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AUTOPHAGY, CANCER AND ASSOCIATED CHEMOTHERAPY

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Abstract
Autophagy is involved in many biological processes, and its dysregulation has been linked to carcinogenesis, tumor-stroma interactions, and cancer therapy resistance.. Autophagy also appears to be a major regulator of the tumor microenvironment and cellular drug response in a number of cancer types, according to an increasing body of research. Our comprehension of the autophagic mechanism, on the other hand, remains limited. The purpose of this investigation was to establish a link between autophagy and cancer, as well as to investigate the mechanism of action of anticancer drugs in relation to autophagy.

1. INTRODUCTION

A cellular mechanism that preserves the normal cell's homeostasis is autophagy. ["Doherty and Baehrecke, 2018, and Galluzzi et al., 2014"].Autophagy's actions in cancer cells are classified as neutral, inhibiting, or encouraging carcinogenesis. Metabolic stress, DNA instability, accumulation, genomic instability, and enhanced carcinogenesis have all been linked to autophagy. Autophagy maintenance may help to prevent cancer, and tumors with autophagy dysfunction are especially vulnerable to anti-angiogenic and DNA-damaging agents, such as anti-angiogenic and DNA-damaging drugs. Cancers that use this mechanism are almost certain to develop if autophagy is not maintained.Recent research has discovered that activating or suppressing autophagy increases the anticancer and therapeutic effects of various non-malignant drugs. This paper discusses the efficacy of cancer medications,cancer, and autophagy.

2. MECHANISM AND PHYSIOLOGICAL FUNCTIONS OF AUTOPHAGY

The study attempts to highlight how to boost clinical prognosis by autophagy after de Duve et al. proposed the definition of autophagy in 1963 [Klionsky, 2007]. "In 2016, when Yoshinori Ohsumi was awarded the Nobel Prize for Physiology or Medicine for his work in elucidating the autophagy process [Levine and Klionsky,2017 and Mizushima, 2018], the role of autophagy in health and disease was highlighted."[Mizushima, 2011].

Autophagy is a degradation system distinguished by the isolation of particular cytoplasmic components in a distinctive double-membrane vesicle known as an autophagy vacuole or autophagosome. ["Ohsumi, 2014"].The autophagosome's subsequent fusion with the lysosome ensures that the vesicle's organelles, misfolded proteins, and bacteria are effectively removed.[Fougeray and Pallet, 2015]. "In order to produce adenosine triphosphate (ATP) and preserve critical cell functions, intracellular components degraded by autophagy are recycled in response to cellular stress conditions, such as growth factors and nutrient deficiency [Yu et al., 2018]. Vomero et al. [2018] viewed autophagy as a pro-survival mechanism that permits cells to adapt to harm by destroying superfluous and faulty self-components; yet, this ability can become a double-edged sword."[Mizushima, 2018; Galluzzi et al., 2017 and Ke, 2019].

Due to the fact that macro-autophagy is considered the primary route of autophagy, we will focus exclusively on macro-autophagy in this study, unless otherwise specified. [Feng et al., 2014; Galluzzi et al., 2017 and Ke, 2019]. "Yeast genetic studies have allowed the discovery and control of a number of 37 autophagy-related proteins encoding the proteins involved in autophagy[Klionsky et al., 2016], with a significant number of these genes evolutionarily retained in humans" [Nakatogawa et al., 2009].

The autophagy machinery activation and adjustment mechanism is carried out by the rapamycin complex 1 mammalian target (mTORC1), serving as an energy level sensor and incorporating upstream signals derived from other pathways, including phosphoinositide 3-kinase. "In the presence of amino acids and growth factors, by inhibiting vacuolar protein sorting 34 (Vps34) and unc-51-like kinase1 (ULK1) complexes, mTORC1 represses autophagy. On the contrary, the dissociation of mTORC1 from the induction complex activates autophagy [Zachari and Ganley, 2017 and Torii et al., 2016] in a low nutrient state, known as hunger. The auto phagosome arises from a pre-autophagosome double-membrane structure called the phagophore, which tends to arise in mammalian cells from various sources, including the plasma membrane, endoplasmic reticulum, and Golgi complex.". "When Beclin-1 is bound to Bcl-2, autophagy is inhibited; instead, the dissociation from Bcl-2 allows Beclin-1 to interact with the phosphatidyl-inositol 3 kinase complex complex and to activate autophagy [Levine et al., 2008 and Russell et al., 2013]. The autophagy-promoting role of Beclin-1 is impaired by the

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antiapoptotic protein Bcl-2. On the contrary, Beclin-1-regulated autophagy protein 1 is a positive regulator of Beclin-1-dependent autophagy, thanks to its ability to bind cytoskeletal motor proteins with the PI3K class III complex [Sun et al., 2018]. The second stage of autophagy involving the expansion and closure of the auto phagosome [Tang et al., 2018 and Kenific and Debnath, 2015] is mediated by two ubiquitin-like conjugation systems: ATG12-ATG5-ATG16 L; light-chain; phosphatidylethanolamine. Light chain 3 lipidată, based on its property of being located in the inner and outer membranes of phagorphs as well as autophagosomes, is the current used as a marker to track autophagy progression [Marinković et al., 2018 and Klionsky et al., 2016].".In this final stage of degradation in autolysosomes, the following autophagous termination routes are presented by Ke [2019]: I reactivating mTOR nourishment suppresses autophagy initiation while simultaneously reforming autophagous lysosomes, thereby terminating autophagy [Yu et al., 2017]; ii) "lisosomal spinster (spin) efflux is required for the formation of autophagous lysosomes" [Rong et al., 2011]; iii) "Cullin 3-Kelch-like protein 20 Despite all scientific efforts, the complete molecular mechanism behind the creation of autophagous autogenous vacuoles throughout the autophagic process remains unknown".

3. AUTOPHAGY AND CANCER ASSOCIATION

The mechanism by which autophagy deficiencies accelerate carcinogenesis is unclear. [Mario et al., 2007Karin, 2006]. "Activation of the PI3K/protein kinase B (AKT) / rapamycin axis mammalian target [LoPiccolo et al., 2008] is the prototypical survival mechanism generally found in human cancer. Different cellular events that could lead to abnormal activation of this pathway and eventually autophagy suppression are known to be: phosphate tumour suppressor and tensin homolog (PTEN) loss removed on PTEN chromosome 10 and tuberculosis sclerosis complex1 and tuberculosis sclerosis complex2, activation or mutation of PI3K class I, overexpression of AKT, constitutive activation of growth The operation of lipid phosphatase, which contributes to the development of a number of cancers, is impaired by multiple mutations or the loss of PTEN function. R-335 was found to be the most critical of the three residues in the PTEN portion to interact with the cell membrane, in common with many other germline mutations, and to be associated with inherited cancer. The mechanism of autophagy control emphasises the function of signalling growth factor activating the PI3K/AKT/mTOR axis, resulting in autophagy inhibition (move pathway). In response to hunger and endoplasmic reticulum (ER) stress, two pathways are responsible for autophagy activation: a) mediated by 5' adenosine monophosphate-activated protein kinase and Ca2+/Calmodulin-dependent protein kinase kinase; b) involving p53 and activation of the damage-regulated autophagy modulator (DRAM). RAS exhibits an autophagy inhibitor (via PI3K class I activation) and an autophagy activator (via the RAF1/MEK1/2/ERK1/2 pathway) in this sense [Chen, 2009]. Autophagy control includes a series of signalling cascades, including p53, as a tumour suppressor protein that, depending on its subcellular localization, plays a dual role in regulating autophagy. By trans-activating its target genes, nuclear p53 promotes autophagy, while cytoplasmic p53 inhibits mainly [Tang et al., 2015]."In this case, p53 inhibits mTOR through "AMP-activated protein kinase and TSC1/TSC2-dependent pathways", transactivating autophagy-inducing genes and boosting autophagy.[Feng et al., 2007].

Several studies have shown that chloroquine, a lysosome-tropic drug that inhibits autophagosome breakdown in lysosomes, improves the anti-cancer activity of cyclophosphamide alkylating agents in a Myc-induced lymphoma model...[Amaravadi et al., 2007].

4. AUTOPHAGY AND CANCER DRUGS

In addition to anticancer drugs or ionising radiation therapy in cancer cells, autophagy usually has two effects[Thorburn et al., 2014]. "The cytotoxic feature known as autophagic cell death, also called programmed cell death of type II [Fulda and Kögel, 2015 and Denton and Kumar, 2019], is one consequence. It is a nonapoptotic type of overactivated autophagy-caused programmed cell death [Booth et al., 2019 and Zhu et al., 2020]."To prevent the damage of drugs or radiation, the cancer cells start autophagy. Drug therapies are thus divided into two groups, one that prevents autophagy and the other that stimulates it.

Golden et al., [2015] and Kumar et al., [2015] indicated that inhibition of autophagy by genomic interaction with autophagous genes ("siRNA targeting Beclin 1, Atg-3, Atg-5 and Atg-7") or pharmacological inhibitors of key components within the autophagy pathway in cancer resistance may be abrogated by drug resistance in cancer therapy. "Chloroquine is a commercially available antimalarial agent that also blocks the fusion of autophagosomes and lysosomes as an autophagy inhibitor feature. The U.S. has licenced chloroquine.In clinical trials, a food and drug administration (FDA) approved autophagy inhibitor is commonly used (Kuroda et al., 2013). Furthermore, hydroxychloroquine is used to suppress autophagy. ABT-737 is an autophagy inhibitor, according to Yang et al. (2016). Furthermore, obatoclax, which has a pan-Bcl-2 inhibitory action, has been shown to significantly suppress autophagy in colorectal cancer and bladder cancer cells. Clarithromycin, a macrolide antibiotic used to treat upper and lower respiratory tract infections as well as Helicobacter pylori, has

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been shown to reduce autophagy [Giulia Petroni et al., 2020]. Resveratrol is a natural polyphenolic chemical obtained from plants that is lethal to certain cancer cells. Resveratrol suppressed the cytoprotective autophagy flux generated by temozolomide or doxorubicin, resulting in synergistic anticancer activity. Quinacrine, also known as mepacrine, is an antimalarial medicine that has been shown to inhibit late-stage autophagy [Golden et al., 2015]."Antroquinonol B was synthesized via acetylation of an antroquinonol molecule. By reducing autophagy, autophagy inhibition increased cisplatin sensitivity in epithelial cancer cells [Liu et al., 2017]. In clinical cancer therapy, numerous novel natural drugs are also present and associated with autophagy ["Zhang et al., 2014 and Guo et al., 2015."In PTEN-deficient prostate cancer cells, Ursolic acid, a pentacyclic triterpenoid derived from natural plants, displayed an autophagic response as a survival mechanism" [Shin et al., 2012]. "Paclitaxel is a drug used to treat many cancer types, including breast cancer, lung cancer, and ovarian cancer, by interfering with the natural breakdown of microtubules during cell division. Acquired paclitaxel autophagy-mediated resistance acts as a significant barrier to effective anticancer effects. The preferential toxicity of paclitaxel-resistant HeLa cervical cancer cells could be increased by 2-Deoxy-D-glucose or 3-methyladenine by decreasing autophagy [Peng et al., 2014]. In addition, autophagous blockade with 3-methyladenine and Bafilomycin A1 improves paclitaxel sensitivity of folliculin-deficient renal cancer cells [Zhang et al., 2013]. Obatoclax may also synergistically facilitate paclitaxel-induced apoptosis by blocking the autophagic flux of bladder cancer [Jiménez-Guerrero et al., 2018]. Tetrandrine is a study of a natural product in our laboratory, and we find that tetrandrine has synergistic antitumor efficacy in combination with chloroquine[Mei et al., 2015]. It has also been documented that pterostilbene can improve the efficacy of chemotherapy approaches in combination with 3-methyladenine or BafilomycineA1 in both chemo-sensitive and chemo-resistant lung cancer cells and in triple-negative breast cancer cells [Hsieh et al., 2013 and Chen et al., 2014]. Bafilomycine A1 [Jung et al., 2016] is enhanced by the anticancer effect of another natural substance product, chaetocin. In addition, by interfering with autophagy [Wang Y et al., 2011], chloroquine has potentiated the cytotoxicity of topotecan in lung cancer cells, and the antitumor efficacy of cucurbitacin I is promoted by synergetic treatment of chloroquine in glioblastoma [Yuan et al., 2013]. In addition, 3-methyladenine may be promoted by autophagy inhibition for cell death of BE(2)-C human neuroblastoma cells after treatment with sulforaphane [Horwacik et al., 2015]."Honokiol is a kind of lignan isolated from the bark, seed cones, and leaves of Magnolia trees. [Lv et al., 2015].

Various cytotoxic drugs are also used in the treatment of tumours that cause tumour cell death by preventing DNA replication and cell division and by providing autophagic response mechanisms. "The chemotherapeutic sensitivity of numerous cancers, including ovarian cancer, glioma cancer, lung cancer, gastric cancer, endometrial cancer and bladder cancer cells, is encouraged by combined treatment of cisplatin with 3-methyladenosine or chloroquine [Zhang et al., 2012; Wu et al., 2015; Fukuda et al., 2015; and Ojha et al., 2016]. Chloroquine and cisplatin coadministration to eradicate mTORC1 activity-mediated autophagy suppression substantially re-sensitized EC109/CDDP cells immune to cisplatin [Yu et al., 2014]. By blocking autophagic flux and improving the sensitivity of highly aggressive epithelial cancer to cisplatin through the PI3K/Akt/mTOR/p70S6K signalling pathway, 4-Acetylantroquinonol B can also serve as an autophagy inhibitor [Liu et al., 2017]. Oxaliplatin, another platinum-based antineoplastic agent, demonstrates drug resistance in colorectal cancer cells through the MEK/ERK signalling pathway and HMGB1-mediated autophagy, and sensitivity can be restored by 3-methyladenine [Liu et al., 2015]."During research, it was discovered that temozolomide-induced cytoprotective autophagy contributes to malignant glioma therapy resistance, which can be alleviated by resveratrol, chrysin, or chloroquine and its analogue quinacrine, which results in a decrease in autophagy and an increase in apoptosis..["Buccarelli et al., 2018; Lin et al., 2012 and Yan et al., 2016"]. "Capsaicin is a major pungent ingredient found in the genus capsicum hot red chilli peppers, emerging as a chemotherapeutic augmenter for the anticancer effects of 5-Fluorouracil in cholangiocarcinoma [Hong et al., 2015]. Moreover, the cytotoxic effect of 5-fluorouracil on colon cancer cells is potentiated by chloroquine and 3-methyladenine [Sasaki et al., 2010 and Li et al., 2010]. Cytarabine is a chemotherapy agent that is primarily used to suppress acute myeloid leukaemia and cancer cells of non-Hodgkin lymphoma by interfering with DNA synthesis." ["Bosnjak et al., 2014"].

Streptomyces-derived drugs Streptomyces peucetius var. bacteria anthracycline is a strain of Streptomyces peucetius that is resistant to anthracycline. Caesius, which is used in cancer chemotherapy for the treatment of numerous malignancies, including breast, ovarian, uterine, bladder, lung, leukaemia, and lymphoma."The potential to increase the antitumor efficacy of doxorubicin in hepatocellular carcinoma and osteosarcoma treatment involving autophagy inhibition was promisingly shown by epigallocatechin gallate, one of the highest green tea catechins [Chen et al., 2014 and Wang and Ding Chen, 2018]."Autophagy-mediated resistance to doxorubicin can be reversed by 3-methyladenine as a classic chemotherapeutic agent for osteosarcoma [Zhao et al., 2014,[Rai et al., 2016].

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5. CONCLUSION

Autophagy may be one of the factors that contribute to cellular survival, which is crucial biologically during cancer progression and medically induced stress. As a result, additional scientific and clinical research will be required to determine whether autophagy is a mechanism of resistance to cancer therapy.

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