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P62 CROSSTALK IN CANCER THROUGH SELECTIVE AUTOPHAGY

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ABSTRACT

p62/SQSTM1 is a stress-inducible protein and contain to regulate one-of-a-kind signal transduction pathways such as cell survival and cell death. LC3 binding proteins resulted in the popularity of autophagy and p62. Moreover, the essential position of p62 in directing ubiquitinated cargos in the direction of autophagy in addition to compaction of these cargos. This multifunctional position of p62 is explained through its capability to engage with numerous key components of various signaling mechanisms. Now not incredibly, p62 is needed for tumor transformation as a result of its roles as a key molecule in nutrient sensing, as a regulator and substrate of autophagy. In this review, we discuss the p62 crosstalk on cancer through selective autophagy.

KEYWORDS: p62, autophagy, ubiquitin.

INTRODUCTION

There is collecting proof clarifying the roles of p62 in amino acid sensing and the oxidative strain reaction, as well as in autophagy receptor for ubiquitinated cargos. p62 possesses a couple of domain names, along with a Phox1 and Bem1p (PB1) domain, a zinc finger (ZZ), nuclear localization signals, a tumor necrosis issue receptor-associated thing 6 (TRAF6) binding domain, a nuclear export signal, an LC3-interacting place (LIR), a Keap1-interacting place (KIR) and a ubiquitin-associated (UBA) domain.[1–3] Similarly, both the aPKCs and p62 harbor a Phox/Bem1p (PB1) protein-protein binding domain that governs their interplay and the interactions of aPKC and p62 with the PB1 domains in their respective precise companions, Par-6 and neighbor of BRCA1 gene 1 (NBR1).[4,5] Autophagy is chargeable for the degradation of p62; therefore, impairment of autophagy is generally accompanied via

large accumulation of p62 accompanied by formation of mixture structures advantageous for p62 and ubiquitin.[2,6,7] This current review will discuss the emerging roles of p62 in mTORC1 and Nrf2 signaling pathway to selective autophagy.

Role of p62 to regulate autophagy

The position for p62 in activation of the mammalian target of rapamycin (mTOR) pathway, that is a core controller of cell growth and autophagy that integrates nutrient sensing and cellular-length manipulates.[8] There are two multiprotein complexes orchestrated through mTOR, mTOR complex (mTORC)1 and mTORC2, p62 particularly includes with mTORC1 thru its binding with raptor, a middle component of mTORC1[8,9] mTORC1 is accountable to inhibition by way of rapamycin and senses more than one cell and environmental cues together with nutrient availability, electricity degrees, protein misfolding, best manage, and boom alerts.[10] Curiously, recent result location p62 in particular inside the amino acid-mediated mTORC1 activation pathway, and add a new piece in the upstream mechanisms regulating nutrient sensing.[8] As a result, in p62-deficient cells amino acid-mediated phosphorylation of the mTORC1 objectives S6K and 4EBP1 is significantly impaired and, in step with decreased mTORC1 pastime, autophagy is upregulated.[8] This will be essential in situations of nutrient deprivation, in which a lack of vitamins reduces mTORC1 interest and upregulates autophagy. Beneath these conditions, the p62-mTORC1-autophagy loop would possibly offer a guard mechanism to ensure the irreversibility of mobile loss of life when vitamins are not available. How mTORC1 senses nutrients is the key query yet to be resolved. Latest studies in mammals, and others involving genetic displays in yeast and flies, have helped to discover important factors in this method.[11] Further, p62 is likewise required for the translocation of mTORC1 to the lysosomal surface[8], which is steady with the initial statement that p62 is placed at Rab7-tremendous overdue-endosomal membranes.[12] That is also steady with recent findings that mTORC1 regulates endocytosis in response to adjustments in environmental factors including nutrient availability.[13] Thinking about the critical function of overdue endosomes and/or lysosomes as factories where amino acids activate mTORC1. Different small GTPases that modulate protein trafficking, along with RalA, Rab5, Rab7, and Arfl, have also been proven to be involved in mTORC1 activation.[14-16] These result suggested that the complicated family members between p62 and autophagy via the functional interactions with mTORC1, an important piece inside the control of cellular survival and increase in cancer cells.

P62 induction in ubiquitinated cargos

Due to the presence of the C-terminal ubiquitin associated (UBA) domain of p62, similarly to the binding potential to LC3, p62 is thought to be a receptor for ubiquitinated cargos inclusive of ubiquitinated aggregates, damaged mitochondria, ubiquitinated midbody rings, ubiquitin-tagged peroxisomes, ubiquitinated microbes, ribosomal proteins, and virus capsid protein, to deliver them to the autophagosomes.[17-19] P62 and other adaptor proteins, together with NBR1[20], mediate the degradation of ubiquitinated cargos through their interaction with ubiquitin.[21] The simultaneous knockout of both p62 and Nrf2 considerably but not completely suppresses the boom in ubiquitin conjugates in Atg7-poor liver and brain.[22] Suppression of autophagy results in marked accumulation of p62 accompanied through the formation of large aggregates advantageous for p62 and ubiquitinated proteins.[23,24] Considerably, similar ubiquitin- and p62 aggregates have been identified in numerous human disorders, together with neurodegenerative diseases (Alzheimer's disorder, Parkinson's ailment and amyotrophic lateral sclerosis), liver issues (alcoholic hepatitis and steatohepatitis), and cancers (malignant glioma and hepatocellular carcinoma).[25] Just like the case of ubiquitin-fantastic aggregates, p62 localizes in damaged mitochondria ubiquitinated by Parkin, which is an E3 ubiquitin ligase related genetically to Parkinson's disorder, and the p62 is known to be fundamental for clustering of such mitochondria within the perinuclear region.[26,27] These results suggested that p62 protein interact with LC3 through UBA domain for degradation of ubiquitinated cargos in several diseases.

P62 acts as an autophagy adaptor for selective degradation

P62 has a UBA area, which paperwork dimer this is destabilized with the aid of ubiquitin binding.[28] The autophagosome-localized protein LC3 performs multiple roles in autophagy which include membrane fusion, cargo selection and autophagosome shipping.[29,53] P62 carries an LIR, which consists of an acidic cluster and hydrophobic residues (DDD and WxxL).[30,31] The acidic cluster and the Trp338 and Leu341 residues of the LIR have interaction with multiple web sites on LC3: basic residues in the N-terminal vicinity and hydrophobic pockets at the floor of the ubiquitin fold.[31] P62 self-oligomerizes in a PB1 domain-based way to sell packaging of ubiquitinated cargos and transport of packaged cargos to the autophagy pathway. The helical filaments functions huge molecular templates to nucleate the developing autophagosomal membrane; the shorter/less compact helical filaments play a role in one-of-a-kind sequestration of ubiquitinated cargo into the forming autophagosome.[32] P62 performs specific and integral roles in selective autophagy:

packaging of ubiquitinated cargos and activation of Nrf2. For the duration of Parkin-mediated mitophagy, depolarized mitochondria are clustered in the perinuclear vicinity in a technique that relies upon on self oligomerization of p62.[33,34] Further, ubiquitinpositive aggregate systems that form beneath defective proteostasis are dispersed via lack of p62.[35,36] Defective shipment meeting as a result of loss of p62 is unlikely to exert a cytotoxic effect, at least in dividing subculture cells, although it may have a destructive effect on nondividing cells and tissues.[37,38] These results suggested that p62 acts as selective autophagy adaptor for selective degradation through packaging of ubiquitinated cargos to deliver them the autophagy pathway.

CONCLUSION

P62 is a nutrient sensor for the activation of the mTORC1 pathway unveils its function now not best as a goal of autophagy, or as a bridge between polyubiquitylated proteins and the autophagosome, however also as a crucial step inside the negative regulation of autophagy in reaction to nutrient availability. Suppression of autophagy is constantly accompanied by means of huge accumulation of a selective substrate for autophagy; p62. Further to its critical function as an assembly issue for ubiquitinated proteins and organelles, whereas these alerts are more desirable via aggregation of signaling complicated via p62, selective turnover of p62 through autophagy.

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