Seminars in Cancer Biology xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Seminars in Cancer Biology

journal homepage: www.elsevier.com/locate/semcancer

Review

Expanding perspectives on the significance of mitophagy in cancer

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ARTICLE INFO

Keywords:
Mitochondria
Mitophagy
Biogenesis
Parkin
BNIP3/BNIP3L
FUNDC1
Cardiolipin
Metabolic reprogramming
Cell fate determination
Inflammasome activation
DNA damage responses

ABSTRACT

Mitophagy is a selective mode of autophagy in which mitochondria are selectively targeted for degradation at the autophagolysosome. Mitophagy is activated by stresses such as hypoxia, nutrient deprivation, DNA damage, inflammation and mitochondrial membrane depolarization and plays a role in maintaining mitochondrial integrity and function. Defects in mitophagy lead to mitochondrial dysfunction that can affect metabolic reprogramming in response to stress, alter cell fate determination and differentiation, which in turn affects disease incidence and etiology, including cancer. Here, we discuss how different mitophagy adaptors and modulators, including Parkin, BNIP3, BNIP3L, p62/SQSTM1 and OPTN, are regulated in response to physiological stresses and deregulated in cancers. Additionally, we explore how these different mitophagy control pathways coordinate with each other. Finally, we review new developments in understanding how mitophagy affects stemness, cell fate determination, inflammation and DNA damage responses that are relevant to understanding the role of mitophagy in cancer.

1. Introduction

Mitophagy is a selective form of general autophagy in which mitochondria are specifically targeted for degradation at the autophagolysosome [1,2]. As such, the process of mitophagy is dependent on the general autophagy machinery, and additionally, relies on a growing cadre of “mitophagy adaptors” and regulatory molecules that are involved in selecting mitochondria for autophagic turnover (see Table 1). While mitophagy can be induced artificially with respiratory chain inhibitors and uncoupling agents, such as carbonyl cyanide 3-chlorophenylhydrazone (CCCP) that depolarize mitochondria, it is also part of the response to key physiological stresses, such as hypoxia and nutrient deprivation [3]. In addition, mitophagy is a programmed component of developmental and differentiation processes, including elimination of paternal mitochondria from the fertilized egg [4–6] and removal of mitochondria during red blood cell production [7,8] and muscle differentiation [9]. By promoting elimination of dysfunctional, supernumery and/or aged mitochondria, mitophagy plays a central role in maintaining mitochondrial and cellular integrity. Conversely, defective mitophagy can lead to loss of tissue homeostasis and development of disease, including cancer [2]. Various mitophagy modulators have been shown to be deregulated in human cancers, including PARK2, BNIP3, BNIP3L, FANCC, p62/SQSTM1, with others likely to emerge as research increases in this area. The challenge in the field is to determine what selective advantage is conferred to the tumor through deregulation of mitophagy and whether mitophagy is acting to promote or to limit tumorigenesis. In this review, we address outstanding questions pertaining to the function and regulation of mitophagy adaptors in cancer, including the extent to which these molecules interact or are co-regulated. We also probe emerging roles for mitophagy in cell fate determination, inflammatory responses and DNA damage responses that contribute to our overall understanding of the role of mitophagy in

Abbreviations: ALS, amyotrophic lateral sclerosis; AR, androgen receptor; ASC, apoptosis-associated speck-like protein containing a CARD; ATM, ataxia telangiectasia mutated; BCL-2, breakpoint cluster locus-2; BCL-XL, BCL2-like 1 long; BNIP3, BCL2 interacting protein 3; BNIP3L, BCL2 interacting protein 3 like; BRCA1, breast cancer 1; CCCP, carbonyl cyanide 3-chlorophenylhydrazone; CK2, casein kinase-2; CL, cardiolipin; DRP1, dynamin related protein 1; ETC, electron transport chain; FA, Fanconi anemia; FANC-C, FA protein C; FUNDC1, FUN 14 domain containing 1; GAP, GTPase activating protein; GDI, GDP dissociation inhibitor; HCC, hepatocellular carcinoma; IMM, inner mitochondrial membrane; IRF3, interferon response factor 3; LC3, microtubule associated protein 1 light chain 3; LIR, LC3 interacting region; mtDNA, mitochondrial DNA; MAVS, mitochondrial anti-viral signaling protein; MFN, mitofusin; NBR1, near BRCA1; NDP52, nuclear dot protein 52; NLRP3, nucleotide binding domain and leucine rich repeat pyrin domain containing 3; NSCLC, non-small cell lung carcinoma; OMM, outer mitochondrial membrane; OPTN, optineurin, p62/SQSTM1; PARK2, Parkin encoding locus; PARK6, PINK1 encoding locus; PARK8, LRRK2 encoding locus; PD, Parkinson's disease; PDAC, pancreatic ductal adenocarcinoma; PGAM5, phosphoglycerate mutase family member 5; PHB-2, prohibitin-2; PINK1, PTEN induced putative kinase 1; PLK1, Polo-like kinase-1; ROS, reactive oxygen species; SRC, Rous sarcoma oncogene; TAX1BP1, Tax1 binding protein 1; TAZ, tafazzin; TBK, TANK binding kinase 1; ULK1, Unc-51-like autophagy activating kinase 1

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http://dx.doi.org/10.1016/j.semcancer.2017.04.008
Received 2 February 2017; Received in revised form 19 April 2017; Accepted 20 April 2017

Table 1
Mitophagy regulators and what we know about them.

Gene/protein	Function in mitophagy	Links to cancer/disease	Reference
PARK6/PINK1	Serine/threonine kinase that undergoes voltage-dependent import and degradation at the IMM; stabilized at the OMM by altered $\Delta\Psi_{mt}$; phosphorylates ubiquitin chains, and Parkin on S65 to derepress its auto-inhibitory activity leading to Parkin recruitment to and activity at the OMM.	PARK6 loss linked to Parkinson's disease.	[31,51]
PARK2/Parkin	E3 ubiquitin ligase, activated by phosphorylation on S65 by PINK1 causing it to localize to the OMM; conjugates ubiquitin chains to numerous OMM proteins, including Mfn2; phospho-Ub chains are bund by autophagy cargo adaptors, like p62, OPTN, NDP52. Antagonized by USP30 and other mitochondrial de-ubiquitinases.	PARK2 inactivating mutations linked to Parkinson's Disease; deleted in human ovarian, breast, lung and bladder cancers; inactivating mutations found in glioblastoma and other cancers; Parkin null mice develop spontaneous liver tumors and are sensitized to radiation-induced lymphoma.	[31,34,50,51]
PARK8/LRRK2	A novel PD predisposition locus encoding a protein that interacts with Miro to promote its degradation, prevents sequestration of mitochondria and inhibits mitophagy. LRRK2 has specific kinase activity for Rab GTPases involved in cellular trafficking (Rab1b, Rab8a, Rab10) and mutant LRRK2 (G2019S) has increased kinase activity for these substrates.	Mutated (*eg.* G2019S) in Parkinson's Disease	[32,46]
Mul1	Mitochondrial E3 ubiquitin ligase that can compensate for loss of Parkin.	Not known.	[54]
PHB2/Prohibitin2	IMM protein involved in processing OPA1 and cristae remodeling; binds LC3 following Parkin-mediated rupture of OMM, acts as an IMM mitophagy adaptor; required for Parkin-mediated mitophagy. Requires PHB1 for stability. Also has a nuclear function regulating activity of E2F, p53 and the AR.	Expression deregulated in breast, prostate and lung cancer but role varies depending on tissue type. PHB1 deletion promotes HCC in mice.	[140,141]
Miro	Anchors kinesins to the OMM; is phosphorylated and cleaved by Parkin/PINK1 activity resulting in reduced mitochondrial motility, possibly isolating damaged mitochondria for mitophagy; differential phosphorylation of Miro can block Parkin recruitment to OMM.	Turnover disrupted in PD.	[32,204,205,206]
BNIP3	OMM mitophagy adaptor that binds LC3 directly to target mitochondria to the autophagosome; induced by hypoxia, nutrient deprivation, oncogenic Ras, FoxO3A, E2F, NF-κB; repressed by pRB and p53; required for mitophagy in fasted liver.	Deleted, silenced or mis-localized in breast, prostate, colon, pancreatic, liver, glioma and other cancers. BNip3 loss accelerates progression to metastasis in mouse models of breast cancer.	[3,18,106,207]
BNIP3L (NIX)	Homolog of BNIP3; induced by hypoxia, p53; required for mitophagy during red blood cell differentiation; interacts with Rheb and LC3.	BNIP3L knockdown promoted tumor growth in a mouse mammary tumor xenograft study.	[7,8,105,207]
Rheb	Small GTPase required for mTORC1 activity; interacts with LC3 and NIX to promote mitophagy induced by switch from glycolytic to oxidative metabolism.	Rheb point mutations found in genomic analyses of kidney and endometrial cancers.	[91]
FUNDC1	OMM protein induced by hypoxia, interacts directly with LC3; LC3 interaction regulated by ULK1, SRC, CK2, PGAM5; accumulates at ER-mito contact sites through interactions with calnexin; essential for hypoxia-induced mitophagy through recruitment of both Drp1 and LC3.	Not known. Knockout mouse has defects in platelet maturation.	[29,122–124]
PGAM5	Serine/threonine phosphatase at the OMM, required for CCCP-induced mitophagy, de-phosphorylates S13 of FUNDC1 to activate it, interacts with PINK1 at OMM in response to altered $\Delta\Psi_{mt}$; protects PINK1 from degradation at IMM; Aged mice develop symptoms of PD.	Pgam5 null mice exhibit a movement disorder as they age, reminiscent of PD.	[124–126]
Bcl2-L13/Bcl-Rambo	Mammalian homologue of Atg32 in yeast; binds LC3 through conserved LIR motif; over-expression induces mito fragmentation and mitophagy in a Parkin-independent manner.	Not known.	[129]
EndophilinB/Bif-1	Fatty acyl transferase required for mitochondrial membrane dynamics; interacts with Beclin1 via UVRAG; colocalizes at Atg9+ puncta, involved in membrane lipid trafficking around mitochondria.	Haploinsufficiency promotes Myc-driven lymphomagenesis in mice;	[130–132]
SMURF	Identified in a screen for genes that are required for xenophagy; also essential for Parkin-induced mitophagy; recruited to mitochondria by altered $\Delta\Psi_{mt}$; has E3 Ub ligase activity but this is not required for mitophagy	Not known.	[52]
FANC-C	Component of the Fanconi Anemia (FA) DNA repair pathway; identified in a screen for genes that rescue selective autophagy; Fanc-C interacts with Parkin, required for mitophagy, localizes to mitochondria, genetically distinct role for FANCC separate from its role in DNA repair. Other FA genes also implicated in mitophagy are FANCA, FANCD1 (BRCA2), FANCD2, FANCF, FANCL, FANCS (BRCA1).	Inactivated in Fanconi Anemia; other FANC genes include BRCA2 and BRCA1 that are deleted in hereditary breast and ovarian cancer.	[53]
Cardiolipin (CL)	IMM phospholipid involved in tethering proteins to cristae including ETC components; stress induces relocalization of CL to OMM; LC3 binds to CL, required for mitophagy involving LC3.	Not known.	[138]
TAZ/tafazzin	Phospholipid trans-acylase that remodels cardiolipin; loss of TAZ blocks mitophagy due to failure of LC3 to recognize CL;	Mutated in Barth syndrome	[139]

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