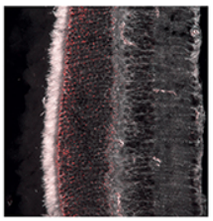
Autophagy



Autophagy

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The DNA damage response and autophagy during cancer development: an antagonistic pleiotropy entanglement

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ADDENDUM

The DNA damage response and autophagy during cancer development: an antagonistic pleiotropy entanglement

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ABSTRACT

The DNA damage response (DDR) pathway is a cardinal cellular stress response mechanism that during cancer development follows an antagonistic pleiotropy mode of action. Given that DDR activation is an energy demanding process, interplay with macroautophagy/autophagy, a stress response and energy providing mechanism, is likely to take place. While molecular connections between both mechanisms have been reported, an open question regards whether autophagy activation follows solely or is entangled with DDR in a similar antagonistic pleiotropy pattern during cancer development. Combing evidence on the spatiotemporal relationship of DDR and autophagy in the entire spectrum of carcinogenesis from our previous studies, we discuss these issues in the current addendum.

Abbreviation: AMPK: AMP-dependent protein kinase; DDR: DNA damage response.

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Disease; genomic instability; macroautophagy; stress; tumor

In nature, each deleterious stimulus is followed by a reactive response in order to preserve homeostasis [1]. This principle is reflected in the "oncogene-induced DNA damage model for cancer development". According to this model, oncogene activation triggers replication stress and subsequently the DNA damage response (DDR) pathway. The latter mobilizes the antitumor barriers of apoptosis and senescence, eliminating incipient cancer cells from the earliest stages of cancer development. As DNA damage accumulates, the cells capacity to repair efficiently in an error-free manner is overwhelmed, shifting to an error-prone repair, leading to genomic instability, breaching the antitumor barriers and eventually facilitating cancer progression. The model explains: First, the emergence of genomic instability as the driving force for tumor development, establishing it as a hallmark of cancer; and second, the breach of the antitumor barriers, as reflected by evasion from apoptosis and escape from senescence [1–3]. Hence, the role of DDR during carcinogenesis comprises a representative paradigm of antagonistic pleiotropy. The term describes the behavior of a molecule, mechanism, cellular state or any other phenotype that behaves in a beneficial manner early and exhibits deleterious properties later in time and life-course [4]. As such, DDR exerts tumor suppressive effects in the early stages and tumor promoting in the advanced stages of cancer. Similar traits have also been described for other molecules, settings and cellular processes such as testosterone, hemoglobinopathy, epithelial-to-mesenchymal transition/EMT, cellular senescence and others.

Given that DDR activation is a highly energy consuming process, an interesting issue that has not been yet addressed by the above-described model relates to the origin of energy resources that are required to support such a function. Autophagy which is a cardinal stress response and an energy- and nutrient-providing mechanism emerges as an attractive candidate [5]. Several links have been reported to take place between DDR and autophagy during carcinogenesis (extensively reviewed in Vessoni et al. 2013 [6] and Eliopoulos et al. 2016 [7]). The DDR pathway is a well orchestrated signaling cascade with ATM (ATM serine/threonine kinase) being a cardinal mediator and TP53/p53 (tumor protein p53) one of the most potent downstream effectors [1]. Both proteins have been shown as essential autophagy regulators. Particularly, ATM activation is associated with suppression of MTOR (mechanistic target of rapamycin kinase) signaling through the AMPK pathway, eventually promoting autophagy [7,8]. Autophagy is also positively regulated by ATM via other routes involving PTEN (phosphatase and tensin homolog) phosphorylation, ATG4C (autophagy related 4C cysteine peptidase) upregulation, CHEK2/CHK2 (checkpoint kinase 2) phosphorylation and FOXK (forkhead box K) nuclear export [8,9].

TP53 was actually the first identified player in the DDR-autophagy connection [7–9]. Currently, it is well established that TP53 exerts a dual control on autophagy that relies on its subcellular localization [10]. Nuclear TP53 can promote autophagy by inhibiting MTOR via transcriptional activation of AMP-dependent protein kinase (AMPK) and PTEN [10]. Additionally, TP53 mediates the transcriptional upregulation of DRAM (DNA damage regulated autophagy modulator), a lysosomal protein involved in autophagy [8,10]. In contrast,

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cytoplasmic TP53 restrains autophagy through AMPK and subsequent MTOR activation [7,8,10].

Regarding regulation of DDR components by autophagy, this matter remains still largely unaddressed [7]. However, some insights have been provided toward this direction. Particularly, autophagy deficiency has been linked with increased proteasomal activity resulting in a robust downregulation of CHEK1/CHK1 (checkpoint kinase 1) [11]. In line with notion, autophagy-deficient cells suffer from replication stress and endogenous DNA damage that is dealt with in a context-dependent manner [11,12]. Of note, accumulation of SQSTM1/p62 (sequestosome 1) due to the impairment of the autophagic flux leads to its direct binding to DDR factors, thus inhibiting the recruitment of DNA repair components [11].

Based on all the above, a question that arises is whether autophagy activation follows solely or in conjunction with DDR a similar antagonistic pleiotropy pattern. Reports dealing with the spatiotemporal features of the DDR-autophagy connection in the entire spectrum of cancer development have shed light on this issue. While in advanced stages they indicate a parallel to DDR upregulation of autophagy and a tumor-promoting behavior; in early stages, two different putatively context-dependent patterns have been recognized, both serving in principle toward a tumor suppressive mode of action. According to the first, autophagy activation follows the early activation of the DDR pathway in precancerous lesions, with the latter always preceding (Figure 1) [12]. As such, autophagy seems to play a beneficial, cell-fitness supporting role allowing cells to prevent or deal with replication stress and DNA damage, thus blocking cancer progression [12]. These outcomes occur under a threshold within the sublethal area of autophagy activity that distinguishes tumor-suppressing from tumor-promoting properties (Figure 1). When that threshold is exceeded, although autophagy levels remain sublethal, they can exert a "dark side" [13]. Autophagy activation is well known to sustain DNA synthesis and assist DNA repair processes such as homologous recombination and non-homologous end joining/NHEJ [7,11]. However, it has been demonstrated that under specific circumstances and beyond the above-mentioned threshold, upregulation of autophagy triggers DNA damage and promotes genomic instability (Figure 1) [13]. While the latter can induce cellular senescence in preneoplastic lesions, according to the initially described model, it can further act as a driving force leading to escape from senescence and cancer progression [3,14]. Further upregulation of autophagy may result in severe genomic instability and cell death. Regarding the second pattern, a detailed, subcellular localization analysis of potent autophagic players in the whole spectrum of laryngeal carcinogenesis, reveals a declined autophagic activity in precancerous lesions (Figure 1) [15]. The latter finding when correlated with the DDR status in the same pathological stages is suggestive of a cancer-inhibiting function to deprive energy at early non-malignant stages and support the DDR mediated anti-tumor restraints (Figure 1) [15]. Cumulatively, all the above favor an antagonistic pleiotropy entanglement between the DDR pathway and autophagy that results in tumor-suppressive effects in the earliest stages and pro-tumorigenic outcomes in the advanced stages of cancer development.

A question that arises relates to how this entanglement can be exploited for novel cancer therapies. In this context, elucidation of the molecular pathways involved in autophagy and its connection with other potent cellular processes such as DNA replication, DDR and DNA repair during cancer is anticipated to unveil potential molecular therapeutic switches. Given that autophagy-deficient cells suffer from replication

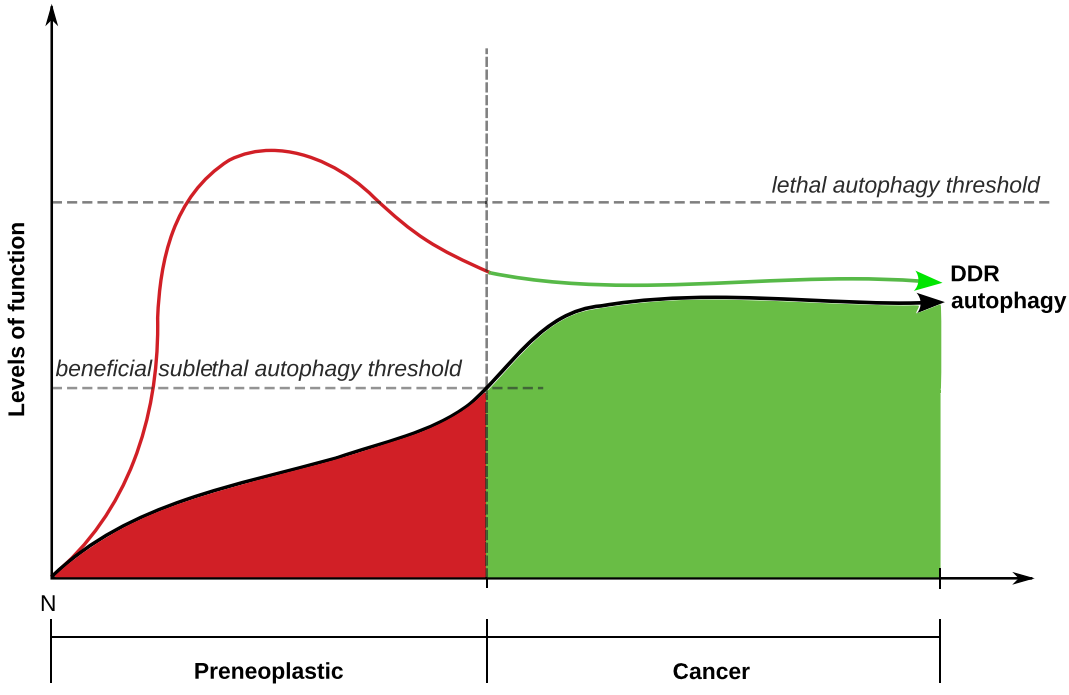

Figure 1. Schematic representation of the DDR-autophagy entanglement during carcinogenesis. The red color represents tumor suppression functions, whereas the green one tumor promoting effects (see the text for more details).

stress, blocking of autophagy in combination with approaches that enhance replication stress, leading to excessive genomic damage and cell death, seems an attractive opportunity for therapeutic purposes [16]. Collectively, in the era of precision medicine, mapping of the mechanisms that govern autophagy per cancer type emerges as an imperative task for the development of effective anticancer strategies.

Disclosure statement

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