AUTOPHAGY
2016, VOL. 12, NO. 5, 898–899
http://dx.doi.org/10.1080/15548627.2015.1121361

Taylor & Francis
Taylor & Francis Group

AUTOPHAGIC PUNCTUM

How autophagy both activates and inhibits cellular senescence

Chanhee Kang and Stephen J. Elledge

Department of Genetics, Harvard Medical School, Division of Genetics, Brigham and Women's Hospital, Howard Hughes Medical Institute, Boston, MA, USA

ABSTRACT

Autophagy and cellular senescence are stress responses essential for homeostasis. While recent studies indicate a genetic relationship between autophagy and senescence, whether autophagy acts positively or negatively on senescence is still subject to debate. Although autophagy was originally recognized as a nonspecific lysosomal degradation pathway (general autophagy), increasing evidence supports a selective form of autophagy that mediates the degradation of specific targets (selective autophagy). Our recent study revealed distinctive roles of selective autophagy and general autophagy in the regulation of senescence, at least in part resolving apparently contradictory reports regarding the relationship between these 2 important homeostatic stress responses.

ARTICLE HISTORY
Received 30 October 2015
Revised 10 November 2015
Accepted 11 November 2015

KEYWORDS
Cellular senescence; DNA damage response (DDR); GATA4; selective autophagy; senescence-associated secretory phenotype (SASP); SQSTM1/p62

Cellular senescence is a terminal arrest of proliferation triggered by various cellular stresses including dysfunctional telomeres, DNA damage, oxidative stress, and oncogenic mutations. Senescence not only prevents the proliferation of damaged cells, thereby preventing tumorigenesis, but also affects the microenvironment through the secretion of proinflammatory cytokines, chemokines, growth factors, and proteases, a feature termed the senescence-associated secretory phenotype (SASP). The SASP increases immune surveillance of damaged cells, thus maintaining tissue homeostasis. With age or persistent damage, however, the SASP from accumulated senescent cells is thought to cause chronic inflammation that may contribute to many human diseases including cancer. In addition to the cell cycle and the SASP, the senescence program also controls other cellular processes and among these is the activation of macroautophagy (hereafter autophagy). Autophagy is an intracellular degradation system that plays a wide variety of physiological and pathophysiological roles, which are sometimes complex. Several studies have indicated that this is also the case for cellular senescence.

The first causal relationship between autophagy and senescence came from oncogene-induced senescence (OIS), showing that autophagy inhibition delays $HRAS^{G12V}$-induced senescence and the SASP. Through a specialized compartment known as the TOR-autophagy spatial coupling compartment (TASCC), autophagy generates a high flux of recycled amino acids and other metabolites, which are subsequently used by MTORC1 for supporting the massive synthesis of the SASP factors and facilitating senescence. However, in contrast to this positive relationship, it has also been reported that autophagy inhibition induces or promotes cellular senescence in normal proliferating cells and paradoxically during $HRAS^{G12V}$-induced senescence, respectively. At least in the former case, increased levels of reactive oxygen species upon autophagy inhibition partially contribute to cellular senescence, indicating the important roles of autophagy in cellular homeostasis. Is there a molecular mechanism that could resolve these apparently conflicting reports about the relationship between autophagy and cellular senescence? One potential explanation is that autophagy may modulate several targets that act in an opposite manner to regulate cellular senescence. Thus, autophagy inhibition could result in different outcomes depending on the timing, duration, or type of its inhibition. Our recent findings suggest this may in fact be the case.

While exploring regulators of cellular senescence, we identified a transcription factor, GATA4, as a key regulator of the SASP and senescence. GATA4 accumulates during cellular senescence, mainly due to its increased protein stability. Interestingly, we found that GATA4 stability is regulated by autophagy. The autophagic receptor protein SQSTM1/p62 mediates the degradation of GATA4 under normal conditions. However, once the cell experiences senescence-inducing stimuli, the interaction between GATA4 and SQSTM1 decreases, and GATA4 escapes from autophagic inhibition and accumulates. This accumulated GATA4 initiates a transcriptional circuit to activate NFKB/NF-κB and the SASP. Senescence induction also increases general autophagy, which contributes to the SASP and cellular senescence through the TASCC. We showed this by temporal regulation of autophagy; transient inhibition of autophagy using an inducible shRNA system causes senescence more efficiently than does continuous inhibition. These data were further supported by the fact that SQSTM1 depletion induces

CONTACT Stephen J. Elledge selledge@genetics.med.harvard.edu Department of Genetics, Harvard Medical School, Division of Genetics, Brigham and Women's Hospital, Room 158D, NRB, 77 Avenue Louis Pasteur, Boston, MA, USA 02115.

cellular senescence more effectively than does depletion of core autophagy regulators, ATG7 or ATG5, under normal conditions. Together, these data suggest that selective autophagy actively suppresses cellular senescence through the degradation of a senescence regulator, GATA4, whereas general autophagy supports senescence transition through the TASCC. Thus, autophagy can act through either an anti- or prosenescence mechanism depending on its type of regulation.

How the interaction between GATA4 and SQSTM1 is regulated is currently unknown. However, we found that GATA4 activation depends on the DNA damage response (DDR) kinases, ATM and ATR, during cellular senescence, suggesting that ATM and ATR regulate the selective autophagy of GATA4. Based on recent findings that phosphorylation of SQSTM1 affects the affinity between SQSTM1 and its substrates, it would be interesting to examine whether ATM and ATR directly phosphorylate either SQSTM1 or GATA4 to decrease their interaction. Another possibility is that ATM and ATR modulate a signal transducer that can regulate the interaction between GATA4 and SQSTM1. SQSTM1 primarily recognizes ubiquitinated substrates, thus either E3 ubiquitin ligases or deubiquitinating enzymes could be involved as a signal transducer. Alternatively, it is possible that other substrates for SQSTM1 increase in an ATM- and ATR-dependent manner during senescence, which outcompete GATA4 for binding with SQSTM1. This is a question for future experiments, as it will provide further information on how autophagy and cellular senescence are intertwined and how the DDR regulates selective autophagy.

Another key question is how general autophagy increases during cellular senescence. One potential mechanism for this regulation would be a key senescence regulatory pathway, the TP53/p53 pathway. Activation of TP53 initiates cell cycle arrest during cellular senescence. This activation, however, is sustained at intermediate levels even after cell cycle arrest is reinforced by the subsequent activation of the CDKN2A/p16 pathway, suggesting that the TP53 pathway may have additional roles beyond cell cycle arrest during senescence. Previous studies have shown that nuclear TP53 can activate transcription of several autophagy-related genes including *ULK1, ATG5*, and *ATG7*. Therefore, sustained TP53 activation might contribute to the activation of general autophagy during cellular senescence.

In summary, the regulation of GATA4 provides an explanation for the conundrum of how autophagy acts in one instance to promote senescence but in another to prevent it. This finding reconciles the conflicting reports and clarifies the complex relationship between autophagy and cellular senescence by showing that basal, selective autophagy acts as an antisenescence mechanism, whereas general autophagy acts as a prosenescence mechanism.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

Funding

This work was supported by NIH grant GM44664 to S.J.E. C.K. is a HHMI fellow of The Jane Coffin Childs Memorial Fund for Medical Research.