The Association Between Autophagy and Ovarian Cancer

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Ovarian cancer is the most common cause of cancer death in all gynecological cancers. The mortality of this cancer is high due to the fact that the symptoms of this disease does not occur until its advanced stage. Surgery, chemotherapy and radiation therapy are current cancer therapies for ovarian cancer. However the recent studies reported that autophagy also can be a novel therapeutic strategy for this cancer. Autophagy leads to cell death when it is activated excessively in the cell and so it can be used for the treatment of neoplastic or chemoresistant ovarian cancer cells. In this review, in order to understand the association between autophagy and ovarian cancer, we summarized the general characteristics of ovarian cancer, autophagy and the relationship between these two concepts.

Key Words: Autophagy, Ovarian cancer, Chemotherapy

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Ovarian Cancer

Ovarian cancer is a disease that begins in the ovaries which are located on each side of the uterus and are important part of the female reproductive system.[1-2] Ovarian cancer is the deadliest of all gynecological cancers in women.[3] In the United States, it strikes approximately 21.000 women each year and 14.600 women die of this cancer annually. Thus, ovarian cancer is the fifth most common cause of cancer deaths in this country.[4-6] Due to the fact that it is difficult to detect this disease in its early stages, the mortality rate of this cancer is high. It isn't easy to detect this illness because it has not any specific symptom in that stage and it has spread beyond the ovary at the time of diagnosis in most patients.[3,5] Although there are new developments in treatment of this disease, the 5-year survival rate for patients who are at the advanced stage of ovarian cancer is under 50%.[6-7]

Tumors which develop in the ovaries, are categorized according to their derivation from three types of cells. These are epithelial, germ and stromal cells and each of them can develop into a different type of tumor.[2,8] The tumors which are originated from germ cells, named as "germ cell tumors". This tumors constitute approximately 5% of ovarian cancers and most of them are benign. "Ovarian stromal cell carcinoma" which is originated from stromal cells, also constitute about 5% of the ovarian cancer. The tumors which are derived from epithelial cells, called as "epithelial ovarian tumors".[2] This type of tumors constitute majority of malignant ovarian tumors and is grouped into different morphologic classes according to appearance of the epithelium in tumors. These classes are serous, mucinous, endometrioid, clear cell, transitional cell tumors (Brenner tumors), mixed epithelial tumors and undifferentiated type.[8-9]

Multiple risk factors which are leading to this cancer, were identified by epidemiologic and molecular-genetic studies.[1] Aging is one of the risk factors and the median age at diagnosis of this cancer is 63 years.[2] Other factors which increase the risk are family history, Breast cancer 1 (BRCA1) and BRCA2 gene mutations, estrogen exposure and endometriosis.[1-3,7,10-11] The most important risk factor for this disease is the family history.[1,7] The more patients have first-degree relatives with ovarian cancer, the more the risk of the cancer increase in these patients.[10] BRCA1 and BRCA2 are classes of genes known as tumor supressors and mutations in these genes are related to breast and ovarian cancer.[1,7] It has been reported that estrogen promotes the growth of cancer cells and so the frequency of ovulation is related to development of ovarian cancer. Women who have less pregnancies, are exposed to estrogen more and so they have an increased risk of ovarian cancer.[2] Endometriosis is the other risk factor for developing ovarian cancer and it occurs due to the spreading of the endometrial-like cells outside the uterus such as on ovaries and peritoneum [2-3]

Although ovarian cancer is called as "silent cancer" by experts because of not having specific symptoms in its early stage, there are several nonspecific symptoms in that stage.

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These are abdominal or pelvic pain, bloating, pressure in the abdomen, nausea which is continuous, loss of appetite, diarrhea or constipation, urinary problems such as frequent urination, unexplained weight gain or loss, ongoing fatigue, menstrual bleeding which is intensive and continues long period and post-menopausal bleeding.[2,4,10] The woman who has these symptoms and if any of them continues for over 2-3 weeks, she should visit a gynecologist, gastroenterologist or internist.[2]

The treatment of ovarian cancer can be applicable by using surgery, chemotherapy, and radiation therapy.[7] Surgery is the main method of this treatment strategies and it is usually followed by an additional chemotherapy or radiation therapy.[7,12] Oophorectomy, hysterectomy or salpingo-oophorectomy can be applied for surgical procedure according to the conditions such as the type and the stage of cancer and the patient's health. Chemotherapy is used more commonly than radiation therapy after surgery. The chemotherapeutic drugs are consist of cisplatin or carboplatin, both platinum compounds, and a taxane such as paclitaxel or docetaxel.[2] Despite the positive respond to the chemotherapy initially, most of the patients have recurrent cancer.[13] The cause of this recurrence is the defective apoptosis which leads to chemoresistance. If there is such a condition, additional chemotherapy is applied to these patients.[2,13] The recent years, clinical trials for treatment of ovarian cancer are focused on autophagy which is an another cell death pathway.[13] Moreover, new treatment strategies such as cancer vaccines, are being investigated and tested.[2] To detect an ovarian cancer at an early stage, the solving of the molecular mechanisms that cause the development of tumor is important[14] (Figure 1).

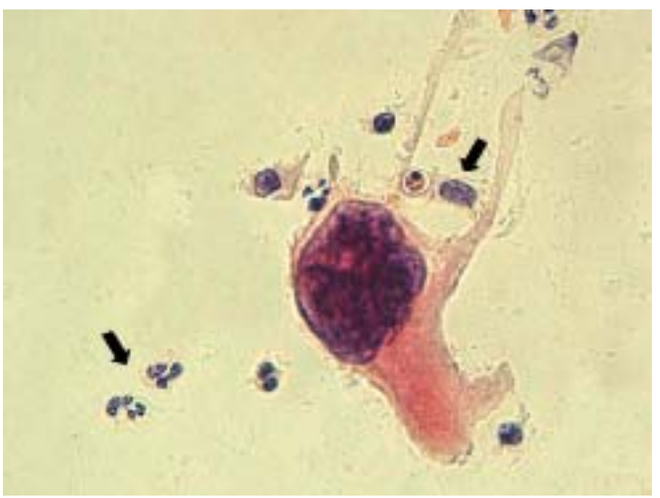

Figure 1: Overview of squamous epithelial carcinoma. This image shows the vaginalsmear of patient who received radiation treatment. This cancer cellis resistant to therapy and it has cytoplasmic extensions, large and more than one nucleus.

Left arrow: PoliMorpho Nuclear Leucocytes (PMNL)
Right arrow: Macrophage

Autophagy and Its Mechanism

The term "autophagy" was first invented by Christian de Duve in 1963. It is derived from the Greek words "auto" and "phagy" and means "eating of oneself".[15-16]

Autophagy is a cellular catabolic process which degrades cytoplasmic components such as long-lived proteins and organelles in lysosomes.[17] This process is modulated in response to various stimuli while it occurs at basal levels under normal conditions. Some of these stimuli are nutrient deprivation, high temperature, low oxygen, hormonal treatment as extracellular origin and defective organelles and accumulation of mutant proteins are as intracellular origin.[18-20] Therefore, autophagy plays crucial roles in diverse diseases including cancer, neurodegenerative diseases, myopathies and infections.[21-22] It has a dual role in cancer; it can promote the survival of cancer cells but also it can play as a tumor cell killing mechanism.[23] Furthermore, autophagy is a type of programmed cell death (PCD). If autophagy is excessively activated in the cells, it causes cell death. This type of the cell death is called as "autophagic cell death" or "type-II PCD". In addition to autophagic cell death, apoptosis is named as "type-I PCD".[18, 24]

Autophagy is an evolutionarily conserved process from yeast to humans. This process comprises of several sequential steps including initation or nucleation, expansion, maturation and degradation.[15,18] Initation phase which is the first step of mechanism, begins with autophagy induction. This induction occurs through the effects of the extacellular and/or intracellular stimuli. In this phase, a crescent-shaped precursor structure that is called as "isolation membrane" or "phagophore", starts to grow at both ends and enwrap cytoplasmic components.[15,22, 26-27] The origin of the isolation membran is still not known well and research about this subject continues. Various models about generation of this membrane have been suggested. It has been proposed that isolation membrane can be done by de novo assembly mechanism in cell or it can originate from the plasma membrane or the membranes of the endoplasmic reticulum, mitochondria and the Golgi in these models.[26,28]

In expansion phase, both ends of isolation membrane grow, expand and eventually close to generate double-membrane vesicle which is called "autophagosome" or "autophagic vacuole".[28-29] During maturation phase, the autophagosome fuses with cytoplasmic endosomal vesicles and generates the structure that is called "amphisome". Amphisome fuses with the lysosome and generates the vesicle that is named as "autolysosome (autophagolysosome)". This pathway has not been found in yeast.[26,28,30-31] The other pathway for maturation phase is that autophagosome does not fuse any cytoplasmic endoplasmic vesicle and directly fuses with lysosome or in yeast and in plant cells with vacuole. The

structure which is a result of this fusion is also called as "autolysosome (autophagolysosome)". In degradation phase, the content of autolysosome and the inner membrane of this structure are degraded by hydrolytic enzymes.[24,26,31] After degradation, the resulting molecules are transported back into the cytoplasm through transport proteins (also known as permeases) which are in the lysosome membrane. These molecules are reused as either building blocks for new macromolecules or as an energy source[21,26] (Figure 2).

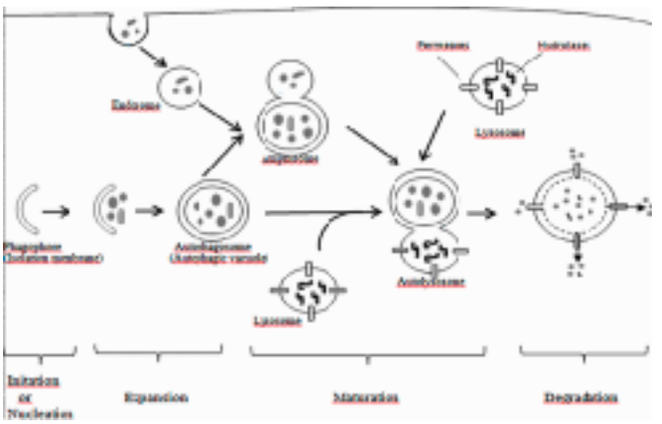

Figure 2: Schematic overview of autophagy. Autophagy comprises ofseveral sequential steps including initation or nucleation, expansion, maturation and degradation. In initiation phase, a crescent-shaped precursor structure that is called as "phagophore" or "isolation membrane" is formed and it enwrappes a portion of the cytoplasm. In expansion phase, both ends of phagophore grow, expand and eventually close to generate double-membrane vesicle which is called "autophagosome" or "autophagic vacuole". In maturation phase, the autophagosome can fuse with cytoplasmic endosomal vesicles and generates the structure that is called "amphisome" .Then amphisome fuses with the lysosome and generates the vesicle that is named as "autolysosome". In this phase, the autophagosome can fuse directly with the lysosome and the product of the fusion is also called as "autolysosome". In degradation phase, the content of autolysosome and the inner membrane of this structure are degraded by hydrolases. The resulting molecules are transported back into the cytoplasm by permeases for reuse in metabolic processes.

This figure is arranged from reference 24.

Autophagy and Ovarian Cancer

Ovarian cancer has the high mortality rate due to the fact that the symptoms do not emerge until the cancer has advanced and metastasized.[3,5,32] Surgery and the following chemotherapy are used for the treatment of this disease, however new clinical researches which are based on cellular mechanisms are being investigated.[1,7,12-13]

There are many studies related to autophagy and ovarian cancer theraphy. One of these studies is about using saquinavir for the treatment of ovarian cancer. Saquinavir is a protease inhibitor which is used for human immunodeficiency virus (HIV) infection and it also has an antineoplastic effect. It has been demonstrated that saquinavir treatment triggers ovarian cancer cell death by inducing endoplasmic reticulum stress and autophagy as well as apoptosis. Furthermore, chemoresistance is a major problem for the treatment of ovarian cancer and saquinavir causes cell death also in chemoresistant ovarian cancer cells.[13] Therefore, saquinavir can be a new therapeutic agent for ovarian cancer.[13]

In the other study, genistein is also used for the treatment of ovarian cancer. Genistein is an isoflavenoid and it naturally occurs abundant in soybean products.[33] It has an antineoplastic activity in breast and endometrial cancers.[34-35] Genistein inhibits glucose uptake by blocking the activity of mammalian facilitative glucose transporter Glut-1 in the cell membrane. Therefore, treatment with genistein has similar effects as glucose deprivation which is one of the inducer of autophagy. So genistein can promote autophagic cell death and it may be a treatment agent for ovarian cancer.[33]

Resveratrol, which is a natural phytoalexin found in grapes, nuts and red wine, was investigated to observe the effect in preventing or treating ovarian cancer. In this in vitro study, some ovarian cell lines (A2780, CaOV3, ES-2, TOV112D and A1947) were used for observing antineoplastic activity of the resveratrol by the inhibition of the growth of some tumor cells. According to these results, resveratrol can induce cell death through apoptosis and autophagy in ovarian cancer cells. Therefore, it has been suggested that resveratrol may be a potential agent for treating ovarian cancer.[6,36]

Another results were also obtained by using resveratrol. In this study, resveratrol blocks glucose uptake and glucose metabolism in human ovarian cancer cells. Therefore nutrient deprivation occurs and this condition induces autophagy in these malignant cells. If autophagy is stimulated constantly and excessively by the resveratrol, the cytoplasm of cancer cells is degraded permanently and thereby the death of ovarian cancer cells can be observed. So resveratrol is used for eliminating cancer cells and therapy of this cancer.[36]

Phospho-enriched protein in astrocytes (PEA-15) is a 15-kDa phosphoprotein which was initially discovered in astrocytes. It was also demonstrated that its expression is also found in a variety of tissue like heart, brain, muscle and adipose tissue. The association between PEA-15 and autophagy has been investigated by in vitro studies and reported that PEA-15 can block cell proliferation of ovarian cancer cell and induce autophagy. Consequently, PEA-15 can be used as a therapeutic agent for ovarian cancer due to the fact that it induces autophagy and it has an antitumor activity.[14,37]

Conclusion: New clinical researches have been made to

understand the association between autophagy and ovarian cancer therapy. These researchesdemonstrated thatthe agents which induce autophagy in ovarian cancer cells are saquinavir, genistein, resveratrol and PEA-15. So these agents promote autophagy and the excessive autophaghy leads to autophagic cell death in ovarian cancer cells. The death ofmalignant and chemoresistant cells of ovarian cancer is occured by this autophagic cell death. Therefore, autophagy can be a novel and an important therapeutic strategy for this cancer. The researches can be done as in vivo and new agents which can induce autophagy can be identified in the future.

Otofaji ve Over Kanser İlişkisi

Over kanseri, tüm jinekolojik kanserler içinde kanser ölümlerinin en yaygın nedenidir. Hastalığın belirtileri, hastalık ileri aşamasına gelene kadar oluşmadığından, bu kanserin ölüm oranı yüksektir. Over kanseri için mevcut tedaviler ameliyat, kemoterapi ve radyasyon tedavisidir. Ancak son zamanlardaki çalışmalar otofajinin de bu kanser için yeni bir tedavi stratejisi olabileceğini bildirmektedir. Otofaji, hücrede çok fazla aktive olduğunda hücre ölümüne yol açmaktadır ve bu nedenle neoplastik veya kemoterapiye dirençli over kanser hücrelerinin tedavisi için kullanılabilir. Otofaji ve over kanseri arasındaki ilişkiyi anlamak için, bu derlemede over kanserinin, otofajinin ve bu iki kavram arasındaki ilişkinin genel özelliklerini özetledik.

Anahtar Kelimeler: Otofaji, Over kanseri, Kemoterapi

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