Polish Journal of Veterinary Sciences Vol. 16, No. 1 (2013), 173–180

DOI 10.2478/pjvs-2013-0026

Review

Autophagy in physiological and pathological processes – selected aspects

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Abstract

This paper describes a model of cell death, called autophagy, one among other typical and atypical processes of cell death. This phenomenon is present in the organism, from conception until death, and is conditioned by many genes of ATG family, or mTOR kinase and specific proteins, like BNIP3. This process plays a very important role not only in physiological functions of the organism but also in pathological, such as Alzheimer or Huntington disease, as well as diseases caused by viruses.

Key words: cell death, autophagy

Introduction

Even though cell death had become a subject of studies already in the XIX century the observations made in the XX century constituted a basis for defining cellular death processes. Nowadays they are classified into five basic types: extrinsic apoptosis, caspase-dependent and caspase-independent intrinsic apoptosis, regulated necrosis, mitotic catastrophe and autophagy. Six atypical forms of cell death are: anoikis, entosis, parthanatos, pyroptosis, netosis and cornification (Galuzzi et al. 2012).

Extrinsic apoptosis is a caspase-dependent form of death that can be initiated by the binding of lethal ligands like FAS/CD25, TNFα and TRAIL to various death receptors. Intrinsic apoptosis is triggered by intracellular stress, including DNA damage and cytosolic Ca^{2+} overload. Regulated necrosis is caspase-independent and possesses no features of apoptosis or autophagy, however it is RIP1- and RIP3- (receptor-interacting protein 1,3) regulated. Mitotic catastrophe is triggered by aberrant mitosis and might be an oncosuppressive mechanism initiated during M phase of the cell cycle. Autophagy is a cytoprotective response activated by dying cells in the attempt to cope with the stress and to "save" the cell to restore homeostasis (Niedźwiedzka-Rystwej and Deptuła 2009, Galuzzi et al. 2012).

Among atypical types of cell death one may enumerate anoikis, which is a special type of intrinsic apoptosis, caused by the absence of cell-to-matrix interactions. Entosis is a cell death mechanism linked to the cell-in-cell phenotype, provoked by the loss of ECM interactions. Parthanatos might be a modification of programmed necrosis, a caspase non-dependent process involving the DNA damage-responsive enzymes, poly(ADP-ribose) polymerases (PARPs), in particular PARP1. Pyroptosis is death of macrophages resulting from bacterial infection with the presence of inflammasome. Netosis is death of neutrophils and eosinophils generated by NET (neutrophil extracellu-

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lar trap). Cornification is a physiological death of the cells of the external layer (Galluzi et al. 2012).

Autophagy

Autophagy is a conservative and phylogenetically old type of cell death which leads to accumulation of large amounts of autophagosomes causing vacuolization of cytoplasm (Lamparska-Przybysz and Motyl 2005, Gajewska et al. 2007, Maruniewicz and Wojtaszek 2007, Deretic and Klionsky 2008, Matryniszyn et al. 2008, Uchiyama et al. 2008, Niedźwiedzka-Rystwej and Deptuła 2009). Four types of autophagy can be distinguished: macro-, and microautophagy, specific autophagy (pexophagy), and chaperone-mediated autophagy (Lamparska-Przybysz and Motyl 2005, Gajewska et al. 2007, Levine and Kroemer 2008, Matryniszyn et al. 2008, Uchiyama et al. 2008, Niedźwiedzka-Rystwej and Deptuła 2009). Macroautophagy is characterized by formation of phagosome which encapsulates organelles that are to be degraded, while microautophagy leads to degradation of only small parts of the cell. Pexophagy is a specific process of peroxisomes; degradation; whereas chaperone-mediated autophagy is responsible for lysosomal degradation of single cytosolic proteins, which are recognized by specific chaperone proteins and transported to lysosomes (Lamparska-Przybysz and Motyl 2005, Gajewska et al. 2007, Levine and Kroemer 2008, Matryniszyn et al. 2008, Uchiyama et al. 2008, Niedźwiedzka-Rystwej and Deptuła 2009).

Induction and proper course of autophagy is regulated by a specific set of genes that control the expression of regulatory proteins, activation of catepsins, as well as proteins responsible for the activation of this process (Gajewska et al. 2007, Niedźwiedzka-Rystwej and Deptuła 2009, Sobolewska et al. 2010). The abovementioned genes belong to an ATG (autophagy) family and include for example: Atg8 (mammalian homolog is named LC3 – light chain 3) – a specific marker of active autophagosomes, and Beclin1 (mammalian homolog of Atg6) that controls autophagy via regulation of vacuolar transport, and induction of the protein complex responsible for autophagosome formation (Gajewska et al. 2007, Deretic and Klionsky 2008, Sobolewska et al. 2010). It has been shown that Beclin1 protein binds with Bcl-2 (B-cell lymphoma 2) inhibiting apoptosis which prevents a simultaneous activation of autophagy and programmed cell death in cells (Deretic and Klionsky 2008). Autophagy is also tightly controlled by mTOR (mammalian target of rapamycin) kinase which is a known nutrient sensor in cells and becomes inactivated during starvation period (Gajewska et al. 2007, Niedźwiedzka-Rystwej and Deptuła 2009, Sobolewska et al. 2010). Recent studies on bovine mammary gland development (Sobolewska et al. 2009) revealed that growth factors: IGF-I and EGF regulate the process of autophagy in epithelial cells through the mTOR signaling pathway. Another important protein engaged in this process is BNIP3 (BCL2/adenovirus E1B 19 kDa-interacting protein3), which determines the fusion of lysosomes by its specific transmembrane (TM) domain (Swoboda and Strządała 2009).

Autophagy has also been linked with innate immune recognition receptors: TLRs (Toll-like receptors) especially: TLR1/TLR2, TLR3, TLR4, TLR7/TLR8 and indirectly TLR9 in macrophages, dendritic cells and neutrophils (Deretic 2011). It was noted that these receptors were activated in the course of the induction of autophagy mediated by Beclin1 (Deretic 2011). Likewise, other innate immune receptors, such as NLRs (Nod-like receptors) were shown to activate autophagy. Studies on mammalian cells revealed that Nod1 and Nod2 were able to interact with Atg16L1 and, additionally, Nod2 induced this process in dendritic cells intensifying the antigen presentation by MHC class II. Further observations showed that interactions with NLRs and autophagy machinery leads to augmented control of the bacterial infections (Shaw et al. 2011). Activation of autophagy can be mediated also by RLRs (Rig-like receptors) (Deretic 2011), while recent investigations revealed a new group of innate immunity receptors – SLRs – sequestasome (p62/SQSTM1) – like receptors, which are mainly responsible for recognition of endogenous bacteria and triggering them into autophagic pathway (Deretic 2011). A characteristic feature of the SLRs' structure is ubiquitin recognition sequence occurring simultaneously with LIR region (LC3-interacting region) (Deretic 2011). So far three receptors belonging to this group have been described: p62, NBR1, and NDP52, all involved in the induction of autophagy during infections caused by bacteria: *Salmonella* sp., *Shigella* sp., *Streptococcus* sp. and *Listeria* sp., as well as Sindbis virus (Deretic 2011). The p62 receptor was also shown to have an ability to accumulate the precursor forms in the cytoplasm, which undergo conversion in the autolysosomes to proteins with antibacterial properties (Deretic 2011). The induction of autophagy may also be caused by IFN-γ, TNF-α, IL-1, IL-2, IL-6 and TGB-β, whereas inhibitors can be IL-4, IL-10, IL-13 (Gade 2011, Harris 2011).

As mentioned above, autophagy can be divided into specific stages and its induction is characterized by formation of autophagosomes within the cytoplasm, a process regulated by many factors. The signals

initiating autophagy are sensed by surface membrane receptors which induce the formation of double membrane structures – phagofores (Deretic and Klionsky 2008) that serve to sequestrate "used" or damaged proteins, or their aggregates, as wells as the whole cellular organelles. When the double membrane surrounds the targeted proteins and organelles a vesicle structure – autophagosome is created. In the next step autophagosome binds with lysosomal membrane enabling the lysosomal enzymes to partially digest the membranes of the vesicle. This stage is defined as fusion and leads to formation of an autolysosome. In the following step the content of the autolysosome is digested by the lysosomal enzymes (Deretic and Klionsky 2008). It should be noted that autophagy, belonging to the typical forms of cell death, contributes also to cell survival (Lamparska-Przybysz and Motyl 2005, Gajewska et al. 2007, Levine and Kroemer 2008, Matryniszyn et al. 2008, Uchiyama et al. 2008, Niedźwiedzka-Rystwej and Deptuła 2009). That is why it is also described as an intracellular degradation system of the cytoplasm content, controlling the removal of many elements and organelles of the cytoplasm, such as mitochondria, or peroxisomes, therefore maintaining the proper homeostasis in the organisms (Lamparska-Przybysz and Motyl 2005, Niedźwiedzka-Rystwej and Deptuła 2009). Autophagy, additionally, regulates some selected tissue-specific processes, including intracellular biogenesis of surfactant and neuromelanin biosynthesis (Lamparska-Przybysz and Motyl 2005, Niedźwiedzka-Rystwej and Deptuła 2009). Additionally it also contributes to the dopaminergic neurons degeneration in the Parkinson diseases and takes part in regulation of aging of the organisms (Lamparska-Przybysz and Motyl 2005, Meijer and Codogno 2006, Deretic and Klionsky 2008, Levine and Kroemer 2008, Matryniszyn et al. 2008). Autophagy is also involved in the adaptation to starvation conditions, as it enables protein digestion, providing cells with essential amino acids during the withdrawal of the amino acids; source from the nutrients, thus maintaining the proper function of the macroorganism (Lamparska-Przybysz and Motyl 2005, Gajewska et al. 2007, Maruniewicz and Wojtaszek 2007, Levine and Kroemer 2008, Matryniszyn et al. 2008, Uchiyama et al. 2008, Niedźwiedzka-Rystwej and Deptuła 2009).

The cells of eukaryotic organisms are able to induce autophagy in the stress conditions by increasing the activity and interactions of several regulatory elements. This type of processes have been characterized most extensively in saprophytic yeasts (*Saccharomycetes cerevisiae)* based on the genetic mutagenesis studies (Mariño and López-Otín 2004). It has been shown that around 25 genes of this species is specifically involved in autophagy, controlling the course of each stage of this process. These genes regulate the signaling pathways, formation of the autophagosome, as well as autophagosome-lysosome fusion (Mariño and López-Otín 2004). So far, several signaling pathways, taking part in autophagy activation and progression, have been described, including Tor pathway (target of rapamycin; serine-treonine kinase), ATG1 (autophagy 1) as well as the PI3K pathway (phosphatidylinositol 3-kinase) and Vps34 (vacuolar protein sorting 34). The Tor pathway serves to sense the changes in nutrient conditions in the organism. In mammals mTOR kinase regulates autophagy in a similar manner to the Tor signaling described in yeasts and plays a significant role in activation of the cytoplasm to vacuole targeting – CVT (Mariño and López-Otín 2004). The second signaling pathway includes the ATG1 gene, whose product is the main component of the hypothetical complex that induces phagosome formation (Matryniszyn et al. 2008). The third signaling pathway is mediated by PI3K in mammals and Vps34 in yeasts and plays a key role in the early stage of autophagosomes formation, as well as contributes to the control of the processes connected with transmembrane transport in the cell (Mariño and López-Otín 2004).

The proteins that take part in the stage of autophagosome formation also can be divided into three subgroups. The first subgroup is defined as the ubiquitin-like system – UBL which includes the protein complex ATG12-ATG5 critical for the formation of the autophagosomes. The second subgroup contains the ATG8 – a soluble cytoplasmic protein, while the third complex depends on the ATG9 protein (Mariño and López-Otín 2004). In the final stage of autophagy, during which the autophagosomes fuse with lysosomes, it is also controlled by many factors regulating different types of vesicular transport. SNARE proteins (small NSF associated proteins receptors) are necessary for the proper maturation of autophagosomes. Although in mammals this process is more complex than in yeasts, in case of both types of organisms it depends on the activity of monomeric GTPases: Rab22 and Rab24 – enzymes responsible for guanosintriphosphate degradation. Among the large number of proteins controlling the process of autophagy the cytoskeletal molecules also play an important role, especially the cytoplasmic microtubules (Mariño and López-Otín 2004).

Autophagy in physiology and pathology

A variety of functions (Fig. 1) that are being assigned to autophagy in mammalian cells can partially

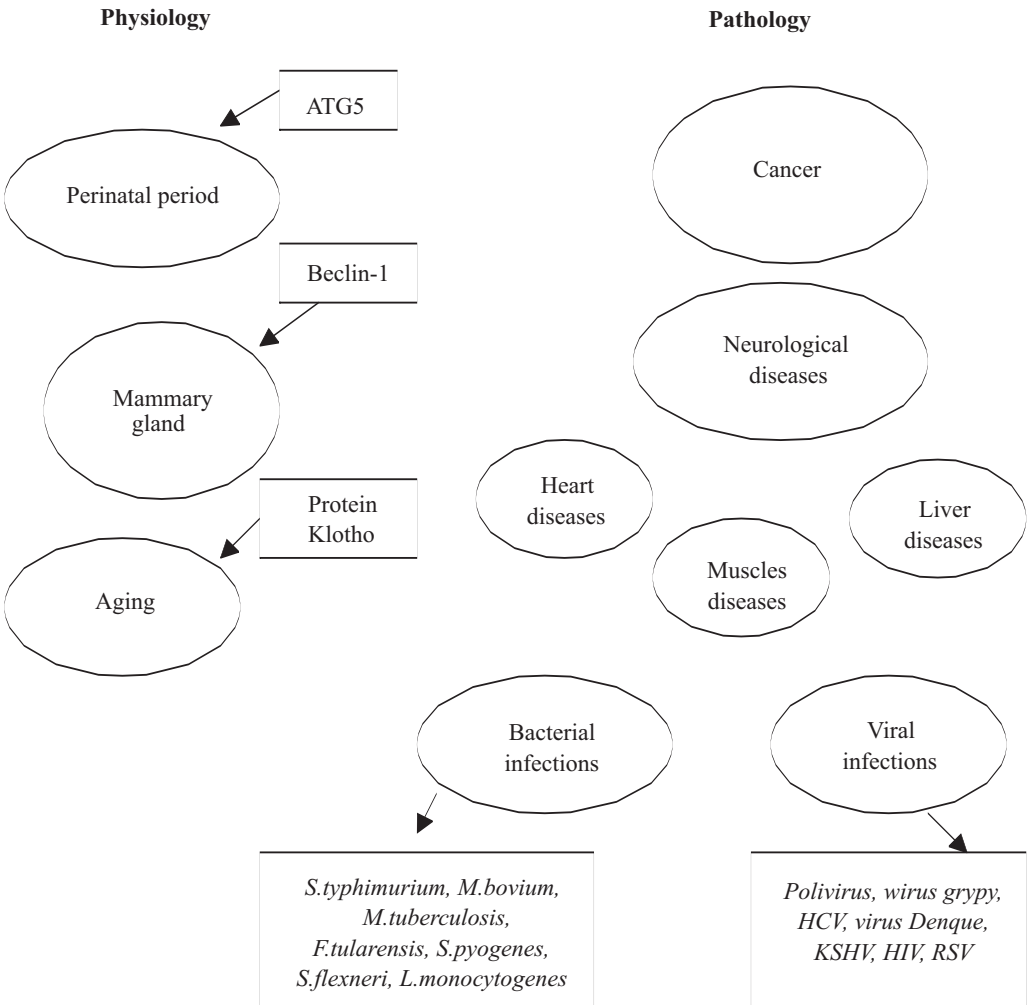

Fig. 1. The role of autophagy in physiology and pathology.

explain the large number of diseases in which this process is involved, predominantly as a "clean up" mechanism of the phagocytic cells of the immune system (Mariño and López-Otín 2004, Niedźwiedzka-Rystwej and Deptuła 2009).

Autophagy in perinatal period

Autophagy is a process necessary for living organisms since the conception. It enables the implantation of an embryo in uterus and proper execution of its first divisions. Studies on mice showed that when embryos were formed by oocytes lacking the Atg5 protein the number of divisions were limited to 4-8 (Niedźwiedzka-Rystwej and Deptuła 2009). The process of autophagy plays also an important function in the first stages of postnatal development during which the newborns undergo an adjustment process to the new way of nutrients intake (Niedźwiedzka-Rystwej and Deptuła 2009). The role of autophagy has also been proven in the remodeling of mammary gland, as during the process of involution a pronounced increase of activity of this process was noted in mammals (Niedźwiedzka-Rystwej and Deptuła 2009, Sobolewska et al. 2010). It was manifested by an elevated Beclin1 expression and a higher percentage of cells showing typical morphological features of autophagy (autophagosomes and autophagolysosomes) (Gajewska et al. 2008). It was also showed that this process was induced in the mammary gland by a decrease in the levels of secreted lactogenic hormones, serving as a defense mechanism during the deficiency of nutritional and bioactive compounds in the gland (Niedźwiedzka-Rystwej and Deptuła 2009, Sobolewska et al. 2010). Recent reports (Gajewska et al. 2008) indicate that in the bovine mammary gland autophagy can be regulated by TGF-β1 (transforming growth factor- β1) and serves as a protective mechanism against the apoptogenic effect of this growth factor. Another novel study describes the role of autophagy in the regulation of oogenesis in *Drosophila*

melanogaster (Barth et al. 2011). The authors have noted that autophagy had an effect on the maturation of *Drosophila melanogaster's* follicle cells.

Autophagy and aging

The studies on longevity and aging have also proven the involvement of autophagy in these mechanisms (Mejer and Codogno 2006, Deretic and Klionsky 2008, Levine and Kroemer 2008). The starting point for investigations concerning the role of autophagy in aging was the observation that a properly balanced diet is among the factors determining longevity. In addition, it has been shown that aging is connected with an impairment of insulin production which affects autophagy activity (Deretic and Klionsky 2008, Levine and Kroemer 2008). One of the factors involved in this process is Klotho protein, a strong anti-aging factor causing disturbance in insulin secretion – a process regarded as a physiological condition in elderly people (Mejer and Codogno 2006). It is assumed that the impairment of insulin synthesis in elderly people is a mechanism responsible for an increased level of autophagy in cells which enables the removal of damaged fragments of the cells. Additionally, during aging an elevated production of reactive oxygen species (ROS) is observed in the mitochondria. Thus autophagy, which enables the elimination of impaired organelles may contribute to increased longevity (Mejer and Codogno 2006, Deretic and Klionsky 2008). However, it should be taken under consideration that the influence of autophagy on longevity is predominantly derived from its function in regulation of the aging process (Mejer and Codogno 2006, Deretic and Klionsky 2008, Levine and Kroemer 2008). The studies on *Caenorhabditis elegans* have proven that activation of autophagy resulted in elongation of the life-span of this organism (Niedźwiedzka-Rystwej and Deptuła 2009). Similar observations were done in the investigations on *Drosophila melanogaster* in which a 50% increase of the life-span was described in the course of autophagy activation (Niedźwiedzka-Rystwej and Deptuła 2009). A recent report by Hubbard and coworkers (2010) has shown that macroautophagy regulates also metabolic processes, since the amount of energy gathered in the form of ATP is decreased when autophagy is blocked, causing a defective cytokines' production.

Autophagy in cancer

Accumulating evidence have demonstrated that autophagy is induced in cancer cells to eliminate the effects of radio-, and chemotherapy which has a negative influence on the outcome of such therapies. On the other hand autophagy can serve to destroy cancer cells, however, its excessive activity may also lead to elimination of normal cells necessary for proper functioning of the organism. Nevertheless, autophagy is proven to be a process that contributes to restriction of tumor size, inhibition of cancer cells growth and their elimination (Deretic and Klionsky 2008, Niedźwiedzka-Rystwej and Deptuła 2009). Since autophagy is induced during restricted nutrients supply, as a mechanism enabling cell survival, it may regulate the elimination of cancer cells. Activation of autophagy in starvation conditions inhibits apoptosis preventing cell death. Nowadays there are attempts to use this property as a support treatment in cancer therapy. Decreasing the activity of autophagy in cells exposed to "hunger" conditions may prevent the development of neoplasia. However, the induction of autophagy by drugs, such as rapamycin, ionizing radiation, or vitamin D analogs, may cause a sustained survival of cancer cells, giving negative results of therapy. Thus, a question has arisen, whether autophagy induced by anticancer therapeutics brings a positive effect to the treatment. The answer to this question is not simple, and is still a matter of debate. Nowadays, there are multiple regulatory pathways known to regulate autophagy, which may lead to development of anticancer therapies, linking the anticancer drugs with regulation of autophagy. In order to elaborate such treatment it is necessary to fully understand the entire mechanism of autophagy, as well as the detailed effects of the therapeutics on the physiological processes, especially in the context of cancer development. Thorough knowledge on cancer progression may determine the direction of autophagy regulation, indicating whether the process should be induced or inhibited in order to control the tumor growth and prevent metastasis (Hippert et al. 2006).

Autophagy in neurological diseases

Autophagy seems to play an important role in neurological diseases and, nowadays the most extensive studies are conducted on its function in Alzheimer's and Huntington's diseases (Mariño and López-Otín 2004). In case of the Alzheimer's disease (AD) insufficient autophagy is observed in the aging brain neurons. In comparison to young human organisms in elderly people the process of autophagy does not progress properly causing an impaired elimination of misfolded and long-lived proteins. The defective autophagy causes disruption of cellular debris elimination and some of these cytoplasmic elements form

characteristic plaques and tangles in the brain tissue, characteristic for people suffering from the AD. An additional induction of autophagy to the proper level, observed in healthy neurons, could bring a solution to this problem. So far, however, none of the conducted studies provided a solid confirmation of this hypothesis and an effective treatment has not been developed yet (Mejer and Codogno 2006, Deretic and Klionsky 2008, Matryniszyn et al. 2008).

Another neurodegenerative disease in which autophagy is pointed as one of the causative sources is Huntigton's disease (HD). In this case it is thought that improper function of autophagy disrupts the elimination of abnormal proteins, being the direct cause of HD. All neurological diseases connected with the improper activity of autophagy lead to a slow and inevitable changes in brain function. In the case of HD studies have been conducted on the use of rapamycin in the treatment. Rapamycin is a biochemical agent known to induce proper activity of autophagy which could enable to eliminate the improper proteins, characteristic for the Huntington's disease progression (Mejer and Codogno 2006, Deretic and Klionsky 2008).

Autophagy in muscle, heart and liver diseases

Similarly to the neurodegenerative diseases, autophagy plays a significant role in the development of the diseases of muscle, heart and liver tissues. In muscle disorders autophagy contributes to a decrease in the improper lysosomal function, whereas a disruption of this process causes an accumulation of autophagosomes in the cytoplasm, leading to its inhibition. Results of the present studies indicate that the disruption of lysosomal functions accounts for the development of myopathies (Levine and Kroemer 2008, Niedźwiedzka-Rystwej and Deptuła 2009). Disturbed process of autophagy is observed in Danon's disease which is characterized by myopathy, resulting from a mutation in lysosomal protein gene LAMP-2 (Lysosomal-associated membrane protein 2). Autophagy is also connected with the development of muscular dystrophy, caused by a mutation in gene encoding dysferin, a transmembrane protein expressed mainly in the muscle sarcolemma (Levine and Kroemer 2008).

Furthermore, a defective autophagy function is connected with some inherent heart diseases, such as: Danon or Pompe disease (Levine and Kroemer 2008). Autophagy is necessary for proper heart functioning, since in stressful conditions this process is induced to supply necessary energy substrates. This property is of an extreme importance in case of heart tissue which uses the highest amounts of energy of all organs in the body. Thus, heart muscle ischemia, as well as heart failure, are characterized by a decreased availability of energy substrates. This energy demand can be partially covered by autophagy, when this mechanism functions properly (Levine and Kroemer 2008). Lately it was shown that in genetic autosomal Pompe disease, there is an accumulation of p62-positive protein aggregates and expression of atrophy-related genes, which results in failure or diminution of heart (Nascimbeni et al. 2012).

The disruption of autophagy is also implied in liver diseases, as this process regulates hepatocytes function. In normal conditions proper levels of autophagy in hepatocytes serve to eliminate the degraded elements of the endoplasmic reticulum which are formed e.g. in the course of α1-antitrypsin accumulation (Levine and Kroemer 2008, Niedźwiedzka-Rystwej and Deptuła 2009).

Autophagy in bacterial infections

The role of autophagy has also been shown in many bacterial infections. It is worth mentioning that this process has been observed for the first time in macrophages infected with *Salmonella typhimurium* (Mariño et al. 2004, Rudnicka et al. 2011). It was shown that this process takes place in human infections with *Mycobacterium bovium*, *M. tuberculosis*, *Francisella tularensis, Streptococcus pyogenes, S. flexneri* and *Listeria monocytogenes* (Fabri et al. 2011, Watson et al. 2012). It was also stated that autophagy restricts pathogen replication, mainly by the interference with signaling pathways, that differ among bacteria, leading to their elimination (Wiwaran et al. 2012). NDP52 (nuclear dot protein 52) and p62, both of which contain LC3 and ubiquitin-binding domains, have been identified as autophagy receptors targeting intracellular ubiquitin-coated pathogens (Wiwaran et al. 2012). It was also shown that autophagy induction by vitamin D leads to *in vitro* antimicrobial activity against *M. tuberculosis* and on this basis p62 proves to be a key adaptor molecule that delivers antimicrobial peptides to the mycobacterial (Fabri et al. 2011). Moreover, it was found that mTOR (mammalian target of rapamycin) is crucial in bacterial infections, as its inhibition by rapamycin seems to be inducing autophagy and lowering the synthesis of many proteins (Fabri et al. 2011). It is also worth stating that there are some bacteria non-sensitive to autophagy, such as *Coxiela burnetti*, which has the ability of "silencing" autophagy in a way letting the bacteria to grow normally (Levine et al. 2011). Similarly to *Coxiela burnetti*, *Brucela abortus* shows the ability of inhibiting the autophagosome fusion, which leads inability of au-

tophagosome forming and the process of autophagy (Ogawa and Sasakawa 2006).

Autophagy in viral infections

Autophagy has been shown to play an important role in the pathogenesis of viral infections (Niedźwiedzka-Rystwej and Deptuła 2009, Wen et al. 2010). Although this process is known to contribute to an elevated antiviral defense in macroorganisms, some viruses possess an ability to block autophagy machinery and use it to increase the replication process in the host cells. Among such pathogens are e.g.: poliovirus, influenza A virus, hepatitis C virus, Dengue virus (Wen et al. 2010). The Kaposi's sarcoma-associated herpesvirus (KSHV), causing Kaposi's sarcoma, also belongs to viruses that adapt autophagy for their replication (Wen et al. 2010). The most up to date reports show additionally that some HIV proteins regulate autophagy. Studies have demonstrated that the HIV envelope protein – ENV – inhibits autophagy induction in dendritic cells, thereby blocking maturation of these cells, as well as the process of antigen presentation after infection with this virus. Another HIV protein, Nef, was shown to block autophagy in the infected cells, contributing to the protection of HIV virions against degradation (Barth et al. 2011). The data on RSV virus (respiratory syncytial virus) showed that autophagy is pivotal in dendritic cells (Morris et al. 2011). Moreover, the observations of varicella and zoster virus (*Herpesviridae*) as well as Herpes simplex virus are the proof of the importance of autophagy in replication of those viruses, as autophagosomes were found as a part of skin changes formation, typical symptoms of infection with the aboves (Carpenter et al. 2011, Wiwaran et al. 2012).

Some of the viruses, such as rotaviruses and parvovirus B19, are able to use autophagy for their effective replication in microorganism by inducing autophagy through NSP4 protein in the neighborhood of autophagosome membrane without any damage (Lee and Iwasaki 2008). Influenza virus A is using autophagy, by accumulation of autophagosomes due to silencing Atg6/Berlin-1 and Atg8/LC3 or due to the protein M2, which blocks the fusion of autophagosome and lizosome, allowing replication of the virus without its damage (Randow and Münz 2012).

Summary

In the recent years the knowledge of autophagy has increased significantly. The main reason for this progress is the development of the molecular biology methods that enabled to conduct detailed investigations. Additionally, studies on the models of transgenic animals markedly contributed to a better understanding of this process. It should be noted that the investigations on the role of autophagy in pathological conditions may result in the development of mechanisms that control this process, leading to elaboration of new treatments of many mammalian diseases.

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