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Role of Autophagy in Cancer suppression and Cancer proliferation

[1]Dr. Vishal Goel, MD, Assistant Professor, Kalpana Chawla Government Medical College & Hospital Karnal, Haryana.

[2]Dr. Jyoti Sethi MD, Professor, Kalpana Chawla Government Medical College & Hospital Karnal Haryana.

[3]Dr Ishu Kansal. Senior Resident, Luxmi Bai Institute of Dental Sciences and Hospital Patiala, Punjab

[4]Dr Sahil Goel. Surgical Resident, Royal Adelaide Hospital, University of Adelaide, Australia.

Corresponding Author: Dr. Vishal Goel, MD, Assistant Professor, Kalpana Chawla Government Medical College & Hospital Karnal, Haryana.

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Abstract

Autophagy is the cleansing process which involves the removal of old damaged organelles. These removed products undergo recycling can be used in the generation of macromolecule. Well maintained autophagic process has the tumor suppressive role. Defects in any steps of autophagy due to loss of autophagic related proteins. Damaged organelle if not be replaced results into initiation of cancer due to oxidative stress. Moreover, it is also seen in advanced tumor cell, autophagic process provide nutrition to tumor cell by metabolic reprograming and it plays a significant role in proliferation of cancer cell. Autophagy protects tumor cells from NK cells and cytotoxic T cells. Autophagy also facilitate detachment of tumor cell from primary site to distant site hence promotes metastasis.

Key words: autophagy, oxidative stress, tumor

Instruction

Autophagy: Autophagy is the process of cleaning out old, damaged abnormal organelles (protein aggregates) inside the cell. It is the process of cellular waste clearance. It is the major intracellular degradation system by which cytoplasmic materials are delivered to and degraded in the lysosome (1,2). However, the purpose of autophagy is not the simple elimination of materials, but instead, autophagy serves as a dynamic recycling system that produces new building blocks and energy for cellular renovation and homeostasis (3).

Factors (various stresses) that induce autophagy

Nutritional stress, Energy stress, Hypoxia, Redox stress, Infections, Endoplasmic reticulum stress, Mitochondrial damage. All of these stresses induce signaling pathways that start the process of autophagy (4). Nutritional deprivation leads to inhibition of mTORC-1 signaling and/or AMPK activation(3).

Tumour suppressive role of autophagy

In normal conditions interaction between ROS and autophagy occurs in a very balanced way to maintain the homeostasis, immune response and ensure survival of cell. Excess ROS up-regulate autophagy by multiple times which further initiates counteracting mechanisms which helps in restoration of Physiological ROS levels. Autophagy prevents the transformation of healthy cell into cancerous cell by removing intracellular waste, reducing oxidative stress and by attenuating tumor promoting inflammation (5).

Important risk factor of cancer initiation is chronic inflammation. Autophagy plays tumour suppressive role by regulating chronic inflammation. It decrease the pro-inflammatory cytokines such as IL-1β and IL-18. Damaged mitochondria is a great source of ROS which activates pro-inflammatory factors such as the NOD-like receptor family, pyrin domain containing 3 (NLRP3) inflammasome, it is multiprotein complex responsible for maturation and secretion of these proinflammatory cytokines. So, Autophagy plays a very important role in tumour suppression by mitophagy (6).

Methew et al have reported that ATG-5/ATG-7 deletion is associated with accumulation of damaged mitochondria leading to increase production of ROS. Mitophagy prevents ROS accumulation and its deleterious effect on DNA mutation. Through elimination of damaged mitochondria (major source of ROS) and consequently autophagy prevents tumorigenesis. Mitophagy selectively degrade mitochondria through PINK-PARKIN and BNIP3 – NIX-FUNC1 pathway which interacts with GABARAP and GABARAPL1 at autophagosomes (7).

Defective autophagy is the main causative factor results into initiation of cancer

Defective autophagy promotes the accumulation of damaged cellular organelles forms large aggregates. Failure in disposal of garbage due to defective autophagy is the source of excessive ROS production especially by damaged mitochondria. This is associated with activation of DNA damage response and cell damage which may lead to chronic inflammatory state. This may partly responsible for the tumor-forming abilities in autophagy-deficient cells and functions as a genotoxic and mutagenic agent and contribute to initiation and progression of cancer (8).

ATG2, ATG4, ATG5, Atg6 (Beclin1) ATG9, ATG12and UVRAG are the proteins involved in autophagic processes. Mutation in these proteins suppress autophagic process. Lack of autophagic process promotes accumulation of damaged cellular parts and proteins that plays role in tumor initiation (9).

Marino G states that mice deficient in ATG4 gene is more prone for fibro-sarcomas when exposed to chemical carcinogens (10). In other study Takamura observed that, deletion of ATG5 and ATG7 in mice stops the autophagic process increases the incidence liver cancer (11).

Autophagy-related gene BECN1 (encoded for Beclin 1 also known as Atg6) is important in the formation of the auto phagophore (12). In mice models Qu X observed that the loss of BECN1 results in a reduction of autophagy that leads to oxidative stress from defective organelle and unfolded protein accumulation (13). This whole process enhance cell proliferation. Several studies have shown that the level of Beclin 1 is decreased in various cancers, such as cervical squamous-cell

carcinomas and hepatocellular carcinomas, human breast, prostate, and ovarian cancers (14).

A variety of proteins, including UV radiation resistance-associated gene (UVRAG) and Bax interacting factor-1 (Bif-1), which associate with BECN1 function as tumor suppressors and positively regulate autophagy. The depletion of UVRAG and decrease of Bif-1 impaired autophagosome formation and autophagy, resulting in increased cancer-cell proliferation in colorectal, gastric, breast, and prostate cancers (15)

Oncogenes may be activated by mTOR, class I PI3K, and AKT, resulting in inhibition autophagic processes while promoting tumor cell growth, proliferation, and survival in cancer (16). Hence in normal cell oncogenes are in suppressed condition which is essential for continuing normal autophagic process. In fact, constitutive activation of the PI3K–Akt–mTOR axis which inhibits autophagy plays a significant role in initiation of cancer.

Mechanism of upgrading autophagic process in advanced tumor cell

Autophagy is a catabolic pathway that aids cancer cells to overcome intracellular or environmental stress, including nutrient deprivation, hypoxia and drugs effect. Tumors are exposed to extremely stressful conditions, including hypoxia and nutrient deprivation. Hypoxia-inducible factor 1 (HIF-1) is a primary transcriptional regulator during hypoxic conditions or during starvation (17).

In hypoxia, HIF-1 stimulates transcription of Regulated in Development and DNA damage response 1 (REDD1) that activates the TSC1/2 complex, thereby inhibiting mTOR activity and promoting autophagy. HIF-1 stimulates AMPK and subsequently induces autophagy via BINP3/Beclin-1(18).

Autophagy is highly regulated by ATP production and AMPK pathway. Therefore, a reduction of ATP production leads to the accumulation of AMP, the activation of AMPK and autophagy. In starvation, autophagy is rapidly induced to high levels and the results in degradation of intracellular components supplies substrates to support metabolism (19).

Autophagy role in sustained proliferation and Metabolic Reprograming

Autophagy catabolizes redundant organelles and proteins thereby channelize various metabolic pathway. Otto Heinrich Warburg was the first author to identify changes in the metabolism of tumor cells (20). He demonstrated that under aerobic condition cancerous cell metabolize approximately 10 folds more glucose to lactate in a given time than in a normal cell, even in the presence of oxygen and fully functioning mitochondria. This effect was termed the Warburg effect, or aerobic glycolysis (21). More lactate secretion due to the Warburg effect can change the extracellular microenvironmental pH, which in turn can activate autophagy. The activation of autophagy by lactate utilization promotes cancer cell survival and tumor growth whereas it has no effect on autophagy and the survival of non-cancer cells (22).

Interestingly the oxidation of lactate by LDHB also participates to lysosome function and activates autophagy in cancer cells (23).

Pyruvate kinase (PKM2) is the final enzyme in the glycolytic pathway that controls the glycolytic flux and is therefore important for preventing accumulation of glycolytic intermediates (24). In cancer, PKM2 breakdown via Chaperone Mediated Autophagy is increased, therefore reduced PKM2 associated with an accumulation of glycolytic intermediates. This metabolic

intermediate to supply subsidiary pathways to fulfil the metabolic demands of proliferating cells in cancer also these intermediates are required for the biosynthesis of cellular components (25).

Although RAS-driven cancers can acquire glutamine by consuming and digesting extracellular albumin through macro-pinocytosis, autophagy may provide an alternative glutamine supply critical in the absence of accessible extracellular protein and amino acids. Glutamine is converted to glutamate by glutamine synthetase-1, which is further metabolized to α-ketoglutarate by glutamate dehydrogenase and consumed for ATP synthesis through TCA cycle under oxidative condition. Glutamine becomes the primary substrate for the mitochondrial TCA cycle and synthesis of fatty acid and NADPH. Overexpression of MYC corelates with expression of cellular transported of glutamine leads to increase consumption of glutamine in cancer (26).

Glutaminolysis derived ammonia activates autophagy even in the hypoxic core of the tumor as an adaptation mechanism to protect against cell death. Ammonia is found in tumors at high concentration in the interstitial fluid [27]. Because ammonia is diffusible, it is proposed that glutaminolysis-derived ammonia activates autophagy through AMPK even in the hypoxic core of the tumor as an adaptation mechanism to protect against cell death in condition of metabolic stress (28).

Most glucose is consumed by glycolysis, and glutamine becomes the primary substrate for the mitochondrial TCA cycle and generation of fatty acids and NADPH. Autophagy supports necessary metabolic rearrangements which makes cancerous cells highly dependent on autophagy for survival (29).

Autophagy, ROS and stoma-tumor relationship

Autophagy plays a crucial and sometimes opposing role in the complex cancer microenvironment. For instance, autophagy in stromal cells such as fibroblasts contributes to tumorigenesis by generating and supplying nutrients to cancerous cells (30)**.** Tumor cells are surrounded by supporting cell that is known as tumor stroma. These tumors stromal cell is made up of myofibroblasts/cancer-associated fibroblasts (CAFs), immune cells, endothelial and adipocyte cells that surrounds the tumor (31).

In tumor stroma, many stress factors are present such as hypoxia, high level of ROS and high metabolic stress. This stress activates the transcription factors HIF-1α and NF-κB leading to the induction of autophagy and mitophagy in the microenvironment surrounding the tumor. Therefore, Autophagic activities are high in stroma as compared to tumor cells (32)

In the stroma high autophagic activity induces aerobic glycolysis produces more lactate. The neighboring cancer cell consumes the secreted lactate to produce ATP through the TCA cycle and oxidative phosphorylation (33). This particular adaptation of cancer cells which depends on autophagy is the metabolic symbiosis based on lactate exchanges between glycolytic, lactate-producing cells (stroma cells) and oxidative, lactate-consuming cells (cancer cells). This cooperation requires the entry of lactate into the cancer cells, a process facilitated by the lactate- proton symporter monocarboxylate transporter type 1 (MCT1) present in cancer associated fibroblast (34).

In cancer cells, lactate is used for oxidative mitochondrial metabolism and for the production of lipids. Thus, there is vectorial transport of energy-rich substrates from the fibroblastic tumor stroma to anabolic cancer cells. So, there is recycling of nutrients in the stroma which helps in providing substrate to adjacent cancer cell (35).

Immune escape or Immunosuppression Natural killer (NK) cell is a lymphocyte involved in that plays a critical role in immune activation against tumor cells. NK cells are able to recognize and rapidly act against malignant cells without prior sensitization. NK cells release cytotoxic granules containing perforin and granzymes to directly lyse tumor cells (36).

Autophagy plays a key role in protecting tumor cells against NK (natural killer cell) and CTL (cytotoxic T lymphocytes). In tumor cells, hostile conditions activate autophagy to sequester and remove the cytotoxic granules such as granzyme B and perforin released by NK and CTL. Autophagy promotes the escape of tumor cells from immune mediated elimination (37).

Antigens which are found in tumor are responsible for eliciting immune response. Tumor antigens are of different classes that are present in the form of products of mutated oncoproteins such as RAS, p53 and BCR-ABL, overexpressed or aberrantly expressed cellular proteins, antigen produced by oncogenic viruses, altered glycoproteins etc (38)

Normally, what happens during early stages of tumorigenesis, our immune system recognise nascent tumor cell because they express neoantigen on MHC-1 molecules and these cancer cells are targeted by NK and CTL cells and eliminated. There are two types of tumor cell. One is highly immunogenic another is less immunogenic. Highly immunogenic tumor cell eliminated by these NK and CTL cells. Less immunogenic tumor cell survives avoid immunogenic recognition and destruction (39).

Autophagy also directly regulates T and natural killer cell activity and is required for mounting T-cell memory responses. NK cells have cytotoxic potential against tumor cells and can target cells that lack MHC-I expression and express the correct balance of activating and inhibitory ligands to NK cell receptors. In many studies it is clear autophagy promotes degradation of MHC-I molecules mediated by NBR1(neighbor of BRCA gene). So, tumor cells may fail to express normal levels of HLA class I molecules, thereby escaping attack by cytotoxic T cells. Decreased surface of MHC-1 molecules leads to impaired recognition by innate or adaptive immune cell, leading to escape for immune-mediated elimination (40, 41, 42).

Autophagy degrades p62 and it releases $pSTAT_3$. $pSTAT_3$ reaches the nucleus upregulate transcription of antiapoptotic genes Bcl-2, Bcl-x, Bcl-XL. This process saves the tumor cells to undergo apoptosis. So, the cancer cell cannot be eliminated. Hence, it is clear autophagy plays significant role in the late stages of tumor development (43,44).

In tumor cells a variety of factors released by macrophages and other stromal cells are believed of cytokines such as TGF-β, IL-10 which are responsible for development of immunosuppressive environment and recruitment of immunosuppressor cell (45).

The Interplay of Autophagy And Metastasis

Metastasis is a multistep process in which allows cancer cells to migrate from primary sites to distant organ sites and establish a secondary tumor. There is conversion of epithelial cancer cell into invasive phenotype during epithelial to mesenchymal transition (EMT). There are a lot of morphological and biochemical changes took place in the epithelial cell (46).

EMT imparts the metastatic properties to the cancer cells and enhance mobility, invasion and resistance to apoptotic stimuli. So, it is seen that the ability of the cells to interact with the surrounding microenvironment has completely re-designed during EMT (47).

Normal epithelial cell tightly holds against each other by adhesion molecule like cadherins, integrins and provide structural integrity (48).

It links the intracellular cytoskeleton with the outside world. The binding of ECM ligands to integrin heterodimers promotes tension-induced conformational changes in the integrin cytoplasmic tail, leading to the recruitment of adaptor proteins, such as TLN (talin) and PXN (paxillin) (49).

Autophagy mediates degradation of focal adhesion proteins mainly through LC3-II. So, this facilitates disassembly of adhesion junctions and migration. This shows that autophagy plays an essential role in the metastatic cascade (50).

In advanced stages of cancer cadherins, integrins, selectins and many other focal adhesion molecules are degraded due to upgradation of autophagic process. in many cancers E-cadherin integrins, selectins molecule is lost. So, it reduces the ability to adhere together and promote the detachments from the primary tumor (51).

In several epithelial tumors, including adenocarcinoma of colon, stomach, breast, E-cadherin function is lost. This reduces the ability of cells to adhere to each other and facilitate their detachment from primary tumor and their advance into surrounding tissue (52).

Connexin-43 (GJA1 gene), a gap junction protein, once internalized is degraded by autophagy after SQSTM1/p62 binding and delivery to autophagosome. In many studies it is observed that connexin-43 is downregulated in breast and prostate cancers (53).

Anoikis Resistance

Cancer cells that spread to distal organs have to resist cell death due to loss of contact with the extracellular matrix (ECM), termed anoikis (54).

It is a form of cell death by apoptosis due to loss of focal adhesion (FA)molecules from extracellular matrix. Lack of cell adhesion activates Bid and Bim, pro-apoptotic molecules that induce the BAX- BAK oligomer on the outer mitochondrial membrane which activate intrinsic apoptosis pathway. The extrinsic pathway also gets activated due to loss of adhesion which facilitate downregulation of FLIP and increased expression of Fas and FasL (55).

When epithelial cells detach from extracellular matrix (ECM) it produces cytotoxic ROS. There is significant changes occur in the metabolism which includes reduction of ATP process. The endoplasmic reticulum kinase (PERK) induced autophagy in response oxidative stress that block Anoikis and promotes the survival of detached epithelial cell i.e., Anoikis resistance (56).

That means autophagy helps in survival of epithelial cells which loses contact during EMT. Through all these process it is clear autophagy plays a significant role in proliferation of cancer.

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