AUTOPHAGY AND ITS RELATIONSHIP WITH VITAMIN E SUCCINATE AND GASTRIC CANCER.

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ABSTRACT

We go through many situations that trigger the generation of wastes in and around our cells. When we starve , our cells starve but when our cells starve, we suffer more and until our cells are satisfied we can not be free from our suffering. Anything that puts our cells through a nutrient deprivation exposes our cells to danger. Few of such situations are starvation, infection, hypoxia, chemotherapy and exposure to radiation. For instance exposure to radiation could generate high number of reactive oxygen species (ROS) which has a potentiality of damaging proteins and organelles. Once this unwanted circumstance sets in, a process is induced to remove the damaged structures. These damaged structures could be removed by an all important process called Autophagy.This process could be induced by Vitamin E Succinate(VES). VES is one of the derivatives of fat-soluble vitamin d-alpha-tocopherol. Induction of Autophagy by VES could be due to its ability to kick out oxidants generated in the body.

Gastric cancer is a deadly disease in which malignant cells form in the lining of the stomach. Gastric cancer is a type of cancer that is also able to generate oxidants in the body. Further more, the treatment of this type of cancer has a potentiality of generating more oxidants in the body.The ionizing radiation, most chemotherapeutic agents and some targeted therapies work through either directly or indirectly generating reactive oxygen species. The relationship of gastric cancer and autophagy is that of a case of “double edged-sword” .Which means that it is able to promote the proliferation of cancer cells and also able to inhibit the cancer cells.

METHODOLOGY

This review work has been made possible by the use of the following: Google scholar, Journals, PubMed and Microsoft word. A search was conducted to find the relevant information by using google scholar. More journals were perused to search for the relevant information. PubMed was also very useful in the search of the relevant information for this review. The illustration of the information in this review was made possible by the use of pathway builder, paint and snipping tool.Words such as autophagy, gastric acancer and vitamin e succinate were typed in the search space to look for the relevant research articles to enable us to write this review.

INTRODUCTION

There are many wastes that are generated within and around the cells of every living organism. Removal of these wastes is very imperative for the cells to remain in a homeostatic state. Some of these wastes include dead organelles,bacteria and toxins. Removal of these wastes could be achieved through an important process

called Autophagy. Through this process, the wastes can be degraded and recycled for energy production. This process is initiated by some stressors which generate the wastes in or around the cell. Some of these stressors include, hypoxia, ROS, infection, and starvation, ionizing radiation. The wastes generated are very damaging to the cell structures. These stressors contribute to the generation of waste which then induces autophagy to remove. Therefore autophagy can be deemed as a garbage control process which helps to clean the cells and put them in a homeostatic state. Just imagine an environment without a waste control system, occupants of such an environment fall prey to many pathologies.Same fate approaches the cells in every living body. Living things go through stressful conditions everyday, such as starvation, infection and radiation. All these are potential generators of wastes in the cells which possibly induce autophagy to get rid of these wastes generated by these factors in order for the cells to stay safe. Any alteration or arrest of this process, could be very detrimental to the normal cells.It has been shown that autophagy plays a vital role in degrading the damaged organelles and providing energy for survival of the cancer cells under treatment Therefore autophay could be very active in a cell during carcinogenesis.

Cancer is a potential condition that can can switch autophagy on continuously. This is because it is able to generate more reactive oxygen species. This condition puts the surrounding cells under severe pressure, therefore structures within these cells become damaged leading to the induction of Autophagy. Autophagy on the other hand, acts to protect the cancer cells through the production of energy.

Gastric cancer is the third leading cause of cancer-related death worldwide[1]. It is a disease in which malignant cells form in the lining of the stomach. The relationship between autophagy and gastric cancer has been a case of double-edged sword. In one way, autophagy promotes proliferation of gastric cancer cells and the other way it inhibits the proliferation of gastric cancer cells. Prior to the cancer cells proliferation, autophagy is induced to remove all these abnormal cells. As a result, proliferation of these abnormal cells are inhibited. Furthermore, when these abnormal cells escape autophagy at the initial stage, they begin to benefit from autophagy. The benefit comes when the damaged structures produced from the negative effect of of these cancer cells are used to generate energy to power the proliferation of these abnormal cells.

Vitamin E succinate (VES) is one of the derivatives of fat-soluble vitamin d-alpha-tocopherol. It has been studied that Vitamin e succinate is able to induce autophgy in human gastric SGC-7901 cells via AKT/AMPK/mTOR pathway [2]. These pathways have been studied to be very important in the autophagic process. AMPK is well known as an energy sensor and can be activated by increased intracellular AMP levels[3]. The mechanistic target of rapamycin (mTOR), an autophagic pathway which is a threonine protein kinase that offers exciting possibilities for novel treatment strategies for a host of neurodegenerative diseases that include Alzheimer's disease, Parkinson's disease, Huntington's disease, epilepsy, stroke and trauma[4]. It is a pathway that also plays a crucial role in apoptosis . Through this, neuronal stem development, precursor cell differentiation, cell senescence and cell survival and ultimate cell fate could be determined.

Vitamin E succinate (VES) has been found to be a potential inducer of autophagy. It is more effective in inducing differentiation,apoptosis and inhibiting proliferation in cancer cells, depending on its concentration.Interestingly,it affects the proliferation of only few of the normal cells[5] .This is really a good news to anyone trying to find a remedy for cancer. Comparatively , this makes vitamin E succinate as a potential best alternative for the treatment and prevention of cancer. However, the mechanism by which it deals with the cancer cells is not completely understood [6]. It is now known that, vitamin E succinate is able to induce autophagy in gastric cancer cells (SGC-7901 CELLS) and the Akt/AMPK/mTor pathway was found to be involved [2].

A multi-step process that is primarily induced by carcinogens leading to the development of cancer is known as Tumorigenesis or carcinogenesis ([8]. Normally, a balance is achieved between proliferation and programmed cell death, in the form of apoptosis, which is then maintained to ensure the integrity of tissues and organs. According to the prevailing accepted theory of carcinogenesis, mutations in DNA and epimutations

that lead to cancer, disrupt these orderly processes by interrupting with the genes regulating the processes, upsetting the normal balance between proliferation and cell death. This results in uncontrolled cell division and the evolution of those cells by natural selection in the body. Gastric malignancy, a malignancy with poor prognosis, is known to be among the common causes of cancer-associated deaths worldwide. Gastric cancer shows a lack of specific symptoms in its early stages and also, its clinical symptoms often do not match the corresponding stage[9]. Gastric cancer is one of the most prevalent cancer types in the world[10]. Gastric cancer ranks 4th among the most common cancers worldwide, and the mortality caused by gastric cancer is 2nd only to lung cancer[9]. Currently, the main treatment for gastric malignancy is chemotherapy, which to some extent is helpful but has some side effects which could be very harmful. An agent which has shown a promising positive effect is Vitamin E succinate . It is able to induce Atophagy in gastric cancer cells. This means that there is a probability of getting rid of the cancer cells when applied at the early stages .When this probability is achieved, then the possiblity of finding a safer treatment for gastric cancer will be at our doorstep. Vitamin E succinate does this by inducing apoptotic cell death in the gastric cancer cells (SGC-7901 CELLS) [2].

Normally, cancer cells are able to escape apoptosis through the arrest of apoptotic factors. Consequently, the induction of apoptotic cell death by vitamin E succinate is very intriguing . The tumor microenvironment is a complex system that is affected by various factors, including hypoxia, acidosis, and immune and inflammatory responses, which have significant effects on tumor adhesion, invasion, metastasis, angiogenesis, and autophagy[11].Eventhough apoptosis and autophagy have the same function in putting the body in a physiologic state, autophagy is more of a biological process whereby large molecules and damaged organelles in the cytoplasm are degraded. A key step during this process is the formation of autophagosomes. Autophagosomes mainly consist of cytoplasmic contents and damaged organelles, such as the mitochondria.

The ability of cells to respond to changes in nutrient availability is essential for the maintenance of metabolic homeostasis and viability. One of the key cellular responses to nutrient withdrawal is the upregulation of autophagy. Recently, there has been a rapid expansion in the knowledge of the molecular mechanisms involved in the regulation of mammalian autophagy induction in response to depletion of key nutrients [11].

Autophagy is one of the three principal mechanisms used by cells to sequester, remove and recycle waste, the others being proteasomal degradation and phagocytosis. In autophagy, macromolecules in the cytosol are engulfed in a newly formed phagocytic body and subsequently digested in a special lysosome that releases the resultant metabolites back into the cytosol.

AN OVERVIEW OF AUTOPHAGY

Autophagy, often referred to as macroautophagy, serves to recycle large chunks of cytoplasm as a source of nutrients, which enables cells to maintain macromolecular synthesis and energy homeostasis during starvation and other stressful conditions. These are the steps through which, autophagy occurs, namely sequestration, degradation, and amino acid/peptide generation. Each of these steps brings about a different function in a variety of cellular contexts[12].

Moreover, cells utilize autophagy to regulate the activity of specific signaling proteins, to remove accumulated damaged organelles or long-lived, aggregate-prone proteins, and to prevent incoming dangers such as intracellular pathogens. From the importance of autophagy stated above, autophagy could be viewed as playing a critical role in the innate immunity. Autophagy also defends the cell against invasion by microorganisms and has important roles in innate and adaptive immunity[13].

Induction of autophagy is brought about by certain developmental states, in response to various hormones, under conditions of nutrient deprivation.

The regulatory pathways are very important for the success of autophagy.

The serine/threonine kinase AKT is also known as protein kinase B. It comprises a group of three isoforms (AKT1, AKT2, and AKT3) in mammals and it is a key propagator of PI3K signaling [4]. These pathways are involved in the various stages of autophagy.

The stages of Autophagy include initiation, Autophagosome synthesis and cargo enclosure, and lastly Proteolysis.

Initiation involves the regulatory pathways whereby various genes, which regulate autophagy, are recruited for autophagy to begin. The following are some the genes that control Autophagy. They are Beclin 1,Mtor, Atg and many more. There are some signaling pathways, which are involved in the initiation of the autophagy.

These include AMPK, MAPK/Erk1/2, and P13K/AKT. These are few of the many

Pathways that are involved in the initiation of the autophagy.

Autophagosome synthesis and cargo enclosure is the second stage in which Autophagy occurs. The autophagosome is a double-membrane vesicle, the size of which can considerably vary from 0.5–1.5μm depending on the substrate, the nature of the autophagy-inducing signal, and the cell type. Firstly, the phagophore engulfs the material that needs to be degraded, which forms a double membrane referred to as Autophagosome around the organelle that is marked for degradation. The autophagosome then travels through the cytoplasm of the cell to a lysosome, and the two organelles fuse. It has been stated that Atg8 plays an important role in the closure of the Autopahagosome. Atg8 is a ubiquitin-like protein in yeast and its mammalian orthologues are LC3, GATE-16 and GABARAP.

Proteolysis is the final stage of the autophagic process to occur which involves the formation of Autolysosome. Proteolysis is the enzymatic process by which proteins are degraded into their component polypeptide or amino acid parts.

Proteolysis is an enzymatic process with most of the enzymes being lysosomal enzymes. Lysosomes are membrane-enclosed organelles that contain an array of enzymes capable of breaking down all types of biological polymers—proteins, nucleic acids, carbohydrates, and lipids.

Part of the degradation of intracellular proteins occurs in the lysosomes and it is mediated by macroautophagy[14].

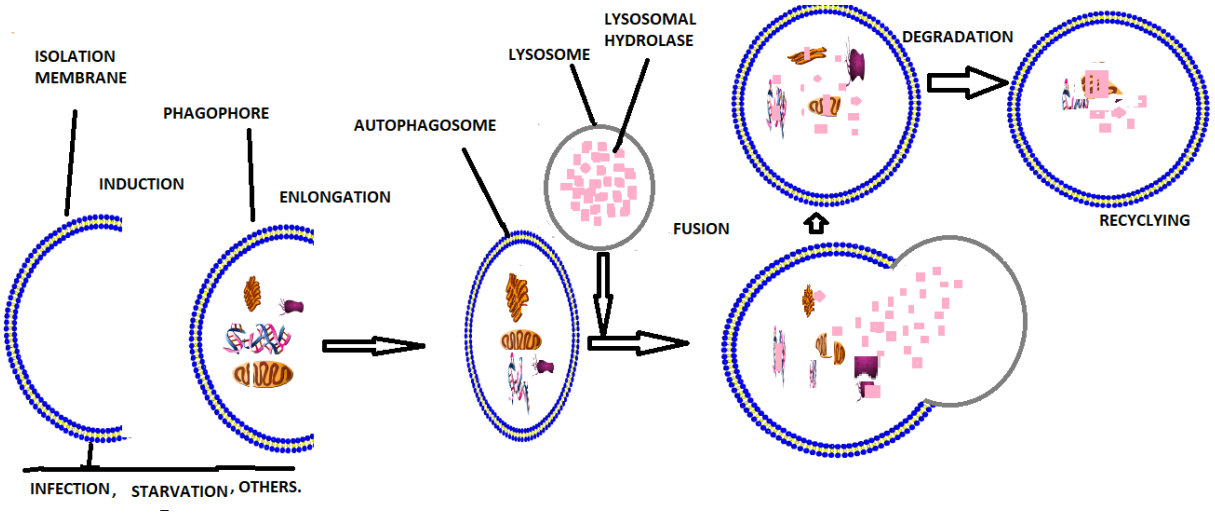

Fig 1. Schematic illustration of how autophagy occurs. The stressors ; infection, starvation and others could induce autophagy.

Elongation is followed by induction. Autophagosome is then formed with

the damaged cytoplasmic structures such as mitochondrion , bacterium ,proteins and endoplasmic recticulum enclosed in an endosome.

Lysosome then fuses with the autophagosome to form autophagolysosome.

This fusion process subjects the damaged structures to the lysosomal enzymes resulting in the degradation.

The degradation results in the production of amino acid, fatty acid and

nucleotides. These are then recycled.

OVERVIEW OF GASTRIC CANCER

Gastric cancer is a prevalent digestive tract tumor and one of the leading causes of cancer-related death worldwide[15]. The most common causes of cancer death are lung cancer (1.38 million, 18.2% of the total), stomach cancer or gastric cancer (738,000 deaths, 9.7%) and liver cancer (696,000 deaths, 9.2%)[16].The majority of gastric cancers are adenocarcinomas which arise from the mucosa of the stomach.

Helicobacter pylori infection represents the strongest known risk factor for the development of gastric cancer[17]. Helicobacter pylori is a Gram-negative bacterium that colonizes the stomach of about half of the global population and represents the greatest risk factor for gastric malignancy[18]. It is a common type of bacterium that grows in the digestive tract, and has a tendency to attack the stomach lining. It is mostly treated by chemotherapy.

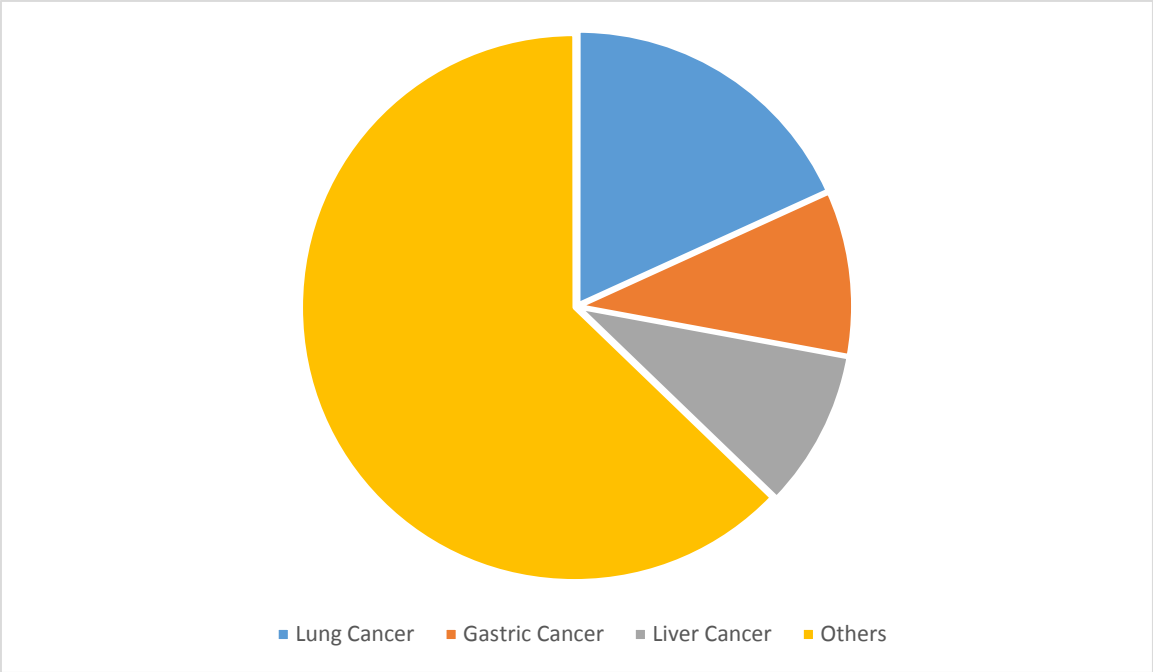

Fig 2 The pie chart above shows percentage of mortality caused by some three common cancers compared with others. Lung cancer ocupying the largest area is the most common cause of death compared with other forms of cancer. Gastric cancer comes in a second place and closely followed by liver cancer.

AUTOPHAGY AND GASTRIC CANCER

The relationship that exists between gastric cancer and autophagy could be one of beneficial or harmful. Induction of autophagy is one of the effects of acute exposure to VaCA Toxin. When there is a prolonged exposure to the toxin, disruption of autophagy occurs by preventing maturation of the autolysosome. There is an evidence, which supports a scenario in which H. pylori-suppressed autophagy-facilitating intracellular survival and persistence of the pathogen, while also generating an environment favoring carcinogenesis.

When there is a release of VaCA Toxin, there is a blockage of antioxidants and other important factors that promote Autophagy. Blockage of these important factors promote oxidative stress production which then decreases expression of Beclin-1. Beclin-1 is a protein that in humans is encoded by the BECN1 gene. It interacts with either BCL-2 or PI3k class III and also plays a critical role in the regulation of both autophagy and cell death.

Central to the pathogenesis and therapeutic development of cancer is the dysregulation that occurs in Autophagy.[19] Perturbations in autophagy are found in gastric cancer[15]. The presumed mechanism of carcinogenesis is the induction of inflammation and consequent gastritis and the initial lesions are involved in a multistage process[20].

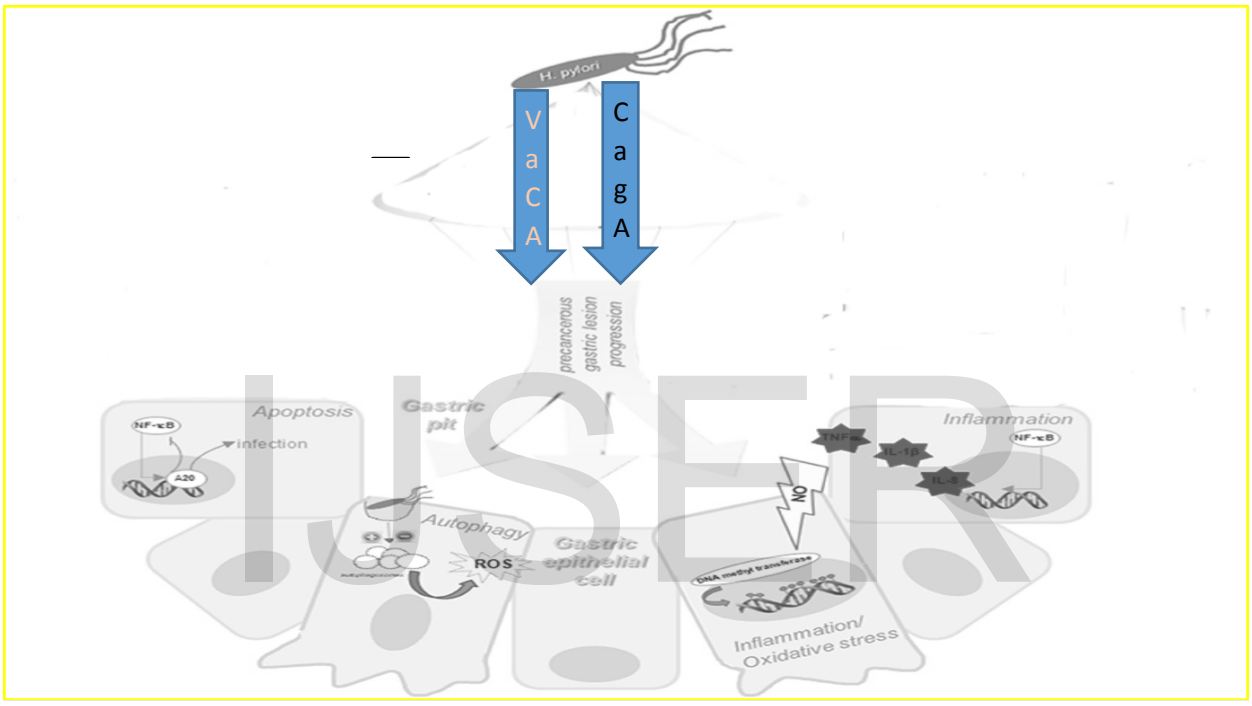

Fig 3 A Schematic illustration of how autophagy is related to gastric cancer.

The two toxins produced by H. pylori act as stress which induce autophagy.

VITAMIN E SUCCINATE AND AUTOPHAGY

Vitamin E succinate (VES), a potential cancer therapeutic agent, potently induces apoptosis and inhibits the growth of various cancer cells [21]. Vitamin E succinate is highly selective for malignant cells, inducing them into apoptotic death largely via the mitochondrial route. It has been demonstrated that blocking early and late autophagy stages enhances the antiproliferative effect of VES.

The function of autophagy in VES-treated SGC-7901 cells was investigated by inhibiting autophagy using 3-methyladenine (3-MA) and chloroquine (CQ)[21]

Vitamin E succinate is able to induce autophagy in gastric cancer cells, however it also able inhibits autophagy induced by ROS. Autophagy has been supposed to promote cancer cell survival or trigger cell death, depending on particular cancer types and tumor microenvironments.

The relationship between autophagy and vitamin E succinate could be linked to it's antioxidative properties. Vitamin E succinate is able to promote autophagy removing oxidative stresses.

In this way, autophagy via vitamin succinate function to maintain homeostasis.

DISCUSSION

We now understand that autophagy is able to create homeostasis by removing dead organelles and damged proteins. Thus, autophagy is the master garbage control process that acts as cellular garbage disposal and recycling system. By so doing , it is able to provide substrate for energy production and biosyntesis in stressful conditions. Some damaged structures such as proteins are broken into their basic units . The amino acids produced are then used to form new proteins.

Autophagy is very important in the carcinogenesis and inflammation.

Autophagy is able to promote or inhibit carcinogenesis. Autophagosome cannot be formed when disruption in the autophagic process is prevented. Formation of autophagosome is very important for Autophagy to be accomplished.

When there is an interruption in the formation of autophagosme , there is initiation of pathogenesis because of the interruption that occurs in the formation of Autophagosome. Typical example is the occurrence of gastric cancer when an interruption caused by the toxin of H. pylori disrupt the Autophagic process.

In all types of autophagy, a core molecular machinery has a critical role in forming sequestering vesicles, the autophagosome, which is the hallmark morphological feature of this Autophagy [22]. , ATG, have been identified that are required for selective and/or nonselective autophagic functions[22].

Gastric cancer is a disease that afflicts many people around the world. It is mostly treated by chemotherapy. Autophagy is induced in the gastric cancer during the initial stages whereby some of the toxins such VacA create a pathologic stress. At this stage, autophagy occurs to remove the damaged cytoplasmic structures.

Autophagy plays context-dependent dual roles in the development and progression of gastric cancer [23]. Autophagy can contribute to tumor suppression and promote cell death. It is also able to promote tumor growth and cell survival. Both of these mentioned above could be done by employing complex regulatory networks. The complex regulatory networks are mediated by p53, PI3K/Akt/mTOR, Ras and microRNA. Among the cellular process associated with these pathways, autophagy is a potential target for anti-tumor therapy [23].

VES induces higher gastric cancer cell apoptosis by combining with human CD4+ T cells than when it is acting alone[24]. Increase in oxidative stress is one of the factors that contribute to the development of gastric cancer. This oxidative stress could be produced by H. pylori, which is a common risk factor for peptic ulcer.

The possibility of vitamin E succinate inducing autophagy in gastric cancer cells may be due to its antioxidative properties. Thus, in a condition of low antioxidative agents, autophagy could be arrested or dysregulated.

When oxidation stress increases, autophagy could be inhibited and this create a possibility for pathogenesis. The possibility of increase in the rate of autophagy and apoptosis in the fetal hippocampus was investigated by combining anesthesia and ketamine in pregnant rats. The results showed that the possibility of the increase in the rate of autophagy could be due to inhibition of antioxidant activity and ROS accumulation[25].

Therefore , in conditions of high amount of oxidants , the rate of Autophagy increases. In gastric cancer for instance, there is high generation of oxidants which leads to induction of Autophagy.

Oxidants could damage the organelles and the proteins in the cells. Vitamin E succinate is an agent which has antioxidative quality. Its antioxidative quality may be due to its ability to induce autophagy.Hence, autoimune funtion of Vitamin E succinate could be due to its relationship with Autophagy.

CONCLUSION

Autophagy, gastric cancer and vitamin E succinate are very important entities which function in their own unique ways to affect the cells.

The relationship between autophagy and gastric cancer could be described as a case of double edged sword. Autophagy could occur to inhibit or promote the proliferation of gastric cancer cells. The relationship between these two entities has been the story of double edged sword. Gastric cancer being able to induce cancer is the fact that, it is able to generate waste in the body.

The main factor is the stress produced by the cancer cells which is the main force behind the induction of autophagy. The other factor could also be traced back to the initial stage of gastric cancer whereby the toxins,

VacA and CagA could induce autophagy. These agents are able to generate oxidative agents which are very powerful for inducing autophagy.

Vitamin E succinate , a derivative of vitamin E is able to induce autophagy via its antioxidative property.

The autoimmune funtion of Vitamin E succinate could be as a result of its ability to induce autophagy.

Vitamin E succinate could induce autophagy in gastric cancer cells. This could be associated with its antioxadative properties.

When the oxidative stress of the cell increases, autophagy could be weakened , arrested or dysregulated.This could be the reason why the cancers cells are able to overcome autophagy. When the cancer cells overcome autophagy, they are able to use it for their benefits.

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