We are IntechOpen, the world’s leading publisher of Open Access books
Built by scientists, for scientists

5,700
Open access books available

139,000
International authors and editors

175M
Downloads

154
Countries delivered to

12.2%
Contributors from top 500 universities

TOP 1%
Our authors are among the most cited scientists

WEB OF SCIENCE™
Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com
Chapter 10

Role of Autophagy in Cancer

Michiko Shintani and Kayo Osawa

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/55315

1. Introduction

Autophagy is a cellular stress-adaptive process in which double-membrane structures called autophagosomes engage in protein degradation, cellular differentiation, apoptosis and antigen processing, and are recycled to sustain cellular metabolism [1-11]. It is a self-digesting mechanism responsible for removal of long-lived proteins and damaged organelles by lysosomes, and opposing roles in cell death and survival have been described for autophagy. Autophagy is a multifaceted process, and alterations in autophagic signaling pathways are frequently observed in cancer. Cancer is a disease generated by mutation, selection and genome instability in the resulting tumor tissue, and is considered to be the second leading cause of death in western countries after heart disease [12, 13]. Autophagy can be activated by various stimuli including hypoxia during the tumor formation [14]. One hypothetical mechanism is that autophagy promotes tumor cell survival in response to diverse stresses [15]. Furthermore, autophagy spatially and temporally regulates tumor development by suppressing tumor growth through regulating cell proliferation in the early stages of tumorigenesis [16]. Conversely, when autophagy is reduced, it contributes to tumor formation and growth by the breakdown of tumor cells following autophagy-related cell death, leading to tumor cell survival [17]. There is a controversy about the roles of autophagy in cancer [1, 3, 18]. In this review, we outline the multiple roles of autophagy in cancer, including gene expression, gene mutation, and chemotherapy.

2. Autophagy-related genes in cancer

2.1. ATG genes

Most recently, molecular genetic analyses have focused on the function of autophagy-related gene (ATG) products. ATG products are implicated in autophagosome formation and associat-
ed pathways. In humans, there are more than 30 known ATG genes, some of which have mononucleotide repeats with seven or more nucleotides. Of the many genes associated with autophagy, ATG genes are the main regulators and implementers of the autophagy process [19].

Beclin-1 (encoded by BECN1 gene, a mammalian orthologue of yeast Atg6) protein, a component of PI3-kinase complexes, is a key regulator in the vesicle nucleation process of autophagic programmed cell death [20-22]. The role of autophagy in tumor suppression is known to be as a result of allelic loss of the essential autophagy genes. Beclin-1 and Beclin-1+/− mice were shown to be tumor prone, indicating that BECN1 is a haploinsufficient tumor suppressor gene [20, 21], and allelic deletion and point mutations of BECN1 gene and loss of Beclin-1 expression is found with high frequency in human breast, ovarian and prostate cancers [22, 23]. Lee et al. detected 11 somatic mutations of the BECN1 gene, including three missense mutations (N8K, P350R and R389C) in coding sequences and eight mutations in introns [24]. These mutations were observed in five gastric, three colorectal, one lung and one breast carcinoma. However, the expression of Beclin-1 is known to be upregulated in colon and gastric cancers [25]. It also reported that Atg4C-deficient mice are prone to tumors [26].

Frameshift mutations of genes with mononucleotide repeats are features of cancers with microsatellite instability (MSI). Mononucleotide repeat frameshift mutations in ATG genes are common in gastric and colorectal carcinomas with high MSI, and possibly contribute to cancer development by deregulating the autophagy process. Kang et al. detected truncation mutations of three genes (ATG2B; c.3120delA, ATG5; c.704delA and ATG9B; c.293delC) in high MSI cancers (gastric and colorectal) by single-strand conformation polymorphism analysis [27]. In particular, ATG5 is a protein involved in the early stage of autophagosome formation [18, 28]. ATG5 high expression was altered in prostate cancers and other data showed a low incidence of ATG5 mutations in gastric hepatocellular, and colorectal cancers with MSI [29, 30]. It is important to identify the expression and mutation status of a gene in cancers to understand its role in cancer development. These frameshift mutations or SNPs in ATG genes may alter the autophagic cell death in cancers and might contribute to the pathogenesis of human cancers.

2.2. UVRAG

As an ATG-related gene, the ultraviolet (UV) radiation resistance-associated gene (UVRAG) was initially identified as a gene that is responsible for the partial complementation of UV sensitivity in xeroderma pigmentosum cells, and binds with Beclin-1/PI3-kinase and Bif-1, a Bax activator to induce autophagy formation and suppress the tumorigenic activity of cancer cells [31, 32]. It has been reported that UVRAG exon 8 frameshift mutations containing c.709delA or c.708_709delAA mutations were found in gastric and colorectal cancers with MSI [33, 34].

2.3. IRGM

In the autophagy pathway, the immunity-related guanosine triphosphatase (GTPase) family, M (IRGM), plays a central function and appears to have an important role in the activation of the pathway. IRGM is located on chromosome 5q33.1, and its mRNA transcripts can be found
in five different 3′-splicing isoforms [35, 36]. Recent evidence indicates that variants of the IRGM locus, especially those in the promoter region, may be correlated with differential expression, and consequently the efficacy of autophagy is affected by alterations in IRGM regulation [36-38]. IRGM has two major SNPs (rs13361189 and rs4958847) associated with chronic inflammatory digestive diseases. It is not known exactly why IRGM rs4958847 but not rs13361189 polymorphism has reported to influence susceptibility to gastric cancer [39].

2.4. RASSF1

The RAS association domain family 1A (RASSF1A) is one of the most epigenetically silenced elements in human cancers. The tumor suppressor gene, RASSF1A, has been reported to play a role in diverse activities including cell cycle regulation, apoptosis and modulation of autophagy or genomic instability [40]. It is also associated with epigenetic silencing of other proteins including that of death-associated protein kinase (DAPK) [41-44]. DAPK is a unique calcium/calmodulin-activated serine/threonine kinase involved in autophagy-related signaling pathways [45-48]. RASSF1A can also promote cell death utilizing the association with the anaphase promoting complex protein cdc20 and the autophagic protein, C19ORF5/MAP1S [49]. Expression of the longer isoform of RASSF1A (39 kDa predicted peptide) is lost or downregulated in many lung tumor lines [50, 51]. Agatheanggelou et al. also reported that RASSF1A inactivation by methylation and loss is a critical step in lung cancer [52]. Epidemiological studies have identified an association between the RASSF1A A133S polymorphism and cancer risk including breast cancer, lung cancer, and hepatocellular carcinoma [53-57]. Moreover, several studies have shown that expression loss by promoter-specific hypermethylation of RASSF1A is one of the most common early events in hepatocellular carcinoma that play important roles in tumorigenesis and metastasis of hepatocellular carcinoma [58, 59]. A133S and S131F polymorphisms resulted in the lost ability of RASSF1A to inhibit growth and cyclin D1 expression, suggesting an important role in tumor suppression [60, 61]. Moreover, Gordon et al. reported that E246K, C65R, R257Q RASSF1A polymorphisms were related to tumor suppressor function [62]. Additional evidence suggests that RASSF1C may be a tumor suppressor gene in prostate and renal carcinoma cells but not in lung cancer cells [63]. It has reported that the loss of RASSF1C results in the downregulation of proliferation of lung and breast cancer cells, suggesting a prosurvival role for RASSF1C [64-66]. Recently, it has been suggested that a possible pathogenic role for RASSF1C in cancer may exist, as its expression was more than 11-fold greater in pancreatic endocrine tumors than in normal tissue [67].

2.5. NOD2

The nucleotide-binding oligomerization domain-containing protein 2 (NOD2) is a member of the Nod-like receptor family and associates with the cell surface membrane. NOD2 activation controls the induction of autophagy, or apoptosis [68-70]. Four major NOD2 single nucleotide polymorphisms are correlated with increased risk of colorectal cancer, and a possible association of the NOD2 P268S polymorphism with rectal and gastric cancers has been identified [71-78]. A recent meta-analysis also provided good evidence that NOD2 R702W, G908R, and most significantly, 3020insC, polymorphisms were associated with increased risk of colorectal
cancer [79]. Other studies also found significant associations with laryngeal, lung, and ovarian cancers [80, 81]. In contrast, Suchy et al. found the association of the TNFα-1,031 T/T genotype and NOD2 3020insC polymorphism may act as a modifier to reduce colorectal cancer risk [82]. Further research of NOD2 polymorphisms and gene–gene interactions will provide a more comprehensive insight into the associations described here.

3. Analysis of autophagy by immunohistochemistry

Recently, the role of autophagy in cancer development and progression has been investigated using immunohistochemistry. Immunohistochemical methods have been developed that supplement the detection of autophagy via genetic analyses. Many antibodies for autophagy detection are routinely used for immunohistochemistry against proteins involved in autophagy pathways [83-86] (Table 1).

| Antibody                        | ref. No |
|---------------------------------|---------|
| LC3 (rabbit polyclonal antibody)| [86]    |
| Source; (1: x, dilution rate)   | Medical & Biological Laboratories, Japan |
| Antigen retrieval method        | Pressure cooker (110C-120C) for 10 min; 10 mM citrate buffer, pH 6.0 |
| Sample type                     | Formalin-fixed, paraffin-embedded specimens |
| Staining pattern                | Invariably granular cytoplasmic staining |

| LC3                             | [100] |
| Source; (1: x, dilution rate)   | Novus Biologicals, USA; (1:400) |
| Antigen retrieval method        | High temperature and pressure, citrate buffer |
| Sample type                     | Formalin-fixed, paraffin-embedded specimens |
| Staining pattern                | Cytoplasmic staining |

| Beclin-1 (rabbit monoclonal antibody) | [95] |
| Source; (1: x, dilution rate)        | Abcam, UK; (1:100) |
| Antigen retrieval method             | Microwave oven for 15 min, 10 mM citrate buffer, pH 6 |
| Sample type                          | Formalin-fixed, paraffin-embedded specimens |
| Staining pattern                     | Cytoplasmic staining |

| Beclin-1 (rabbit polyclonal antibody) | [97] |
| Source; (1: x, dilution rate)        | Abcam, UK; (1:100) |
| Antigen retrieval method             | Microwave oven, 10 mM citrate buffer, pH 6 |
| Antibody | Sample type | ref. No |
|----------|-------------|---------|
| **Bclin-1** (rabbit polyclonal antibody) | Formalin-fixed, paraffin-embedded specimens | [25] |
| **Source**; (1: x, dilution rate) | Novus Biologicals, USA | |
| **Antigen retrieval method** | Pressure cooker inside a microwave oven at 700 W for 30 min, 10 mM citrate buffer, pH 6.0 | |
| **Sample type** | Microarray recipient block was constructed containing paraffin-embedded colorectal adenocarcinoma tissue samples from 103 archival patient specimens | |
| **Staining pattern** | Cytoplasmic staining | |
| **Source**; (1: x, dilution rate) | Cell Signaling, USA; (1:100) | [100] |
| **Antigen retrieval method** | High temperature and pressure, citrate buffer | |
| **Sample type** | Formalin-fixed, paraffin-embedded specimens | |
| **Staining pattern** | Cytoplasmic staining | |
| **BIF-1** (mouse monoclonal antibody) | | [98] |
| **Source**; (1: x, dilution rate) | Imgenex, USA; (1:2500) | |
| **Antigen retrieval method** | standard cell conditioning (Ventana Medical Systems, USA) | |
| **Sample type** | Formalin-fixed, paraffin-embedded core sections on a tissue array | |
| **Staining pattern** | Cytoplasmic staining | |
| **ATG5** (rabbit polyclonal antibody) | | [30] |
| **Source**; (1: x, dilution rate) | Abcam, UK; (1:800) | |
| **Antigen retrieval method** | Pressure cooker inside a microwave oven at 700 W for 30 min, 10 mM citrate buffer, pH 6.0 | |
| **Sample type** | Formalin-fixed, paraffin-embedded specimens | |
| **Staining pattern** | Cytoplasmic and/or nuclear | |

**Table 1.** Immunohistochemical analysis of autophagy-related proteins.
3.1. Proteins involved in autophagy

3.1.1. LC3

Microtubule-associated protein 1 light chain 3 (LC3) is an autophagosomal orthologue of yeast ATG8, with approximately 30% amino acid homology [87, 88]. LC3 is a specific marker of autophagosome formation. LC3-I is localized to the cytoplasm, whereas LC3-II binds to autophagosomes [89].

3.1.2. Beclin-1 (ATG6)

Beclin-1 is a mammalian homolog of the yeast ATG6 protein. The expression of Beclin-1 protein has been reported in tumor tissues such as breast, ovarian, prostate, lung, brain, stomach and colorectum [25, 90]. Beclin-1 was found to be deregulated in human cancers and may play a role in the tumorigenesis and/or progression of human cancers [21, 91]. It is required for autophagic induction and is a haploinsufficient tumor suppressor.

3.1.3. ATG5

ATG5 is a key regulator of autophagic and apoptotic cell death, and is involved in the early stages of autophagosome formation [18, 28]; binding of ATG5 with ATG12 contributes to autophagosome formation, which sequesters cytoplasmic materials before lysosomal delivery [18]. It is suggested that ATG5 is involved in both apoptotic and autophagic cell death [92].

3.1.4. Bax-interacting factor -1

Bax-interacting factor-1 (Bif-1) protein is a member of the endophilin B family, which plays a critical role in cell death, including autophagy and apoptosis. Loss of Bif-1 suppresses programmed cell death and promotes tumorigenesis [93, 94].

3.1.5. GABARAP

Gamma-aminobutyric acid type A receptor-associated protein (GABARAP) is one of the mammalian homologue of yeast ATG8. It is involved in autophagosome formation during autophagy and was first identified in the brain, but is widely expressed in a variety of normal tissues. Recent reports have suggested that GABARAP is an essential component of autophagic vacuoles in addition to its role as an intracellular trafficking molecule [87,88].

3.2. Expression of autophagy-related proteins in gastrointestinal cancers

Recent reports have demonstrated the expression of autophagy-related proteins in gastrointestinal carcinomas. Chen et al. examined the expression levels of Beclin1 in gastric carcinomas and adjacent normal gastric mucosal tissues by immunohistochemistry. According to their results, high levels of Beclin-1 expression were observed in 90/155 (58.1%) of gastric carcinomas, in 24/60 (40.0%) of adjacent mucosal tissues and in 13/30 (43.3%) of normal gastric mucosa tissues (P=0.036). Decreased expression of Beclin-1 in cancer cells was significantly correlated
with poor differentiation, nodal and distant metastasis, advanced TNM stage, and tumor relapse. More importantly, decreased expression of Beclin-1 was associated with shorter survival as evidenced by univariate and multivariate analysis. Chen et al. concluded that decreased expression of Beclin-1 in gastric carcinoma may be important in the acquisition of a metastatic phenotype, suggesting that decreased Beclin-1 expression, as examined by immunohistochemistry, is an independent biomarker for poor prognosis of patients with gastric carcinoma [95].

In contrast, using a tissue microarray approach, Ahn et al. investigated Beclin-1 protein expression in 103 colorectal and 60 gastric carcinoma tissues by immunohistochemistry. The expression of Beclin-1 was detected in 50/60 (83%) of gastric carcinomas and 98/103 (95%) of colorectal carcinomas. Conversely, the normal mucosal cells of both the stomach and colon showed no or very weak expression of Beclin-1. There was no significant association of Beclin-1 expression with clinicopathological characteristics, including invasion, metastasis and stage. Their data indicate that Beclin-1 inactivation by loss of expression may not occur in colorectal and gastric cancers. Rather, increased expression of Beclin-1 in the malignant colorectal and gastric epithelial cells compared with their normal mucosal epithelial cells suggests that neo-expression of Beclin-1 may play a role in both colorectal and gastric tumorigenesis [25].

An et al. analyzed ATG5 protein expression by immunohistochemistry and ATG5 somatic mutations by single-strand conformation polymorphism in cancer cells and the normal mucosal cells of gastrointestinal tissues. Their results showed that ATG5 protein was well expressed in normal stomach, colon, and liver epithelial cells, while it was lost in 21/100 (21%) of gastric carcinomas, 22/95 (23%) of colorectal carcinomas, and 5/50 (10%) of hepatocellular carcinomas. Furthermore, such loss of ATG5 expression was observed in the cancers irrespective of the histological subtypes and TNM stages. Also, they found that only 1.5% (2/135) of these cancers harbored ATG5 mutations. They suggested that loss of ATG5 expression may play a role in the pathogenesis of some gastric and colorectal cancers [30].

Colorectal carcinoma is one of the most common cancers in the world and the incidence rate is rising. Miao et al. performed experiments to investigate a possible correlation between GABARAP expression in colorectal carcinoma and clinicopathological parameters, including patient survival times. Their results showed that the expression of GABARAP protein was significantly higher in colorectal cancers (51.5%) than the adjacent matched non-tumor tissues (33.0%), and overexpression of GABARAP was significantly correlated with a low grade of differentiation and shortened overall survival. They described GABARAP protein expression as a new prognosis marker in colorectal carcinoma [96].

Li et al. analyzed the expression of Beclin-1 protein in stage IIIIB colon carcinoma by immunohistochemistry and correlated it with survival. Their results showed Beclin-1 immunostaining was distributed in the plasma membrane, cytoplasm and nuclei of tumor cells in 98/115 cases (85.2%). Modest or no Beclin-1 expression was observed in adjacent non-cancerous tissues. Higher levels of Beclin-1 expression were strongly associated with longer survival. Both univariate analysis and multivariate analysis showed that Beclin-1 expression levels and invasive depth of primary mass (T stage) were independent
prognostic factors. They suggested that Beclin-1 is a favorable prognostic biomarker in locally advanced colon carcinomas [97].

Bif-1 protein plays a critical role in cell death, including autophagy and apoptosis. Coppola et al. examined Bif-1 expression level in colorectal carcinoma using semiquantitative immunohistochemistry and microarray analysis of archival specimens. Bif-1 expression was negative in 23/102 (22.5%) of colorectal carcinomas. Moderate to strong Bif-1 staining was identified in 37/102 (36.3%) of the tumors, and weak staining was noted in 42/102 (41.2%). Moderate to strong Bif-1 immunoreactivity was shown in 26/38 (68.4%) normal colorectal mucosa, and none were negative. In 12/38 (31.6%) cases, the normal colorectal mucosa demonstrated weak Bif-1 stain. The mean staining scores (intensity and percentage of positively stained cells) for colorectal carcinomas and normal colorectal mucosa differed significantly ($P$=0.0003). The percentage of cases with negative expression also differed significantly between normal colorectal mucosa and colorectal carcinoma ($P$=0.002). Decreased Bif-1 expression in colorectal carcinomas was confirmed at the mRNA level by microarray analysis. They concluded Bif-1 was downregulated during the transition from normal colorectal mucosa to colorectal adenocarcinoma, a novel finding in agreement with the tumor suppressor function of Bif-1 [98].

LC3 is one of the most useful markers of autophagy. Yoshioka et al. evaluated LC3 expression in gastrointestinal cancers by immunohistochemistry to elucidate the role of autophagy in human cancer development. LC3 expression was compared with Ki-67 staining and expression of carbonic anhydrase IX, a hypoxic marker. LC3 was expressed in the cytoplasm of cancer cells, but not in non-cancerous epithelial cells. Furthermore, high expression of LC3 was observed in 56/106 (53%) of esophageal, 22/38 (58%) of gastric and 12/19 (63%) of colorectal cancers. The immunoreactive score (intensity and percentage of positively stained cells) of LC3 gradually increased during the early stages of esophageal carcinogenesis in low- and high-grade intraepithelial neoplasia and T1 carcinoma, but did not change in later cancer progression (T2–T4 carcinomas). In early esophageal carcinogenesis, LC3 expression correlated with the Ki-67 labeling index ($P$=0.0001), but showed no significant association with carbonic anhydrase IX expression. In esophageal cancers, LC3 expression did not correlate with various clinicopathological factors, including survival. LC3 is also upregulated in various gastrointestinal cancers and is partly associated with Ki-67 index. Their results suggest that LC3 expression is advantageous to cancer development, especially in early-phase carcinogenesis. Taken together, these findings suggest that LC3 expression is advantageous to cancer development in early phase of carcinogenesis [99].

Ahn et al. reported that Beclin-1 expression was detected in 95% of colorectal carcinomas examined. In contrast, normal mucosal cells of colon showed no or very weak expression of Beclin-1. There was no significant association of Beclin-1 expression with clinicopathological characteristics, including invasion, metastasis and stage [25].

Guo et al. performed experiments to investigate the utility of Beclin-1 and LC3, in predicting the efficiency of cetuximab in the treatment of advanced colorectal cancer. Their results showed that Beclin-1 and LC3 expression was significantly correlated ($r=0.44$, $P<0.01$), and patients with low Beclin-1 expression had longer progression-free survival than those with high Beclin-1 expression [100].
4. Autophagy in cancer chemotherapy

One of the standard modalities for treatment of patients with cancer is chemotherapy. Cytotoxic drug treatment often triggers autophagy, particularly in apoptosis-defective cells, and this excessive cellular damage combined with attempts to remediate that damage through progressive autophagy can promote autophagic cell death [101]. Platinum-containing cisplatin is one of the most extensively used chemotherapeutic agents, and remains the first-line treatment in various types of cancer [102]. Cisplatin-based chemotherapy frequently resulted in acquired resistance of cancer cells. Sirichanchuen et al. indicated that the levels of LC3-related autophagy were significantly lower in cisplatin resistant cells, and autophagosome formation was dramatically reduced in the resistant cells [103]. Patients with low LC3 expression had a higher objective response rate amongst advanced colorectal cancer patients treated with cetuximab-containing chemotherapy [100]. Expression of ATG5 sensitizes tumor cells to chemotherapy, but its silencing results in resistance to cisplatin therapy combined with AKT inhibitor treatment, thus revealing a key role for autophagy in chemoresistance [92]. Autophagic cell death is activated in cancer cells that are derived from different tissues in response to anticancer therapies [101, 104]. Combination therapy with erlotinib and cisplatin is an effective treatment against erlotinib-resistant cancer by targeting (downregulating) ATG3-mediated autophagy and induction of apoptotic cell death. Autophagy may delay apoptotic cell death caused by DNA-damaging agents and hormonal therapies such as tamoxifen. On the contrary, autophagy has a role as a cell survival pathway. Therefore, autophagy is also induced as a protective and survival mechanism. A major regulator of autophagy is the mammalian target of rapamycin (mTOR) pathway, which consists of two distinct signaling complexes known as mTORC1 and mTORC2 [105]. Thus, results all suggest the role of autophagy in attenuation of chemotherapy-induced cell death or survival.

5. Conclusion

Autophagy is involved in metabolism, cell-death, stress response and carcinogenesis. Several key autophagic mediators containing ATG-related proteins, LC3, Bif-1, GABARAP, UVRAG, IRGM, RASSF1, or NOD2, play pivotal roles in autophagic signaling networks in cancer. By these tumor-suppressive mechanisms in early-stage carcinogenesis, autophagy promotes genomic stability in carcinomas, and possibly contributes to cancer development. Furthermore, immunohistochemical methods have been developed that supplement the detection of autophagy via genetic analyses. These are especially important since diagnosis of autophagic vacuoles using the classical method of electron microscopy is time-consuming, labor-intensive and costly. Many antibodies for autophagy detection are routinely used for immunohistochemistry. These autophagosomes then fuse with lysosomes to generate autolysosomes. Therefore, LC3 is an efficient and reliable marker for the detection of autophagosome formation.

Autophagy or ‘self-eating’ is frequently activated in tumor cells treated with chemotherapy. In cancer therapy, adaptive autophagy in cancer cells sustains tumor growth and survival in
the face of the toxicity of cancer therapy. However, in certain circumstances, autophagy mediates the therapeutic effects of some anticancer agents. During tumor development and in cancer therapy, autophagy has been reported to have paradoxical roles in promoting both cell survival and cell death.

Autophagy may play a variety of physiological roles in cancer progression at each stage in various cancers. Further investigations are required to clarify the biological role of autophagy-related proteins so as to estimate their potential value in the diagnosis and treatment of cancer.

Author details

Michiko Shintani* and Kayo Osawa

1 Department of Biophysics, Kobe University Graduate School of Health Sciences, Kobe, Japan
2 Department of International health, Kobe University Graduate School of Health Sciences, Kobe, Japan

References

[1] Edinger AL, Thompson CB. Death by design: apoptosis, necrosis and autophagy. Curr Opin Cell Biol 2004;16(6) 663–669.
[2] Levine B, Klionsky, DJ. Development by self-digestion: molecular mechanisms and biological functions of autophagy. Dev. Cell 2004; 6(4) 463–477.
[3] Baehrecke EH. Autophagy: dual roles in life and death? Nat Rev Mol Cell Biol 2005;6(6) 505–510.
[4] Deretic V. Autophagy in innate and adaptive immunity. Trends Immunol 2005; 26(10) 523–528.
[5] Degenhardt K, Mathew R, Beaudoin B, Bray K, Anderson D, Chen G, Mukherjee C, Shi Y, Gélinas C, Fan Y, Nelson DA, Jin S, White E. Autophagy promotes tumor cell survival and restricts necrosis, inflammation, and tumorigenesis. Cancer Cell 2006; 10(1) 51–64.
[6] Berry DL, Baehrecke EH. Growth arrest and autophagy are required for salivary gland cell degradation in Drosophila. Cell 2007; 131(6) 1137–1148.
[7] Levine B, Deretic V. Unveiling the roles of autophagy in innate and adaptive immunity. Nat Rev Immunol 2007; 7(10) 767–777.
[8] Maiuri MC, Zalckvar E, Kimchi A, Kroemer G. Self-eating and self-killing: crosstalk between autophagy and apoptosis. Nat Rev Mol Cell Biol 2007; 8(9) 741–752.
[9] Mizushima N. Autophagy: process and function. Genes Dev. 2007;21(22) 2861–2873.

[10] Schmid D, Munz C. Innate and adaptive immunity through autophagy. Immunity 2007; 27(1) 11–21.

[11] Maiuri MC, Zalckvar E, Kimchi A, Kroemer G. Self-eating and self-killing: crosstalk between autophagy and apoptosis. Nat Rev Mol Cell Biol. 2007; 8(9) 741–752.

[12] Minino AM. Tech. Rep. 64. Hyattsville, Md, USA: NCHS Data Brief; 2009. Death in the United States.

[13] Canada S. Leading Causes of Death in Canada. Government of Canada Publications; 2011.

[14] Liang C, Lee JS, Inn KS, Gack MU, Li Q, Roberts EA, Vergne I, Deretic V, Feng P, Akazawa C, Jung JU. Beclin1-binding UVRAG targets the class C Vps complex to coordinate autophagosome maturation and endocytic trafficking. Nat Cell Biol. 2008; 10(7) 776–787.

[15] Mizushima N, Levine B, Cuervo AM, Klionsky DJ. Autophagy fights disease through cellular self-digestion. Nature 2008; 451(7182) 1069–1075.

[16] Levine B. Cell biology: autophagy and cancer. Nature. 2007;446(7137) 745-747.

[17] Tsuchihara K, Fujii S, Esumi H. Autophagy and cancer: dynamism of the metabolism of tumor cells and tissues. Cancer Lett 2009; 278(2) 130–138.

[18] Klionsky DJ. Autophagy: from phenomenology to molecular understanding in less than a decade. Nat Rev Mol Cell Biol 2007; 8(11) 931–937.

[19] Mizushima N, Yoshimori T, Ohsumi Y. The role of Atg proteins in autophagosome formation. Annu Rev Cell Dev Biol. 2011; 27:107-32.

[20] Yue Z, Jin S, Yang C, Levine AJ, Heintz N. Beclin 1, an autophagy gene essential for early embryonic development, is a haploinsufficient tumor suppressor. Proc Natl Acad Sci U S A 2003;100(25) 15077–15082.

[21] Qu X, Yu J, Bhagat G, Furuya N, Hibshoosh H, Troxel A, Rosen J, Eskelinen EL, Mizushima N, Ohsumi Y, Cattoretti G, Levine B. Promotion of tumorigenesis by heterozygous disruption of the beclin 1 autophagy gene. J Clin Invest 2003;112(12) 1809–1820.

[22] Liang XH, Jackson S, Seaman M, Brown K, Kempkes B, Hibshoosh H, Levine B. Induction of autophagy and inhibition of tumorigenesis by beclin 1. Nature 1999; 402(6762) 672–676.

[23] Aita VM, Liang XH, Murty VV, Pincus DL, Yu W, Cayanis E, Kalachikov S, Gilliam TC, Levine B. Cloning and genomic organization of beclin 1, a candidate tumor suppressor gene on chromosome 17q21. Genomics 1999; 59(1) 59–65.
[24] Lee JW, Jeong EG, Lee SH, Yoo NJ, Lee SH. Somatic mutations of BECN1, an autophagy-related gene, in human cancers. APMIS 2007; 115(6) 750–756.

[25] Ahn CH, Jeong EG, Lee JW, Kim MS, Kim SH, Kim SS, Yoo NJ, Lee SH. Expression of beclin-1, an autophagy-related protein, in gastric and colorectal cancers. APMIS 2007; 115(12) 1344–1349.

[26] Mariño G, Salvador-Montoliu N, Fueyo A, Knecht E, Mizushima N, López-Otín C. Tissue-specific autophagy alterations and increased tumorigenesis in mice deficient in Atg4C/autophagin-3. J Biol Chem. 2007; 282(25) 18573–18583.

[27] Kang MR, Kim MS, Oh JE, Kim YR, Song SY, Kim SS, Ahn CH, Yoo NJ, Lee SH. Frameshift mutations of autophagy-related genes ATG2B, ATG5, ATG9B and ATG12 in gastric and colorectal cancers with microsatellite instability. J Pathol. 2009; 217(5) 702–706.

[28] Hammond EM, Brunet CL, Johnson GD, Parkhill J, Milner AE, Brady G, Gregory CD, Grand RJ. Homology between a human apoptosis specific protein and the product of APG5, a gene involved in autophagy in yeast. FEBS Lett. 1998; 425 (3) 391–395.

[29] Kim MS, Song SY, Lee JY, Yoo NJ, Lee SH. Expressional and mutational analyses of ATG5 gene in prostate cancers. APMIS. 2011;119(11) 802–807.

[30] An CH, Kim MS, Yoo NJ, Park SW, Lee SH. Mutational and expressionnal analyses of ATG5, an autophagy-related gene, in gastrointestinal cancers. Pathol Res Pract. 2011; 207(7): 433–437.

[31] Liang C, Feng P, Ku B, Dotan I, Canaani D, Oh BH, Jung JU. Autophagic and tumour suppressor activity of a novel Beclin1-binding protein UVRAG. Nat Cell Biol. 2006; 8(7) 688–699.

[32] Takahashi Y, Coppola D, Matsushita N, Cualing HD, Sun M, Sato Y, Liang C, Jung JU, Cheng IJ, Mule J, Pledger WJ, Wang HG. Bif-1 interacts with Beclin 1 through UVRAG and regulates autophagy and tumorigenesis. Nat Cell Biol. 2007; 9(10) 1142–1151.

[33] Ionov Y, Nowak N, Perucho M, Markowitz S, Cowell JK. Manipulation of nonsense mediated decay identifies gene mutations in colon cancer cells with microsatellite instability. Oncogene 2004; 23: 639–645.

[34] Kim MS, Jeong EG, Ahn CH, Kim SS, Lee SH, Yoo NJ. Frameshift mutation of UVRAG, an autophagy-related gene, in gastric carcinomas with microsatellite instability. Hum Pathol 2008; 39(7) 1059–1063.

[35] Bekpen C, Xavier RJ, Eichler EE. Human IRGM gene “to be or not to be”. Semin Immunopathol 2010; 32(4) 437–444.

[36] Parkes M, Barrett JC, Prescott NJ, Tremelling M, Anderson CA, Fisher SA, Roberts RG, Nimmo ER, Cummings FR, Soars D, Drummond H, Lees CW, Khawaja SA, Bagnall R, Burke DA, Todhunter CE, Ahmad T, Onnie CM, McArdle W, Strachan D, Be-
Role of Autophagy in Cancer
http://dx.doi.org/10.5772/55315

the G, Bryan C, Lewis CM, Deloukas P, Forbes A, Sanderson J, Jewell DP, Satsangi J, Mansfield JC; Wellcome Trust Case Control Consortium, Cardon L, Mathew CG. Sequence variants in the autophagy gene IRGM and multiple other replicating loci contribute to Crohn’s disease susceptibility. Nat Genet 2007; 39(7) 830–832.

[37] Intemann CD, Thye T, Niemann S, Browne EN, Amanua Chinbuah M, Enimil A, Gyapong J, Osei I, Owusu-Dabo E, Helm S, Rüsch-Gerdes S, Horstmann RD, Meyer CG. Autophagy gene variant IRGM -261T contributes to protection from tuberculosis caused by Mycobacterium tuberculosis but not by M. africanum strains. PLoS Pathog. 2009; 5(9) e1000577.

[38] Prescott NJ, Dominy KM, Kubo M, Lewis CM, Fisher SA, Redon R, Huang N, Stranger BE, Blaszczzyk K, Hudspith B, Parkes G, Hosono N, Yamazaki K, Onnie CM, Forbes A, Dermitzakis ET, Nakamura Y, Mansfield JC, Sanderson J, Hurles ME, Roberts RG, Mathew CG. Independent and population-specific association of risk variants at the IRGM locus with Crohn’s disease. Hum Mol Genet 2010; 19(9) 1828–1839.

[39] Burada F, Plantinga TS, Ioana M, Rosentoul D, Angelescu C, Joosten LA, Netea MG, Saftoiu A. IRGM gene polymorphisms and risk of gastric cancer. J Dig Dis. 2012;13(7) 360–365.

[40] Lerman MI, Minna JD The 630-kb lung cancer homozygous deletion region on human chromosome 3p21.3: identification and evaluation of the resident candidate tumor suppressor genes. The International Lung Cancer Chromosome 3p21.3 Tumor Suppressor Gene Consortium. Cancer Res. 2000; 60(21) 6116 –6133.

[41] Yu J, Ni M, Xu J, Zhang H, Gao B, Gu J, Chen J, Zhang L, Wu M, Zhen S, Zhu J. Methylation profiling of twenty promoter-CpG islands of genes which may contribute to hepatocellular carcinogenesis. BMC Cancer. 2002;2: 29

[42] Schagdarsurengin U, Wilkens L, Steinemann D, Flemming P, Kreipe HH, Pfeifer GP, Schlegelberger B, Dammann R. Frequent epigenetic inactivation of the RASSF1A gene in hepatocellular carcinoma. Oncogene. 2003; 22(12)1866–1871.

[43] Fischer JR, Ohnmacht U, Rieger N, Zemaitis M, Stoffregen C, Kostrzewa M, Buchholz E, Manebold C, Lahm H. Promoter methylation of RASSF1A, RAR beta and DAPK predict poor prognosis of patients with malignant mesothelioma. Lung Cancer. 2006; 54(1) 109–116.

[44] Jing F, Yuping W, Yong C, Jie L, Jun L, Xuanbing T, Lihua H. CpG island methylator phenotype of multigene in serum of sporadic breast carcinoma. Tumor Biology. 2010; 31(4):321–331.

[45] Dallol A, Agathanggelou A, Fenton SL, Ahmed-Choudhury J, Hesson L, Vos MD, Clark GJ, Downward J, Maher ER, Latif F. RASSF1A interacts with microtubule-associated proteins and modulates microtubule dynamics. Cancer Research. 2004; 64(12) 4112–4116.
[46] Min SS, Jin SC, Su JS, Yang TH, Lee H, Lim DS. The centrosomal protein RAS association domain family protein 1A (RASSF1A)-binding protein 1 regulates mitotic progression by recruiting RASSF1A to spindle poles. Journal of Biological Chemistry. 2005; 280(5) 3920–3927.

[47] Bialik S, Kimchi A. The death-associated protein kinases: structure, function, and beyond. Annual Review of Biochemistry. 2006; 75:189–210.

[48] Gozuacik D, Kimchi A. DAPk protein family and cancer. Autophagy. 2006; 2(2)74–79.

[49] Liu L, Xie R, Yang C, McKeenan WL. Dual function microtubule- and mitochondria-associated proteins mediate mitotic cell death. Cellular Oncology. 2009; 31(5) 393–405.

[50] Whang YM, Kim YH, Kim JS, Yoo YD. RASSF1A suppresses the c-Jun-NH2-kinase pathway and inhibits cell cycle progression. Cancer Res. 2005; 65(9) 3682–3690.

[51] Whang YM, Park KH, Jung HY, Jo UH, Kim YH. Microtubule-damaging agents enhance RASSF1A-induced cell death in lung cancer cell lines. Cancer. 2009; 115(6)1253–1266.

[52] Agathanggelou A, Bièche I, Ahmed-Choudhury J, Nicke B, Dammann R, Baksh S, Gao B, Minna JD, Downward J, Maher ER, Latif F. Identification of novel gene expression targets for the Ras association domain family 1 (RASSF1A) tumor suppressor gene in non-small cell lung cancer and neuroblastoma. Cancer Res. 2003; 63(17) 5344–5351.

[53] Schagdarsurengin U, Seidel C, Ulbrich EJ, Kölbl H, Dittmer J, Dammann R. A polymorphism at codon 133 of the tumor suppressor RASSF1A is associated with tumorous alteration of the breast. Int J Oncol. 2005; 27 (1) 185–191.

[54] Gao B, Xie XJ, Huang C, Shames DS, Chen TT, Lewis CM, Bian A, Zhang B, Olopade OI, Garber JE, Euhus DM, Tomlinson GE, Minna JD. RASSF1A polymorphism A133S is associated with early onset breast cancer in BRCA1/2 mutation carriers. Cancer Res. 2008; 68(1) 22–25.

[55] Bergqvist J, Latif A, Roberts SA, Hadfield KD, Laloo F, Howell A, Evans DG, Newman WG. RASSF1A polymorphism in familial breast cancer. Fam Cancer. 2010; 9(3) 263–265.

[56] Kanzaki H, Hanafusa H, Yamamoto H, Yasuda Y, Imai K, Yano M, Aoe M, Shimizu N, Nakachi K, Ouchida M, Shimizu K. Single nucleotide polymorphism at codon 133 of the RASSF1 gene is preferentially associated with human lung adenocarcinoma risk. Cancer Lett. 2006; 238(1) 128–134.

[57] Bayram S. RASSF1A Ala133Ser polymorphism is associated with increased susceptibility to RASSF1A Ala133Ser polymorphism is associated with increased susceptibility to hepatocellular carcinoma in a Turkish population. Gene. 2012; 498(2) 264–269.
[58] Schagdarsurengin U, Wilkens L, Steinemann D, Flemming P, Kreipe HH, Pfeifer GP, Schlegelberger B, Dammann R. Frequent epigenetic inactivation of the RASSF1A gene in hepatocellular carcinoma. Oncogene. 2003; 22 (12) 1866–1871.

[59] Hu L, Chen G, Yu H, Qiu X. Clinicopathological significance of RASSF1A reduced expression and hypermethylation in hepatocellular carcinoma. Hepatol Int. 2010; 4 (1) 423–432.

[60] Hamilton G, Yee KS, Scrace S, O’Neill E. ATM regulates a RASSF1A-dependent DNA damage response. Curr Biol. 2009;19(23) 2020–2025.

[61] Bayram S. RASSF1A Ala133Ser polymorphism is associated with increased susceptibility to hepatocellular carcinoma in a Turkish population. Gene. 2012; 498(2) 264–269.

[62] Gordon M, El-Kalla M, Baksh S. RASSF1 Polymorphisms in Cancer. Mol Biol Int. 2012;2012: 365213.

[63] Li J, Wang F, Protopopov A, Malyukova A, Kashuba V, Minna JD, Lerman MI, Klein G, Zabarovsky E. Inactivation of RASSF1C during in vivo tumor growth identifies it as a tumor suppressor gene. Oncogene. 2004; 23(35):5941–5949.

[64] Amaar YG, Minera MG, Hatran LK, Strong DD, Mohan S, Reeves ME. Ras association domain family 1C protein stimulates human lung cancer cell proliferation. Am J Physiol Lung Cell Mol Physiol. 2006; 291(6) L1185–L1190.

[65] Reeves ME, Baldwin SW, Baldwin ML, Chen ST, Moretz JM, Aragon RJ, Li X, Strong DD, Mohan S, Amaar YG. Ras-association domain family 1C protein promotes breast cancer cell migration and attenuates apoptosis. BMC Cancer. 2010;10: 562.

[66] Malpeli G, Amato E, Dandrea M, Fumagalli C, Debattisti V, Boninsegna L, Pelosi G, Falconi M, Scarpa A. Methylation-associated down-regulation of RASSF1A and up-regulation of RASSF1C in pancreatic endocrine tumors. BMC Cancer. 2011;11: 351

[67] Barnich N, Aguirre JE, Reinecker HC, Xavier R, Podolsky DK. Membrane recruitment of NOD2 in intestinal epithelial cells is essential for nuclear factor-κB activation in muramyl dipeptide recognition. J Cell Biol, 2005; 170 (1) 21–26.

[68] Inohara N, Koseki T, del Peso L, Hu Y, Yee C, Chen S, Carrio R, Merino J, Liu D, Ni J, Núñez G. Nod1, an Apaf-1-like activator of caspase-9 and nuclear factor-kappaB. J Biol Chem. 1999; 274 (21) 14560–14567. 231

[69] Ogura Y, Inohara N, Benito A, Chen FF, Yamaoka S, Nunez G. Nod2, a Nod1/Apaf-1 family member that is restricted to monocytes and activates NF-kappaB. J Biol Chem. 2001; 276 (7) 4812–4818.

[70] Travassos LH, Carneiro LA, Ramjeet M, Hussey S, Kim YG, Magalhães JG, Yuan L, Soares F, Chea E, Le Bourhis L, Boneca IG, Allaoui A, Jones NL, Núñez G, Girardin Role of Autophagy in Cancer

http://dx.doi.org/10.5772/55315
SE, Philpott DJ. Nod1 and Nod2 direct autophagy by recruiting ATG16L1 to the plasma membrane at the site of bacterial entry. Nat Immunol, 2010; 11 (1) 55–62.

[71] Alhopuro P, Ahvenainen T, Mecklin JP, Juhola M, Järvinen HJ, Karhu A, Aaltonen LA. NOD2 3020insC alone is not sufficient for colorectal cancer predisposition. Cancer Res. 2004; 64(20) 7245–7247.

[72] Kurzawski G, Suchy J, Kładny J, Grabowska E, Mierzejewski M, Jakubowska A, Debniak T, Cybulski C, Kowalska E, Szych Z, Domagała W, Scott RJ, Lubiński J. The NOD2 3020insC mutation and the risk of colorectal cancer. Cancer Res. 2004; 64(5)1604–1606.

[73] Papaconstantinou I, Theodoropoulos G, Gazouli M, Panoussopoulos D, Mantzaris GJ, Felekouras E, Bramis J. Association between mutations in the CARD15/NOD2 gene and colorectal cancer in a Greek population. Int J Cancer. 2005; 114(3) 433–435

[74] Roberts RL, Gearry RB, Allington MD, Morrin HR, Robinson BA, Frizelle FA. Caspase recruitment domain-containing protein 15 mutations in patients with colorectal cancer. Cancer Res. 2006; 66(5) 2532–2535

[75] Lakatos PL, Hitre E, Szalay F, Zinober K, Fuszek P, Lakatos L, Fischer S, Osztovits J, Gemela O, Veres G, Papp J, Ferenci P. Common NOD2/CARD15 variants are not associated with susceptibility or the clinicopathologic characteristics of sporadic colorectal cancer in Hungarian patients. BMC Cancer. 2007; 7: 54.

[76] Tuupanen S, Alhopuro P, Mecklin JP, Jarvinen H, Aaltonen LA. No evidence for association of NOD2 R702W and G908R with colorectal cancer. Int J Cancer. 2007; 121(1) 76–79.

[77] Rigoli, L, Di Bella, C, Fedele, F, Procopio, V, Amorini M, Lo Giudice,G, Romeo, P, Pugliatti, F, Finocchiaro, G, Lucianò, R, & Caruso, RA. TLR4 and NOD2/CARD15 genetic polymorphisms and their possible role in gastric carcinogenesis. Anticancer Res. (2010). , 30(2), 513-517.

[78] Szeliga J, Sondka Z, Jackowski M, Jarkiewicz-Tretyn J, Tretyn A, Malenczyk M. NOD2/CARD15 polymorphism in patients with rectal cancer. Med Sci Monit. 2008; 14(9) CR480–CR484.

[79] Tian Y, Li Y, Hu Z, Wang D, Sun X, Ren C. Differential effects of NOD2 polymorphisms on colorectal cancer risk: a meta-analysis. Int J Colorectal Dis. 2010 Feb;25(2): 161–168.

[80] Lubiński J, Huzarski T, Kurzawski G, Suchy J, Masojć B, Mierzejewski M, Lener M, Domagała W, Chosia M, Teodorczyk U, Medrek K, Debniak T, Złowocka E, Gronwald J, Byrski T, Grabowska E, Nej K, Szymańska A, Szymańska J, Matyjasik J, Cybulski C, Jakubowska A, Górski B, Narod SA. The 3020insC Allele of NOD2 Predisposes to Cancers of Multiple Organs. Hered Cancer Clin Pract. 2005; 3(2) 59–63.
[81] Kutikhin AG. Role of NOD1/CARD4 and NOD2/CARD15 gene polymorphisms in cancer etiology. Hum Immunol. 2011;72(10) 955–968.

[82] Suchy J, Kluszy-Grabowska E, Kladny J, Cybulski C, Wokolorczyk D, Szymańska-Pasternak J, Kurzawski G, Scott RJ, Lubiński J. Inflammatory response gene polymorphisms and their relationship with colorectal cancer risk. BMC Cancer. 2008; 8:112.

[83] Rosenfeldt MT, Nixon C, Liu E, Mah LY, Ryan KM. Analysis of macroautophagy by immunohistochemistry. Autophagy. 2012; 8(6) 963-969.

[84] Martinet W, De Meyer GR, Andries L, Herman AG, Kockx MM. Detection of autophagy in tissue by standard immunohistochemistry: possibilities and limitations. Autophagy. 2006; 2(1) 55-57.

[85] Yang ZJ. Measurement of autophagy-related proteins by immunohistochemistry/tissue microarray to characterize autophagy: problems and considerations. Am J Physiol Gastrointest Liver Physiol. 2012; 302(11) G1356-G1357.

[86] Shintani M, Sangawa A, Yamao N, Miyake T, Kamoshida S. Immunohistochemical analysis of cell death pathways in gastrointestinal adenocarcinoma. Biomed Res. 2011; 32(6) 379-386.

[87] Tanida I, Ueno T, Kominami E. LC3 conjugation system in mammalian autophagy. Int J Biochem Cell Biol. 2004; 36(12) 2503-2518.

[88] Hemelaar J, Lelyveld VS, Kessler BM, Ploegh HL. A single protease, Apg4B, is specific for the autophagy-related ubiquitin-like proteins GATE-16, MAP1-LC3, GABARAP, and Apg8L. J Biol Chem. 2003; 278(51) 51841-51850.

[89] Kabeya Y, Mizushima N, Ueno T, Yamamoto A, Kirisako T, Noda T, Kominami E, Ohsumi Y, Yoshimori T. LC3, a mammalian homologue of yeast Apg8p, is localized in autophagosome membranes after processing. EMBO J. 2000; 19 (21) 5720-5728.

[90] Karantza-Wadsworth V, White E. Role of autophagy in breast cancer. Autophagy 2007; 3(6) 610-613.

[91] Cai MY, Zhang B, He WP, Yang GF, Rao HL, Rao ZY, Wu QL, Guan XY, Kung HF, Zeng YX, Xie D. Decreased expression of PinX1 protein is correlated with tumor development and is a new independent poor prognostic factor in ovarian carcinoma. Cancer Sci. 2010; 101(6) 1543–1549.

[92] Yousefi S, Perozzi R, Schmid I, Ziemiecki A, Schaffner T, Scazzopazza L, Brunner T, Simon HU. Calpain-mediated cleavage of Atg5 switches autophagy to apoptosis. Nat Cell Biol. 2006; 8(10) 1124–1132.

[93] Cuddeback SM, Yamaguchi H, Komatsu K, Miyashita T, Yamada M, Wu C, Singh S, Wang HG. Molecular cloning and characterization of Bif-1: a novel SH3 domain-containing protein that associates with Bax. J Biol Chem. 2001; 276 (23) 20559-20565.
[94] Pierrat B, Simonen M, Cueto M, Mestan J, Ferrigno P, Heim J. SH3GLB, a new endo-
phlin-related protein family featuring an SH3 domain. Genomics. 2001; 71(2)
222-234.

[95] Chen YB, Hou JH, Feng XY, Chen S, Zhou ZW, Zhang XS, Cai MY. Decreased expres-
sion of Beclin 1 correlates with a metastatic phenotypic feature and adverse prognosis of gastric carcinomas. J Surg Oncol. 2012; 105(6) 542-547.

[96] Miao Y, Zhang Y, Chen Y, Chen L, Wang F. GABARAP is overexpressed in colorectal carcinoma and correlates with shortened patient survival. Hepatogastroenterology. 2010; 57(98) 257-261.

[97] Li BX, Li CY, Peng RQ, Wu XJ, Wang HY, Wan DS, Zhu XF, Zhang XS. The expression of beclin 1 is associated with favorable prognosis in stage IIIIB colon cancers. Autophagy. 2009; 5(3) 303-306.

[98] Coppola D, Khalil F, Eschrich SA, Boulware D, Yeatman T, Wang HG. Down-regulation of Bax-interacting factor-1 in colorectal adenocarcinoma. Cancer. 2008; 113(10) 2665-2670.

[99] Yoshioka A, Miyata H, Doki Y, Yamasaki M, Sohma I, Gotoh K, Takiguchi S, Fuji-
waray, Uchiyama Y, Monden M. LC3, an autophagosome marker, is highly ex-
pressed in gastrointestinal cancers. Int J Oncol. 2008; 33(3) 461-468.

[100] Guo GF, Jiang WQ, Zhang B, Cai YC, Xu RH, Chen XX, Wang F, Xia LP. Autophagy-related proteins Beclin-1 and LC3 predict cetuximab efficacy in advanced colorectal cancer. World J Gastroenterol. 2011; 17(43) 4779-4786.

[101] Kondo Y, Kanzawa T, Sawaya R, Kondo S. The role of autophagy in cancer development and response to therapy. Nat Rev Cancer 2005; 5(9) 726–734.

[102] Yin M, Yan J, Voutsina A, Tibaldi C, Christiani DC, Heist RS, Rosell R, Booton R, Wei Q. No evidence of an association of ERCC1 and ERCC2 polymorphisms with clinical outcomes of platinum-based chemotherapies in non-small cell lung cancer: a meta-
analysis. Lung Cancer. 2011; 72(3) 370–377.

[103] Sirichanchuen B, Pengsuparp T, Chanvorachote P. Long-term cisplatin exposure impairs autophagy and causes cisplatin resistance in human lung cancer cells. Mol Cell Biochem. 2012; 364(1-2)11–18.

[104] Apel A, Herr I, Schwarz H, Rodemann HP, Mayer A. Blocked autophagy sensitizes resistant carcinoma cells to radiation therapy. Cancer Res. 2008; 68(5) 1485–1494.

[105] Kim KW, Hwang M, Moretti L, Jaboin JJ, Cha YI, Lu B. Autophagy upregulation by inhibitors of caspase-3 and mTOR enhances radiotherapy in a mouse model of lung cancer. Autophagy. 2008; 4(5) 659–668.