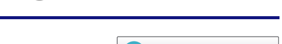
AUTOPHAGY
2021, VOL. 17, NO. 10, 3260–3261
https://doi.org/10.1080/15548627.2021.1953848



AUTOPHAGIC PUNCTUM

All cells are created equal in the sight of autophagy: selective autophagy maintains homeostasis in senescent cells

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ABSTRACT

Macroautophagy/autophagy is a sophisticated quality control program that limits cellular damage and maintains homeostasis, being an essential part of several lifespan-promoting interventions. However, autophagy is also necessary for full establishment of cellular senescence, a causal factor for many age-related diseases and aging. What lies ahead of us to unravel such a paradoxical role of autophagy in senescence is to identify specific targets degraded by autophagy during senescence and determine their importance in the senescence regulatory network. Recently, we developed the "Selective autophagy substrates *I*dentification *P*latform (SIP)" to advance these goals, providing a rich set of autophagy substrate proteins involved in senescence. Our study demonstrated that selective autophagy coordinates the stress support networks in senescent cells by degrading multiple regulatory components, echoing its homeostatic roles in normal cells. Targeting this type of selective autophagy might provide a unique opportunity to develop non-senescence addiction-based therapeutic strategies for senotherapy by disturbing the homeostatic state of senescent cells.

ARTICLE HISTORY
Received 21 June 2021
Revised 30 June 2021
Accepted 6 July 2021

KEYWORDS
Autophagy interactome; cellular senescence; inflammation; oxidative stress; proteostasis; regulated protein stability; selective autophagy; stress support networks

Senescence is adynamic process of cell cycle arrest with several distinctive features, including cellular hypertrophy, metabolic change, stress resistance, and pro-inflammatory secretory phenotypes. Senescence can cause aging in two different, but not mutually exclusive, ways: senescence intrinsically depletes stem cells and extrinsically inflames the tissue microenvironment through the senescence-associated secretory phenotypes (SASP). Senotherapy, which aims to limit the detrimental effects of senescence by either eliminating senescent cells (senolytics) or modulating the SASP (senostatics), holds great promise for aging treatments. Gene expression profiling of senescent cells led to the development of the first generation of senotherapy, such as treatment with navitoclax and dasatinib/quercetin that target anti-apoptotic BCL2/B cell lymphoma 2 family of proteins and dependence receptors, respectively. Despite their potent effects on several age-related diseases, these drugs have undesirable side effects, including toxicity. Moreover, they are effective on only asubset of senescent cells. Thus, efforts to identify additional vulnerabilities of senescent cells are required for developing "next-generation" senotherapy, which provides anew therapeutic opportunity in the fight against aging.

One critical regulator of senescence is autophagy, alysosomal degradation pathway essential for cellular homeostasis. autophagy is reported to suppress senescence but is counterintuitively necessary for full senescence. While its anti-senescence role has been extensively studied, it remained elusive until recently as to how autophagy promotes senescence establishment. This was mainly due to alack of understanding about specific targets degraded by autophagy and their importance in the senescence regulatory network. Recently, we combined aquantitative proteomics analysis of autophagy components with protein stability profiling to develop an integrated platform called the sip that fills such agap [1]. Using the sip, we have found, validated, and characterized selective autophagy substrates in senescence, uncovering adetailed mechanism by which autophagy coordinates the homeostatic state of senescence.

We constructed asenescence-associated autophagy interactome (SAAI) that consists of 634 interactions among 360 candidate proteins and identified atotal of 10 proteins plus the EIF3 complex as autophagy substrates involved in senescence. By dissecting their role in senescence, we found that selective degradation of the regulatory components by autophagy modulates the stress support network in senescent cells: (1) SQSTM1/p62-dependent selective autophagy of KEAP1 activates the NFE2L2/NRF2 anti-oxidant program, promoting resistance to oxidative stress in senescent cells; (2) CALCOCO2/NDP52-dependent selective autophagy of EIF3 components limits protein translation, relieving proteotoxic stress during senescence; (3) OPTN-dependent selective autophagy of TNIP1 disables the negative feedback loop of the NFKB/NF-KB pathway, enhancing senescence-associated inflammation. inhibiting such autophagic regulations severely disturbs the homeostatic state of senescence, by either sensitizing senescent cells to agiven stress (e.g., oxidative stress, proteotoxic stress) or suppressing its paracrine senescence activity through the reduced SASP. Therefore, our study not only highlights the cellular logic of senescence regulation by autophagy but also provides new therapeutic targets for senolytics and senostatics, which could be essential parts of the "War on Aging" in our generation.

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The next important questions are two-fold. First, what is the molecular switch for how such selective autophagy is turned on during senescence? It is plausible to assume that post-translational modification, such as ubiquitination and phosphorylation, and liquid-liquid phase separation (LLPS) play key roles. For example, we showed that phosphorylation of SQSTM1 at S349 increases during senescence, which has been shown to enhance the affinity toward its ubiquitinated substrates. It would be interesting to examine which signaling pathway is responsible for such regulation. One potential candidate is the MTOR pathway, which mysteriously maintains activity during senescence and has been previously shown to phosphorylate SQSTM1. In the case of OPTN-TNIP1 interaction, we showed that the intrinsically disordered regions of OPTN and TNIP1 are critical. Based on recent findings that several autophagy substrates undergo LLPS and that LLPS is driven by weak multivalent interactions through intrinsically disordered regions, it would be interesting to examine whether LLPS is involved in selective autophagy of TNIP1. Currently, it is unclear how the EIF3 complex is subject to CALCOCO2-dependent autophagy. Because only asubset of EIF3 subunits was discovered in the SAAI, it is possible that only asubset of EIF3 proteins can be targeted by autophagy. Identification of the component-specific post-translational modification or its tendency for LLPS may help us understand the mode of autophagic regulation of the EIF3 complex. Second, what are the roles for autophagic regulation of the remaining substrate proteins identified from our study? In particular, we identified multiple components of spliceosome and metabolic pathways in the SAAI. As senescent cells are reported to display alternative splicing events and rewire their metabolic pathways, it would be interesting to examine to what extent selective autophagy contributes to such remodeling during senescence. This could provide additional actionable therapeutic targets for senotherapy.

In summary, our recent study unravels the intertwined relationship between senescence and autophagy, two critical processes related to aging. In addition, our work lays the foundation for future studies that reveal and target novel vulnerabilities of senescent cells through the tailored modulation of selective autophagy, affecting aging and multiple age-related diseases.

Acknowledgments

This work was supported by the Suh Kyungbae Foundation (SUHF-17020068) and the National Research Foundation of Korea (NRF-2019R1C1C1006386, NRF-2020R1A5A1018081, and 2020R1I1A1A01072779).

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This work was supported by the Suh Kyungbae Foundation (SUHF-17020068) and the National Research Foundation of Korea (NRF-2019R1C1C1006386, NRF-2020R1A5A1018081, and 2020R1I1A1A01072779).

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