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Review

Therapeutic targeting of autophagy in cancer. Part II: Pharmacological modulation of treatment-induced autophagy

Anika Nagelkerke[a,b], Johan Bussink[b], Anneke Geurts-Moespot[a], Fred C.G.J. Sweep[a], Paul N. Span[b,*]

[a] Department of Laboratory Medicine, Radboud university medical center, PO Box 9101, 6500 HB, Nijmegen, The Netherlands
[b] Department of Radiation Oncology, Radboud university medical center, PO Box 9101, 6500 HB, Nijmegen, The Netherlands

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ABSTRACT

Autophagy, the catabolic pathway in which cells recycle organelles and other parts of their own cytoplasm, is increasingly recognised as an important cytoprotective mechanism in cancer cells. Several cancer treatments stimulate the autophagic process and when autophagy is inhibited, cancer cells show an enhanced response to multiple treatments. These findings have nourished the theory that autophagy provides cancer cells with a survival advantage during stressful conditions, including exposure to therapeutics. Therefore, interference with the autophagic response can potentially enhance the efficacy of cancer therapy.

In this review we examine two approaches to modulate autophagy as complementary cancer treatment: inhibition and induction. Inhibition of autophagy during cancer treatment eliminates its cytoprotective effects. Conversely, induction of autophagy combined with conventional cancer therapy exerts severe cytoplasmic degradation that can ultimately lead to cell death. We will discuss how autophagy can be therapeutically manipulated in cancer cells and how interactions between the conventional cancer therapies and autophagy modulation influence treatment outcome.

1. Introduction

Autophagy is a cellular degradation process in which cells digest old, redundant or damaged organelles and proteins, thereby generating energy. The term autophagy often refers to the non-selective bulk degradation process known as macroautophagy. However, there are also other forms of autophagy: chaperone-mediated autophagy and microautophagy. This review is dedicated to macroautophagy (hereafter referred to as autophagy).

Exposure to cancer treatments subjects cells to stress. This can be either in the form of DNA damage (chemo- or radiotherapy), inhibition of cell proliferation, or impairment of growth factor- and metabolic-signalling. As a result of this stress therapies elicit an autophagic response in cancer cells, which helps to yield energy and appears to be initially aimed at cell survival. However, if the stress is too severe or too prolonged, autophagy can become cytotoxic and lead to cell death. Multiple chemotherapeutics, radiotherapy, hormone therapy and several targeted therapies induce autophagy in different cancer types [1–14], providing a survival advantage for cancer cells during treatment. Therefore, interference with autophagy represents a rational therapeutic strategy. Autophagy modulation may counteract resistance to established cancer therapies or enhance the effect of these therapies.

In this review, we will describe the current data on autophagy modulation as an anti-cancer strategy. We will show that interaction between treatments is crucial for the outcome of therapy.

2. The mechanism of autophagy

The genes and proteins that comprise the basic machinery of the process of autophagy have been the topic of extensive research and multiple review papers [15–18]. In short, autophagy involves the formation of double membrane vesicles, in which cytoplasmic content is sequestered. This involves the action of multiple autophagy-related (ATG) proteins, such as Beclin1 (the mammalian homologue of yeast ATG6) and LC3B (the mammalian homologue of

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* Corresponding author at: Department of Radiation Oncology 874, Radboud university medical center, PO Box 9101, 6500 HB Nijmegen, The Netherlands. Tel.: +31 24 3616845; fax: +31 24 3568350.
E-mail addresses: anika.ducker-nagelkerke@radboudumc.nl (A. Nagelkerke), jan.bussink@radboudumc.nl (J. Bussink), anneke.geurts-moespot@radboudumc.nl (A. Geurts-Moespot), fred.sweep@radboudumc.nl (F.C.G.J. Sweep), paul.span@radboudumc.nl (P.N. Span).

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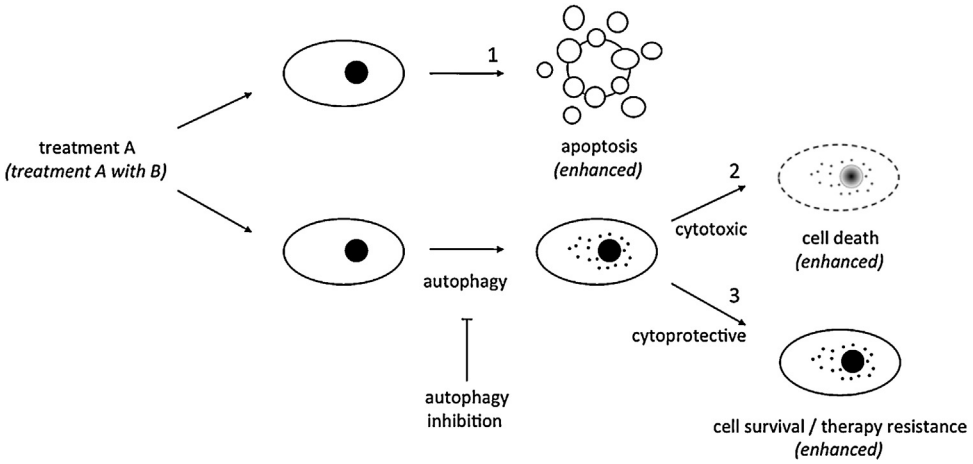

Fig. 1. Outcome of treatment interactions in cancer cells. Treatment A can have different effects on cancer cells: (1) Cancer cell death by apoptosis. (2) Cell death by cytotoxic autophagy. (3) Cell survival by cytoprotective autophagy. Combining treatment A with treatment B exaggerates these effects, either synergising or antagonising. Depending on the nature of the treatment(s) and the combination, 1, 2 or 3 will be the main reaction. However, in a heterogeneous cell population 1, 2 and 3 may be present simultaneously. Addition of an autophagy inhibitor will: (1) Have no effect. (2) Inhibit cytotoxicity. (3) Inhibit cell survival by driving cells into apoptosis. Autophagy inhibition in situation 2 should be avoided as it counteracts cell death.

yeast ATG8). The content of autophagosomes is degraded by fusion with lysosomes. For a comprehensive overview of the core molecular pathways in autophagy, as well as of the signalling routes that influence autophagy, we refer to part I of this review.

3. Modulation of autophagy as cancer therapy

Autophagy can lead to contradictory endpoints: cell survival and death. Survival represents a self-defence mechanism to withstand therapy-induced cell death. However, excessive and prolonged autophagy impedes cell recovery and survival. This induces a cell death programme, known as autophagic cell death or programmed cell death type II, but can also stimulate apoptosis [19]. Both repression and stimulation of autophagy are therefore realistic therapeutic approaches (see Fig. 1). (Hyper)activation of autophagy forces tumour cells into autophagic cell death. Autophagic cell death differs from apoptosis as it is associated with an increased formation of autophagosomes and is caspase-independent. The use of anticancer agents that provoke autophagic cell death could be particularly beneficial when apoptosis is defective and cancer cells should be driven into non-apoptotic types of cell death. Conversely, inhibition of autophagy prevents its use as a survival mechanism during therapy. In cells with intact apoptotic signalling, autophagy inhibition could drive cells into apoptosis. Interference with autophagy can be accomplished by modulation of several pathways at various levels (see part I of this review). Consequently, the number of treatments that have an effect on autophagy is vast. Supplementary Table 1 provides a (non-exhaustive) list of compounds with autophagy modulating properties. The possible combinations with these treatments are even more immense. Several treatment interactions between different compounds are given in supplementary Table 2. Some of these interactions will be discussed below. Many of the compound listed in supplementary Table 1 are analysed in clinical trials, both as single agents and in combinations with other therapies.

Supplementary Tables S1 and S2 can be found, in the online version, at doi:10.1016/j.semcancer.2014.06.001.

3.1. Autophagy induction

3.1.1. mTOR inhibitors

Mechanistic target of rapamycin (mTOR) is a key repressor of autophagy. Therefore, mTOR inhibition, leading to the activation of the ULK-complex (UNC-51-like kinase-complex), is a valuable approach to stimulate autophagy. Treatment with the mTOR inhibitor rapamycin has marked anti-tumour effects in MCF-7 and MDA-MB-231 xenografted tumours, mostly because of inhibition of angiogenesis [20]. Rapamycin reduces carcinogen-induced lung tumours in a murine model [21]. In addition, concurrent administration of rapamycin with radiation significantly increases breast cancer cell death [10] and also sensitises radiotherapy resistant hepatocellular carcinoma to radiation [22]. Concurrent administration of RAD001, a rapamycin-derivative, and radiotherapy increases sensitivity to radiation in both breast cancer cells [23] as well as prostate cancer cells [24]. Recently, combining autophagy activation by mTOR inhibition with radiation was shown to induce cellular senescence in cancer cells and xenografts [25]. This leads to enhanced cytotoxic effects.

Nevertheless, inhibiting mTOR may have unwanted side-effects. Treatment with RAD001 results in a significant occurrence of distant metastases in a rat model of pancreatic cancer [26]. mTOR inhibitors, whilst repressing mTOR-signalling, also activate AKT [27,28]. This may counteract their anti-cancer effects. Combining mTOR inhibitors with AKT inhibitors enhances anti-tumour properties of mTOR inhibitors [27–30].

3.1.2. AMPK induction

mTOR-signalling can also be disrupted through AMP-activated protein kinase (AMPK), for example by metformin. Metformin is an inhibitor of the mitochondrial electron transport chain complex I, which leads to decreased ATP production and increased AMP. This causes AMPK induction and mTOR inhibition. Metformin has cytostatic effects in several cancer cell lines and decreases tumourigenesis in a rodent cancer model [31]. The combination of chemotherapy and metformin is more harmful for breast cancer cells than the treatment with chemotherapy or metformin alone [32]. In prostate cancer cells, metformin synergises with 2-deoxyglucose [33]. Metformin inhibits 2-deoxyglucose-induced autophagy and instead forced cells into apoptosis. Metformin has been reported to improve tumour oxygenation and hence radiotherapy response [34]. Conversely, there are reports that combining metformin reduces cell death induced by chemotherapy [35,36].