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Jofer Andree Zamame Ramirez

Dissertação apresentada à Faculdade de Medicina, Universidade Estadual Paulista "Júlio de Mesquita Filho", Câmpus de Botucatu, como parte dos requisitos necessários para a obtenção do título de Mestre em Patologia.

Orientador: Prof. Dr. Ramon Kaneno

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“Aprender a leer es lo más importante que me ha pasado en la vida”.

Mario Vargas Llosa

Índice

Autophagy in tumor cells: a mechanism of carcinogenesis and resistance to chemotherapeutic agents

Revisão da literatura apresentada na forma de manuscrito, redigido de acordo com as normas para submissão à revista Cellular Oncology (Springer). Porcentagem de similaridade com textos da literatura=6.7% de acordo com a plataforma Academic Plagiarism.

Autophagy in tumor cells: a mechanism of carcinogenesis and resistance to chemotherapeutic agents

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Abstract

Autophagy is a dynamic physiological macromolecular process, whereby intracellular substrates are exposed to lysosomes for degradation and recycling of damaged organelles, alleviating cellular stress conditions. Several studies have shown that autophagy plays a critical role in tumoral cell survival, performing a protective role by correcting carcinogenic damages. However, this physiological process can be subverted in some cells, leading to the promotion of carcinogenesis or allowing cell escape by increasing its resistance to chemotherapeutics. This review covers the basic mechanisms and genes involved in autophagy as well as the controversial findings on their role tumor cells; we also reviewed the processes by which drug resistance may be determined, for a better understanding of how autophagy works and how it can be handled as an antitumor therapeutic intervention.

1. Introduction: Autophagy as a physiological process

The term autophagy was first used by deDuve in 1963(1), and was defined by Klionsky in 2003 as "self-eating" at subcellular level(2). Since then, many scientists have investigated the mechanisms that trigger this process. Current definition of autophagy is a conserved cellular degradation process, in which portions of cytosol and organelles are sequestered into a double-membrane vesicle, called autophagosome and fused with lysosome for breakdown and eventual recycling of resulting macromolecules(3). This process is required for the maintenance of cellular homeostasis and generation of amino acids to sustain viability during periods of nutrient privation, or under other kinds of metabolic stress like intracellular bacterial or viral infections, mutations or exposition to drugs(4-6).

The autophagy process has three different forms: macroautophagy, microautophagy, and chaperone-mediated autophagy(3). Macroautophagy, which is often simply referred as autophagy, is the most characterized form and has been extensively investigated (4, 6, 7), being defined as the sequestration of a bulk of cytoplasm and organelles in a double-membrane vesicle called phagophore. This phagophore is originated from endoplasmatic reticulum and formed by expansion of autophagosome, and fuses with lysosome, forming autophagolysosome. Inside autophagolysosome, damaged organelles are degraded by lysosomal hydrolases, and finally, the resultant *ATP* and peptides are used to keep the cell viability (3, 8). In contrast, microautophagy is characterized by direct uptake of cytoplasmic substrates by invagination of lysosomal membrane, while chaperone-mediated autophagy occurs by shuttling soluble proteins into the lysosome, via lysosomal chaperone proteins such as *hsc70*(3, 8).

Survival and homeostatic functions of autophagy have been evolutionarily conserved from yeast to mammalian. When cells have rich nutrient condition, autophagy is produced

at low levels (basal autophagy), providing tissues with a cleaning mechanism, to control intracellular quality through cytoplasmic rotation and removal of damaged or unnecessary organelles (9-12). However, when a cell is under different kinds of stress, such as nutrient deprivation, hypoxia, intracellular infections (13) and exposition to drugs(14), autophagy is rapidly induced in order to maintain the amino acid pool in the cytoplasm, and cell survives possibly through protein neo-synthesis, energy production and gluconeogenesis(12), that maintain cell *ATP* production.

Autophagy involves a concerted action of highly conserved gene products and is controlled by two pathways involved in the regulation of cell growth and metabolism, the *mTOR* (mammalian target of rapamycin) and the *AMPK* (*AMP-activated protein kinase*) /*UVRAG* (*UV irradiation resistance associated gene)* signaling pathways. During normal situations (nutrient availability), *mTOR complex I* (*mTORCI*) inhibits autophagy since it phosphorylates *Atg13*, causing disaggregation of *ULK1 complex* (*ULK1, Atg13 and FIP200*), required to form autophagosome. However, when *mTOR* is inhibited by dephosphorylation (caused by cell starvation), *ULK1* complex works and autophagy is induced (8). Conversely, *AMPK*, is activated during energy deprivation or hypoxia by increased conversion of *ADP to ATP*, and can inactivate *mTORC1*, and trigger autophagy (10, 11). In parallel, *AMPK* and *UVRAG* pathways activate the pro-autophagy kinase *Vps34* (*Class III PI3 Kinase*) by phosphorylating and recruiting *beclin-1* (proautophagy and tumor suppressor gene), which produces *PI(3)P* that is essential for to initiate autophagosomes. Autophagy triggering is illustrated in Figure 1.

4. Conclusion

Although the controversy about the action of autophagy as tumor promoter or tumor suppressor, there is evidence that it inhibition helps to kill tumor cells mostly dependent on the kind of tumor and the therapeutic agents to be associated with. Therefore, we need a better understanding of the functional relevance of autophagy in the tumor microenvironment and enhance the ongoing dialogue between the laboratory and clinical researches in order to provide a new focus on therapeutic strategy to prevent resistance and increase the effects of cancer therapies.

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