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EDITORIAL

Parkin in cancer: Mitophagy-related/unrelated tasks

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Abstract

Dysfunctional mitochondria may produce excessive reactive oxygen species, thus inducing DNA damage, which may be oncogenic if not repaired. As a major role of the PINK1-Parkin pathway involves selective autophagic clearance of damaged mitochondria *via* a process termed mitophagy, Parkin-mediated mitophagy may be a tumor-suppressive mechanism. As an alternative mechanism for tumor inhibition beyond mitophagy, Parkin has been reported to have other oncosuppressive functions such as DNA repair, negative regulation of cell proliferation and stimulation of p53 tumor suppressor function. The authors recently reported that acute ethanol-induced mitophagy in hepatocytes was associated with Parkin mitochondrial translocation and colocalization with accumulated 8-OHdG (a marker of DNA damage and mutagenicity). This finding suggests: (1) the possibility of Parkin-mediated repair of damaged mitochondrial DNA in hepatocytes of ethanol-treated rats (ETRs) as an oncosuppressive mechanism; and (2) potential induction of cytoprotective mitophagy in ETR hepatocytes if mitochondrial damage is too severe to be repaired. Below is a summary of the various roles Parkin plays in tumor suppression, which may or may not be related to mitophagy. A proper understanding of the various tasks performed by Parkin in tumorigenesis may help in cancer therapy by allowing the PINK1-Parkin pathway to be targeted.

Key words: Cancer; Ethanol; Liver; Mitophagy; Parkin; PINK1; 8-OHdG

Core tip: A large number of studies have found that the impaired Parkin function or downregulation of expression may induce cancer initiation and progression *via* mitophagy-related/unrelated mechanisms. Thus, there is a growing belief that Parkin may have tumor suppressor effects. Based on literature and on the authors' recent publications regarding animal models of alcohol abuse, this paper highlights the various roles of Parkin in the suppression of oncogenesis. Proper understanding of Parkin functions may have therapeutic implications in the treatment of various cancers.

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Mutations in the Parkin gene are frequently associated with Parkinson's disease (PD). They lead to defects in autophagic clearance of damaged mitochondria *via* mitophagy, resulting in the characteristic neuronal loss observed in PD[1]. Parkin-mediated mitophagy is characterized by accumulation of PINK1 on the outer mitochondrial membrane (OMM) of damaged mitochondria and subsequent mitochondrial translocation of Parkin and ubiquitination of numerous OMM proteins, followed by clearance of these organelles *via* the microtubule-associated protein light chain 3 (LC3)-mediated autophagic machinery[1,2]. Parkin-mediated ubiquitination of OMM proteins stimulates the recruitment of different LC3 interacting region-containing autophagy receptors which bind ubiquitin-tagged OMM proteins, including p62, optineurin and NBR1[2]. Dysfunctional mitochondria can transform cells and promote tumorigenesis, suggesting that mitophagy may function as a tumor suppressor mechanism[2]. A number of recent studies have investigated the involvement of mitophagy in tumor suppression, with results including the finding that insufficient mitophagy resulted in oncocytic formation in heterogeneous thyroid Hürthle cell tumors[3]. However, a growing body of evidence suggests that Parkin also plays a role in cancer as a putative tumor suppressor. Parkin$^{-/-}$ mice exhibited enhanced hepatocyte proliferation associated with upregulation of endogenous follistatin, resulting in the induction and progression of hepatocellular carcinoma (HCC)[4]. Upon autophagy activation the Atg4 cysteine protease first cleaves pro-LC3 at the C-terminus, thus forming LC3-Ⅰ. Induction of Atg7 conjugates phosphatidylethanolamine (PE) to LC3-Ⅰ, forming LC3-Ⅱ (essential form of LC3 for mitophagosome formation). The Atg5/12/16 complex also acts as an E3 ligase, promoting PE conjugation to LC3[2]. Mice with systemic mosaic deletion of Atg5 and liver-specific Atg7$^{-/-}$ mice develop benign liver adenomas[5]. Parkin deficiency results in overexpression of its substrates, mitotic defects, genomic instability and tumorigenesis[6]. Downregulation of Parkin protein has been observed in HCC, whereas Parkin overexpression inhibits the migration and invasion of multiple cancer cells[7]. Parkin has been reported to contribute to the functions of p53 - another tumor suppressor - *via* regulation of the energy metabolism (especially the Warburg effect) and antioxidant defense[8]. Paradoxically, in some cases Parkin activity may be required for KRAS-driven tumors to maintain mitochondrial quality control and buffer oxidative stress, making it a pro-survival protein[7]. KRAS mutant pancreatic adenocarcinoma has been reported to rely on autophagy and mitophagy to supply bioenergetic intermediates for the TCA cycle. Mitophagy also appears to be a prosurvival mechanism in immortal baby mouse kidney epithelial cells ectopically expressing oncogenic HRAS or KRAS by removing damaged mitochondria[9].

Seitz and Stickel[10] reported that animal models of alcohol abuse have clearly identified ethanol as a hepatic carcinogen *via* mechanisms related to excessive reactive oxygen species and acetaldehyde production, altered methylation and reduction of retinoic acid in hepatocytes. Recently the authors[11,12] and others[13] investigated Parkin-mediated hepatic mitophagy in animal models of acute and chronic alcoholism. The authors found that acute ethanol administration (5 g/kg) to adult rats enhanced hepatocyte mitophagy, which was associated with Parkin mitochondrial translocation and colocalization with accumulated 8-OHdG - a marker of oxidative nuclear and mitochondrial DNA (mtDNA) damage and mutagenicity[11,12,14,15]. Accordingly, Parkin co-localization with accumulated 8-OHdG in hepatocyte mitochondria of acute ETRs may be a signal for mitophagy induction *via* the triggering of Parkin mitochondrial translocation[12,16]. It may also be a stimulus for DNA repair and prevention of oncogenesis, as endogenous Parkin has a reported physical association with mtDNA[12,17] and translocates to nuclei interacting with proliferating cell nuclear antigen in cultured neuronal cells affected by oxidative DNA damage[18]. In addition, Parkin-deficient mice have been reported to show increased 8-oxoguanine in the cerebral cortex. Parkin's promotion of DNA repair may therefore be an important mechanism in the suppression of cancer and neurodegenerative diseases[18,19]. The authors' findings in animal models of ethanol-induced mitophagy may support the above-mentioned literature regarding the tumor suppressor roles of Parkin, which may or may not be mitophagy-related. Parkin has additionally been reported to regulate two additional cytoprotective mechanisms on cellular exposure to oxidative stress: (1) induction of mitochondrial-derived vesicle formation[12,16,20]; and (2) suppression of mitochondrial spheroid formation[11,21,22]. Further studies are needed to determine whether Parkin regulates these two mechanisms in cancer cells and to evaluate the impact of any such regulation on tumorigenesis[23].

The authors believe that their recent publications on animal models of alcoholism and the work of others may provide evidence for Parkin-mediated oncosuppression, which may have implications in cancer therapy.

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