inhibition of autophagy in neurological disease would appear to depend on the specific disease and maybe its stage.

As outlined in this review, much remains to be understood how autophagic pathways are integrated with cell death pathways, and, in particular, how protective autophagy and ACD contribute to proliferative and degenerative pathologies. From our present understanding, autophagy modulation seems to require a targetted approach for each specific pathology, both in relation to cancer and neurodegeneration. Clearly, more work is required before the therapeutic modulation of autophagy becomes an established clinical tool.

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References

[1] G. Kroemer, L. Galluzzi, P. Vandenabeele, et al., Classification of cell death: recommendations of the Nomenclature Committee on Cell Death 2009, Cell Death Differ. 16 (2009) 3–11.
[2] S. Pattingre, A. Tassa, X. Qu, et al., Bcl-2 antiapoptotic proteins inhibit Beclin 1-dependent autophagy, Cell 122 (2005) 922–939.
[3] I. Beau, M. Mehrpour, P. Codogno, Autophagosomes and human diseases, Int. J. Biochem. Cell Biol. 43 (2011) 460–464.
[4] C. Liang, Negative regulation of autophagy, Cell Death Differ. 17 (2010) 1807–1815.
[5] M.A. Delgado, V. Deretic, Toll-like receptors in control of immunological autophagy, Cell Death Differ. 16 (2009) 976–983.
[6] T. Noda, N. Fujita, T. Yoshimori, The late stages of autophagy: how does the end begin?, Cell Death Differ 16 (2009) 984–990.
[7] A. Longatti, S.A. Tooze, Vesicular trafficking and autophagosome formation, Cell Death Differ. 16 (2009) 956–965.
[8] A. Eisenberg-Lerner, S. Bialik, H.U. Simon, Life and death partners: apoptosis, autophagy and the cross-talk between them, Cell Death Differ. 16 (2009) 966–975.
[9] T. Vellai, Autophagy genes and ageing, Cell Death Differ. 16 (2009) 94–102.
[10] N. Kourtis, N. Tavernarakis, Autophagy and cell death in model organisms, Cell Death Differ. 16 (2009) 21–30.
[11] M.C. Maiuri, E. Tasdemir, A. Criollo, et al., Control of autophagy by oncogenes and tumor suppressor genes, Cell Death Differ. 16 (2009) 87–93.
[12] X.H. Liang, S. Jackson, M. Seaman, et al., Induction of autophagy and inhibition of tumorigenesis by beclin 1, Nature 402 (1999) 672–676.
[13] Y. Takahashi, C.L. Meyerkord, H.G. Wang, Bif-1/endophilin B1: a candidate for crescent driving force in autophagy, Cell Death Differ. 16 (2009) 947–955.
[14] J. Zhang, P.A. Ney, Role of BNIP3 and NIX in cell death, autophagy, and mitophagy, Cell Death Differ. 16 (2009) 939–946.
[15] T.R. Burton, S.B. Gibson, The role of Bcl-2 family member BNIP3 in cell death and disease: NIPping at the heels of cell death, Cell Death Differ. 16 (2009) 515–523.
[16] M.C. Maiuri, G. Le Toumelin, A. Criollo, et al., Functional and physical interaction between Bcl-X(L) and a BH3-like domain in Beclin-1, EMBO J. 26 (2007) 2527–2539.
[17] D. Tadokoro, S. Takahama, K. Shimizu, et al., Characterization of a caspase-3-substrate kinome using an N- and C-terminally tagged protein kinase library produced by a cell-free system, Cell Death Dis. 1 (2010) e89.
[18] J.P. Cheng, V.M. Betin, H. Weir, et al., Caspase cleavage of the Golgi stacking factor GRASP65 is required for Fas/CD95-mediated apoptosis, Cell Death Dis. 1 (2010) e82.
[19] E. Wirawan, L. VandeWalle, K. Kersse, et al., Caspase-mediated cleavage of Beclin-1 inactivates Beclin-1-induced autophagy and enhances apoptosis by promoting the release of proapoptotic factors from mitochondria, Cell Death Dis. 1 (2010) e18.
[20] J.S. Lee, Q. Li, J.Y. Lee, et al., FLIP-mediated autophagy regulation in cell death control, Nat. Cell Biol. 11 (2009) 1355–1362.
[21] M. Castedo, K.F. Ferri, G. Kroemer, Mammalian target of rapamycin (mTOR): pro- and anti-apoptotic, Cell Death Differ. 9 (2002) 99–100.
[22] C.H. Jung, S.H. Ro, J. Cao, et al., mTOR regulation of autophagy, FEBS Lett. 7 (2010) 1287–1295.
[23] N. Silver, G.B. Proctor, M. Arno, et al., Activation of mTOR coincides with autophagy during ligation-induced atrophy in the rat submandibular gland, Cell Death Dis. 1 (2010) e14.
[24] R. Kang, D. Tang, N.E. Schapiro, et al., The receptor for advanced glycation end products (RAGE) sustains autophagy and limits apoptosis, promoting pancreatic tumor cell survival, Cell Death Differ. 4 (2010) 666–676.
[25] G. Melino, V. DeLaurenzi, K.H. Vousden, p73: friend or foe in tumorigenesis, Nat. Rev. Cancer 2 (2002) 605–615.
[26] T. Schilling, E.S. Schleithoff, A. Kairat, et al., Active transcription of the human FAS/CD95/TNFRSF6 gene involves the p53 family, Biochem. Biophys. Res. Commun. 387 (2009) 399–404.
[27] R. Tomasini, T.W. Mak, G. Melino, The p53 family, aneuploidy and cancer, Trends Cell Biol. 18 (2008) 244–252.
[28] J.G. Gong, A. Costanzo, H.Q. Yang, et al., Regulation of the p53 homolog p73 by c-Abl tyrosine kinase in cell death response to cisplatin, Nature 399 (1999) 806–809.
[29] G. Melino, F. Bernassola, M. Ranalli, et al., p73 induces apoptosis via PUMA transactivation and Bax mitochondrial translocation, J. Biol. Chem. 279 (2004) 8076–8083.
[30] S. Ramadan, A. Terrinoni, M.V. Catani, et al., p73 induces apoptosis by different mechanisms, Biochem. Biophys. Res. Commun. 331 (2005) 713–717.
[31] J.M. Rosenbluth, D.J. Mays, A. Jiang, et al., Differential regulation of the p73 cistrome by mammalian target of rapamycin reveals transcriptional programs of mesenchymal differentiation and tumorigenesis, Proc. Natl. Acad. Sci. USA 108 (2011) 2076–2081.
[32] V. Janson, A. Johansson, K. Grankvist, Resistance to caspase-8 and -9 fragments in a malignant pleural mesothelioma cell line with acquired cisplatin-resistance, Cell Death Dis. 1 (2010) e78.
[33] L. Flanagan, J. Sebastià, L.P. Tuffy, et al., XIAP impairs Smac release from the mitochondria during apoptosis, Cell Death Dis. 1 (2010) e49.

[34] J. Scheiman, K.V. Jamieson, J. Ziello, et al., Extraribosomal functions associated with the C terminus of the 37/67 kDalaminin receptor are required for maintaining cell viability, Cell Death Dis. 1 (2010) e42.
[35] A. Ashkenazi, Directing cancer cells to self-destruct with pro-apoptotic receptor agonists, Nat. Rev. Drug Discov. 12 (2008) 1001–1012.
[36] S. Schneider-Jakob, N. Corazza, A. Badmann, et al., Synergistic induction of cell death in liver tumor cells by TRAIL and chemotherapeutic drugs via the BH3-only proteins Bim and Bid, Cell Death Dis. 1 (2010) e86.
[37] C.R. Reis, A.M. van der Sloot, A. Natoni, et al., Rapid and efficient cancer cell killing mediated by high-affinity death receptor homotrimerizing TRAIL variants, Cell Death Dis. 1 (2010) e83.
[38] R. Garzon, G. Marcucci, C.M. Croce, Targeting microRNAs in cancer: rationale, strategies and challenges, Nat. Rev. Drug Discov. 10 (2010) 775–789.
[39] M. Acunzo, R. Visone, G. Romano, et al., miR-130a targets MET and induces TRAIL-sensitivity in NSCLC by downregulating miR-221 and 222, Oncogene (2011) (doi:10.1038/onc.2011.260).
[40] N. Bhatnagar, X. Li, S.K. Padi, et al., Downregulation of miR-205 and miR-31 confers resistance to chemotherapy-induced apoptosis in prostate cancer cells, Cell Death Dis. 1 (2010) e105.
[41] N.M. Alajez, W. Shi, A.B. Hui, et al., Enhancer of Zeste homolog 2 (EZH2) is overexpressed in recurrent nasopharyngeal carcinoma and is regulated by miR-26a, miR-101, and miR-98, Cell Death Dis. 1 (2010) e85.
[42] L. Insabato, I. Amelio, M. Quarto, et al., Elevated expression of the tyrosine phosphatase SHP-1 defines a subset of high-grade breast tumors, Oncology 6 (2009) 378–384.
[43] K.M. Chu, S. Minogue, J.J. Hsuan, et al., Differential effects of the phosphatidylinositol 4-kinases, PI4KIIα and PI4KIIIβ, on Akt activation and apoptosis, Cell Death Dis. 1 (2010) e106.
[44] F. Guardiola-Serrano, A. Rossin, N. Cahuzac, et al., Palmitoylation of human FasL modulates its cell death-inducing function, Cell Death Dis. 1 (2010) e88.
[45] C.C. Jiang, F. Lai, K.H. Tay, et al., Apoptosis of human melanoma cells induced by inhibition of B-RAFV600E involves preferential splicing of bimS, Cell Death Dis. 1 (2010) e69.
[46] P.C. Wu, Q. Wang, Z.M. Dong, et al., Expression of coxsackie and adenovirus receptor distinguishes transitional cancer states in therapy-induced cellular senescence, Cell Death Dis. 1 (2010) e70.
[47] A. Sayeed, Z. Meng, G. Luciani, et al., Negative regulation of UCP2 by TGFβ signaling characterizes low and intermediate-grade primary breast cancer, Cell Death Dis. 1 (2010) e53.
[48] E. Hervouet, F.M. Vallette, P.F. Cartron, Impact of the DNA methyltransferases expression on the methylation status of apoptosis-associated genes in glioblastomamultiforme, Cell Death Dis. 1 (2010) e8.
[49] E. White, C. Karp, A.M. Strohecker, et al., Role of autophagy in suppression of inflammation and cancer, Curr. Opin. Cell Biol. 22 (2010) 212–217.
[50] J.Y. Guo, H.Y. Chen, R. Mathew, et al., Activated Ras requires autophagy to maintain oxidative metabolism and tumorigenesis, Genes Dev. 25 (2011) 460–470.
[51] M. Rossi, E.R. Munarriz, S. Bartesaghi, et al., Desmethylclomipramine induces the accumulation of autophagy markers by blocking autophagic flux, J. Cell Sci. 122 (2009) 3330–3339.
[52] R.K. Amaravadi, D. Yu, J.J. Lum, et al., Autophagy inhibition enhances therapy-induced apoptosis in a Myc-induced model of lymphoma, J. Clin. Invest. 117 (2007) 326–336.
[53] J. Han, W. Hou, L.A. Goldstein, et al., Involvement of protective autophagy in TRAIL resistance of apoptosis-defective tumor cells, J. Biol. Chem. 283 (2008) 19665–19677.
[54] R.R. Ruela-de-Sousa, G.M. Fuhler, N. Blom, et al., Cytotoxicity of apigenin on leukemia cell lines: implications for prevention and therapy, Cell Death Dis. 1 (2010) e19.
[55] M.L. Marino, S. Fais, M. Djavaheri-Mergny, et al., Proton pump inhibition induces autophagy as a survival mechanism following oxidative stress in human melanoma cells, Cell Death Dis. 1 (2010) e87.
[56] A. Colell, J.E. Ricci, S. Tait, et al., GAPDH and autophagy preserve survival after apoptotic cytochrome c release in the absence of caspaseactivation, Cell 129 (2007) 983–997.
[57] J. Sotelo, E. Briceno, M.A. Lopez-Gonzalez, Adding chloroquine to conventional treatment for glioblastomamultiforme: a randomized, double- blind, placebo-controlled trial, Ann. Intern. Med. 144 (2006) 337–343.
[58] M.D. Bareford, M.A. Park, A. Yacoub, et al., Sorafenib enhances pemetrexed cytotoxicity through an autophagy-dependent mechanism in cancer cells, Cancer Res. 71 (2011) 4955–4956.
[59] F. McCoy, J. Hurwitz, N. McTavish, et al., Obatoclax induces Atg7-dependent autophagy independent of beclin-1 and BAX/BAK, Cell Death Dis. 1 (2010) e108.
[60] N. Heidari, M.A. Hicks, H. Harada, GX15-070 (obatoclax) overcomes glucocorticoid resistance in acute lymphoblastic leukemia through induction of apoptosis and autophagy, Cell Death Dis. 1 (2010) e76.
[61] H.L. Bennett, J.T. Fleming, J. O'Prey, et al., Androgens modulate autophagy and cell death via regulation of the endoplasmic reticulum chaperone glucose-regulated protein 78/BiP in prostate cancer cells, Cell Death Dis. 1 (2010) e72.
[62] L. Deng, J. Feng, R.R. Broaddus, The novel estrogen-induced gene EIG121 regulates autophagy and promotes cell survival under stress, Cell Death Dis. 1 (2010) e32.
[63] S.N. Sivananthan, A.W. Lee, C.G. Goodyer, et al., Familial amyloidprecursor protein mutants cause caspase-6-dependent but amyloid β-peptide-independent neuronal degeneration in primary human neuron cultures, Cell Death Dis. 1 (2010) e100.
[64] M.F. Cordeiro, L. Guo, K.M. Coxon, et al., Imaging multiple phases of neurodegeneration: a novel approach to assessing cell death in vivo, Cell Death Dis. 1 (2010) e3.
[65] S. Sarkar, B. Ravikumar, R.A. Floto, et al., Rapamycin and mTOR-independent autophagy inducers ameliorate toxicity of polyglutamine-expanded huntingtin and related proteinopathies, Cell Death Differ. 16 (2009) 46–56.
[66] I.S. Seong, E. Ivanova, J.M. Lee, et al., CAG repeat implicates a dominant property of Huntingtin in mitochondrial energy metabolism, Hum. Mol. Genet. 14 (2005) 2871–2880.
[67] C. Saft, J. Zange, J. Andrich, et al., Mitochondrial impairment in patients and asymptomatic mutation carriers of Huntington's disease, Mov. Disord. 20 (2005) 674–679.
[68] J. Sassone, C. Colciago, P. Marchi, et al., Mutant Huntingtin induces activation of the Bcl-2/adenovirus E1B 19-kDa interacting protein (BNip3), Cell Death Dis. 1 (2010) e7.
[69] T.A. Yacoubian, S.R. Slone, A.J. Harrington, et al., Differential neuroprotective effects of 14-3-3 proteins in models of Parkinson's disease, Cell Death Dis. 1 (2010) e2.
[70] A. Lanzillotta, I. Sarnico, R. Ingrassia, et al., The acetylation of RelA in Lys310 dictates the NF-κB-dependent response in post-ischemic injury, Cell Death Dis. 1 (2010) e96.
[71] S.V. Yelamanchili, A.D. Chaudhuri, L.N. Chen, et al., MicroRNA-21 dysregulates the expression of MEF2C in neurons in monkey and human SIV/HIV neurological disease, Cell Death Dis. 1 (2010) e77.
[72] E. Fujita, H. Dai, Y. Tanabe, et al., Autism spectrum disorder is related to endoplasmic reticulum stress induced by mutations in the synaptic cell adhesion molecule, CADM1, Cell Death Dis. 1 (2010) e47.
[73] N. Mizushima, B. Levine, A.M. Cuervo, et al., Autophagy fights disease through cellular self-digestion, Nature 451 (2008) 1069–1075.
[74] A.R. Winslow, D.C. Rubinsztein, Autophagy in neurodegeneration and development, Biochim. Biophys. Acta 1782 (2008) 723–729.
[75] A. Iwata, J.C. Christianson, M. Bucci, et al., Increased susceptibility of cytoplasmic over nuclear polyglutamine aggregates to autophagic degradation, Proc. Natl. Acad. Sci. USA 102 (2005) 13135–13140.
[76] B. Ravikumar, C. Vacher, Z. Berger, et al., Inhibition of mTOR induces autophagy and reduces toxicity of polyglutamine expansions in fly and mouse models of Huntington disease, Nat. Genet. 36 (2004) 585–595.
[77] S.J. Cherra, C.T. Chu, Autophagy in neuroprotection and neurodegeneration: a question of balance, Future Neurol. 3 (2008) 309–323.
[78] J.A. Lee, F.B. Gao, Inhibition of autophagy induction delays neuronal cell loss caused by dysfunctional ESCRT-III in frontotemporal dementia, J. Neurosci. 29 (2009) 8506–8511.
[79] Q. Li, H. Li, K. Roughton, et al., Lithium reduces apoptosis and autophagy after neonatal hypoxia-ischemia, Cell Death Dis. 1 (2010) e56.
[80] B. Levine, D.J. Klionsky, Development by self-digestion: molecular mechanisms and biological functions of autophagy, Dev. Cell 6 (2004) 463–477.
[81] D.J. Klionsky, The molecular machinery of autophagy: unanswered questions, J. Cell Sci. 1 (2005) 7–18.