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How Oncogenic Viruses Exploit p62-Mediated Selective Autophagy for Cancer Development

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Mini Review

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Mini Review

The 2016 Nobel Prize in Physiology or Medicine was awarded to Dr. Yoshinori Ohsumi for his discoveries of mechanisms for autophagy. Autophagy is a fundamental and conserved cellular program essential for maintaining cellular homeostasis. Unlike non-selective autophagy (including mitophagy) that sorts harmful or surplus cellular contents to the lysosomes for degradation and recycling, selective autophagy is mediated by an increasing pool of receptors, such as p62, NBR1, TAX1BP1, NDP52, OPTN, BCL2L13, FUNDC1, CCDC50, TRIMs, and TOLLIP, and is generally invoked by certain stresses to specifically target functional substrates for lysosomal degradation to modulate various cellular responses [1- 4].

The role of autophagy in cancer is still under debate. However, it is now generally accepted that autophagy counteracts tumorigenesis at early stages, whereas promotes metabolism, survival, and progression of already established cancers [5-7]. As such, oncogenic viruses are known to induce non-selective autophagy and inhibit the final stage of autophagy at their early stage of infection for optimal replication and oncogenic transformation, but induce autophagy in their latency to facilitate their persistence, as well as tumor initiation, metastasis and development [8-11].

Interestingly, a few recent reports highlight the emerging roles of p62-mediated selective autophagy in the latency maintenance and cancer development in the setting of oncogenic viral infections. We provide some general information in this short overview on how oncogenic viruses promote oncogenesis by exploiting this autophagy mechanism.

Oncogenic Viruses Activate P62-Mediated Selective Autophagy in Their Latency

The discovery of the cellular mechanism of oxygen sensing has awarded the 2019 Nobel Prize in Physiology and Medicine, highlighting its importance in cellular functions. Reactive oxygen/nitrogen species (ROS/RNS, referred to ROS hereafter) are produced by extracellular or intracellular stresses such as cancer chemotherapeutic drugs, and mitochondria produce the majority of ROS [12]. The mitochondria in malignant cells are functionally and structurally deregulated and are able to overproduce ROS [13]. Cancer hypoxia also induces intracellular ROS through the mechanisms involving the hypoxia-inducible factor (HIF) family of transcription factors [14]. Of note, ROS production can be directly induced by signaling pathways downstream of viral oncoproteins in the latency, including EBV LMP1 and EBNA1 [15-17], HTLV1 Tax [18], KSHV LANA [19,20], and HPV E6 and E7 [21,22].

ROS activate various transcription factors such as NFκB, AP1, HIF1α and STAT3 essential for cancer initiation and development, control the expression of various tumor suppressor genes such as p53, Rb, and pTEN [23], and also induce autophagy [24,25]. ROS are a double-edged sword, depending on their levels; they either promote cell-autonomous apoptosis and anticancer immunosurveillance,

or promote chronic inflammation that favors carcinogenesis under certain conditions [26]. ROS represent a crucial component of the tumor microenvironment, in which ROS incites inflammation, and excess inflammation in turn causes oxidative stress, ultimately perturbing genomic instability that promotes malignant transformation [27,28].

Notably, ROS also trigger the activation of the antioxidative defense, with the Keap1-NRF2 pathway being the master antioxidative defense mechanism that plays a role in cancer (Figure 1) [29-31]. The transcription factor NRF2, a member of the basic leucine zipper (bZIP) family, is constitutively ubiquitinated for proteasomal degradation under normoxia by the Ub E3 ligase complex Keap1/Cul3/RBX1. ROS trigger autophagic degradation of Keap1, resulting in the accumulation and activation of NRF2. As the master regulator of oxidative and inflammatory Stresses, NRF2 transactivates about 250 genes, including p62, Keap1, Cox-2, iNOS, PRDX1, HIF1, NQO1, HMOX1, GSTs, and NRF2 itself [32,33]. Due to its importance in redox homeostasis, quick activation of NRF2 is a hallmark in response to ROS under various stresses [34-36].

The ubiquitin sensor and selective autophagy receptor p62 is one of the most important transcriptional targets of NRF2. In turn, phosphorylated p62 (S349) binds to Keap1 and disrupts Keap1-NRF2 interaction, promoting NRF2 stabilization and activation in a positive regulatory circuit [37,38]. Induction of p62 expression is a prerequisite for consequent activation of p62- mediated selective autophagy, which also requires autophagosome biogenesis and site-specific PTMs of p62, including phosphorylation of S403 and ubiquitination of K7/K420 [39].

Importantly, recent studies have indicated that oncogenic viruses induce p62 expression in their latency, through different mechanisms, including the Keap1-NRF2 pathway [40,41]. We have shown that EBV and HTLV1 activate p62-mediate selective autophagy in their latency [42]. To further explore the mechanisms, we have accumulated evidence showing that EBV and HTLV1 induce p62, partially by NFκB that is activated downstream of LMP1 and Tax signaling pathways, respectively, and also likely by the Keap1-NRF2 pathway (to be published).

p62-mediated Selective Autophagy Serves as an Alternative DNA Damage Response Mechanism

ROS are the major cause of endogenous DNA damage, including double-strand DNA breaks (DSBs), which is directly linked to many human diseases including cancer [43-45]. Eukaryotic organisms have developed complicated mechanisms to repair DNA damage to ensure genomic integrity, and thus the DNA repair machinery represents a highly complex defense mechanism [46]. Homologous recombination (HR) and non-homologous end-joining (NHEJ) are two major mechanisms responsible for the repair of DSBs [47].

ROS production and DNA damage are the most common features of cancers and chronic viral infections [48,49]. Most cancers, if not all, harbor deficient traditional DNA repair mechanisms [50]. As such, viral infections can hijack the traditional DNA repair mechanisms. As a part of DNA damage response (DDR), p62-mediated selective autophagy serves as an alternative DNA repair mechanism in these settings, allowing these cancer or infected cells to escape DNA damage- induced cell death, by selectively targeting degradation of p62 itself and other DDR-related proteins such as RAD51 (Figure 1) [51,52].

We have shown that a well-controlled autophagy-p62 interplay renders EBV-infected cells with the ability to balance pro-survival DNA damage resistance and pro-mutagenic genomic perturbation under oxidative stress [42,53], and have defined two distinct roles for the autophagy-p62 interplay in this setting: cytoplasmic p62 mediates selective autophagy, and nuclear p62 upon autophagy inhibition represses DNA repair at least by promoting proteasome-mediated degradation of CHK1 and RAD51 [42]. These original findings disclose novel mechanisms underneath LMP1-mediated oxidative DDR. Elucidating how p62-mediated autophagy regulates DDR is necessary for improving our understanding of its mechanistic role in viral latency and oncogenesis.

p62-mediated Selective Autophagy Suppresses the Antitumor cGAS-STING Innate Immune Pathway

DNA fragments derived from DNA damage, if left unrepaired, can accumulate in the cytoplasm and serves as a major category of damage-associated molecular patterns (DAMPs), which are recognized by host germline-encoded pathogen recognition receptors (PRRs) [54-57], leading to chronic inflammation that promotes immunosenescence, inflammaging, and the development of tumor microenvironment under certain conditions [27,28,58,59].

Among these PRR pathways, the cGAS-STING pathway plays the most important role in sensing endogenous damaged DNA fragments (Figure 1) [60-62]. p62-mediated selective autophagy inhibits cGAS-STING signaling through different mechanisms. In turn, the cGAS-STING pathway promotes p62-mediated selective autophagy. Mechanistically, there are

multiple points of crosstalk between these two processes, including that TBK1 targets both IRF3 (also STING) and p62 for activation [39], that STING can directly induce autophagy [63-66], and that p62-mediated selective autophagy can selectively target cGAS and STING for autophagic degradation (Figure 1) [67].

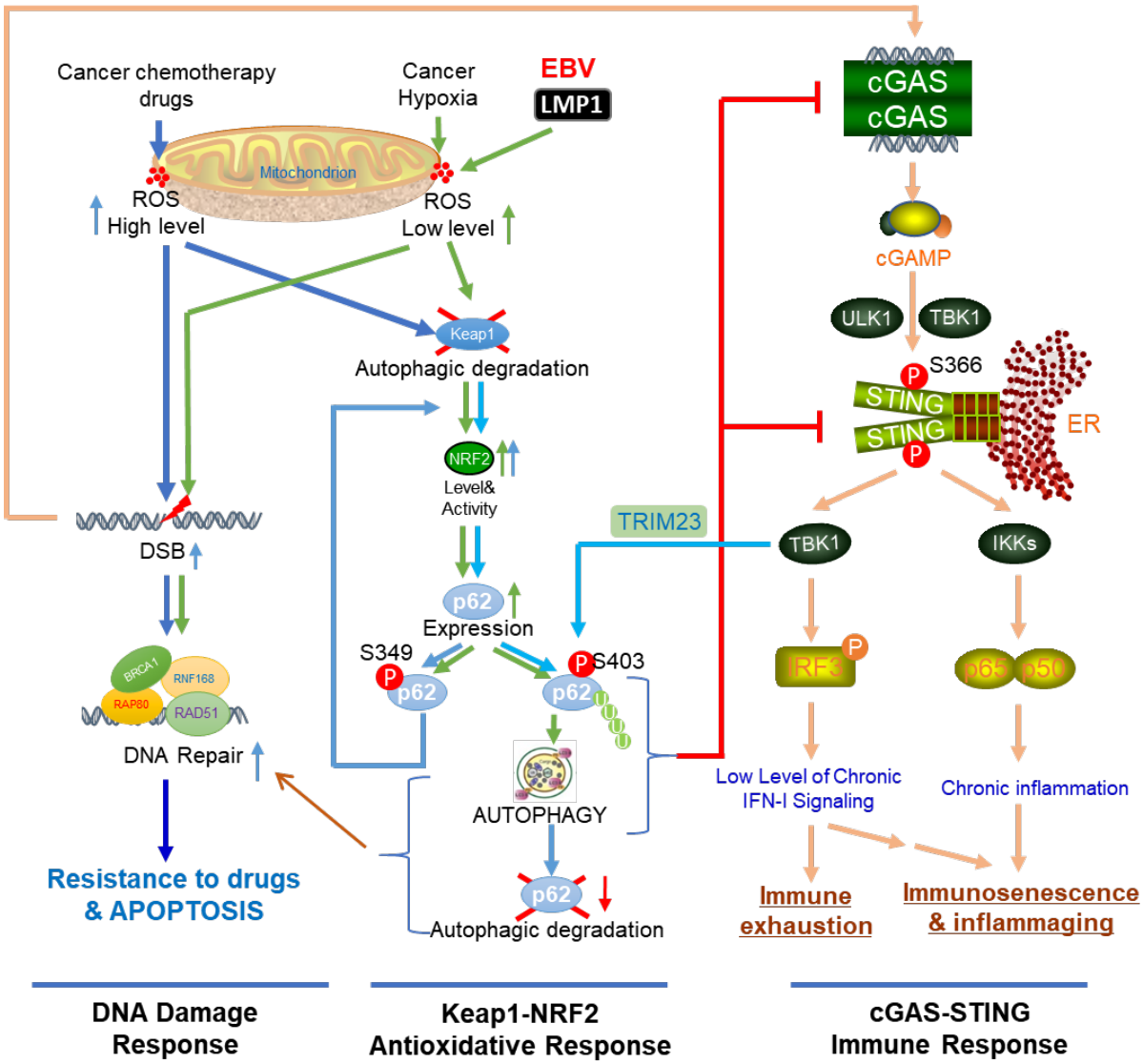

Figure 1: Autophagy mediates the crosstalk of oxidative stress with the Keap1-NRF2 antioxidative response, the DNA damage response, and the cGAS-STING-mediated antitumor immune response.
ROS are produced by various stresses, such as viral infections, cancer chemotherapeutic drug treatments, and cancer hypoxia, as well as by signaling pathways triggered by oncogenic viral proteins. Different levels of ROS result in distinct outcomes, through the activation of: 1) DDR. p62-mediated selective autophagy is induced by ROS and promotes DNA repair in cancer cells, conferring to drug resistance. massive DNA damage that cannot be repaired causes cell death;
2) antioxidative response. The master antioxidant transcription factor NRF2 remains at low protein levels. ROS promote the accumulation and activation of NRF2 in an autophagy-dependent manner. Activated NRF2 induces the expression of a pool of target genes, including p62 that is required for the induction of p62-mediated selective autophagy; and 3) DNA sensing pathways, with the cGAS-STING pathway being the major one. p62-mediated selective autophagy suppresses the cGAS-STING-mediated signaling, and in turn, the cGAS-STING pathway promotes p62-mediated selective autophagy.

Perspectives on Cancer Therapy

Aberrant redox homeostasis, deficient DDR machinery, chronic inflammation, genomic instability, evasion of the immune response, and resistance to cell death are among the hallmarks of cancer [68-70]. Autophagy plays a crucial role in the crosstalk of these hallmarks, and frequently contributes to cancer chemoresistance [71,72]. The indispensable requirement of autophagy for the survival of many cancer cells suggests targeting autophagy may serve as a viable therapeutic strategy [73-79]. All anticancer chemotherapeutic agents (such as etoposide and doxorubicin) produce ROS, which are able to induce autophagy as well as DNA damage to mount the cGAS-STING immune response that triggers cell death and tumor rejection in cancer cells [80,81]. Inhibition of physiological autophagy (both selective and non-selective) can lead to cell death in cancers [24]. Lysosome inhibitors, such as hydroxychloroquine, inhibit autophagy and are clinically important for treating drug-resistant cancers [82].

However, inhibition of autophagy activity alone is not specific for cancer therapy although several autophagy inhibitors are in clinical trials. Combined targeting a cellular mechanism, especially the cGAS-STING pathway that is specifically coupled with autophagy, in a given cancer context may improve clinical efficacy and specificity.

Competing Interests

The authors declare that they have no competing interests.

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