GATA get a hold on senescence

Liam D. Cassidy[1] and Masashi Narita[1]

[1] University of Cambridge, Cancer Research UK Cambridge Institute, Robinson Way, Cambridge, CB2 0RE, UK

* Correspondence: masashi.narita@cruk.cam.ac.uk

One Sentence Summary: GATA4, a substrate of p62-mediated selective autophagy, is a key mediator of senescence and its associated secretory phenotype.

Cellular senescence is a state of ‘permanent’ cell cycle arrest associated with a hyper-activated pro-inflammatory secretory phenotype, conferring diverse functionality in a wide range of pathophysiological processes, such as wound healing, aging, and cancer (*1*). Understanding what processes mediate this senescence associate secretory phenotype (SASP) is becoming a key area of research. One such candidate effector mechanism is macroautophagy (herein referred to as autophagy), a major intracellular degradation system, but whether it promotes or inhibits senescence is disputed (*2*). On page xxx of this issue, Kang et al. begin to unravel this paradox and provide new insights into the mechanisms by which the SASP is regulated (*3*).

While initially described as a non-specific lysosomal-degradation system, with critical roles in energy homeostasis and the quality control of macromolecules and intracellular organelles, autophagy is becoming increasingly associated with adapter-mediated degradation of specific targets, and as such an integral mediator of cellular phenotypes (*4*). Kang et al. identified the transcription factor GATA4 as a substrate of p62-mediated selective autophagy, demonstrating that stabilization of GATA4 is both sufficient and partially necessary for induction of senescence and the SASP. Because global autophagy is activated during senescence in various contexts (*2*), the data raises an interesting question: what is a net contribution of autophagy to senescence?

Kang et al. addressed this question using an inducible RNAi against ATG5 or ATG7, essential genes for autophagy. They show that inhibition of autophagy stabilizes GATA4 thereby triggering senescence, but this effect is greatest upon a transient inhibition of autophagy. Long-term autophagy inhibition actually led to a failure to induce senescence. These data lead to a model wherein selective autophagy and

global autophagy have opposing effects on the SASP (see figure). Consistently, depletion of p62, which is required for GATA4 degradation but not for general autophagy, induces senescence more efficiently than ATG5/7 depletion. Therefore, differences in the relative contribution between selective and global autophagy may explain in part, the apparent discrepancies regarding the role of autophagy in senescence.

Compared to the downstream functionality of the SASP, its upstream regulation is a relatively unexplored area, and only a few such effectors have been described. Two of these, the DNA damage response (DDR) regulators ATM/ATR and p38MAPK, both converge on the transcription factor NFκB, which drives transcription of major SASP components cooperatively with C/EBPβ (*5*). Kang et al. show that ATM/ATR signaling, but not p53, is required for GATA4 liberation from p62-directed autophagy during senescence. Once stabilized GATA4 activates NFκB by up-regulating at least two factors, TRAF3IP2 and IL-1α: the former is likely to be a direct transcriptional target of GATA4, and the latter is a unique SASP component which can act upstream of NFkB. TRAF3IP2 is best described as an NFkB activating protein in the IL-17 signaling cascade, but has also been shown to activate p38MAPK and C/EBPβ (*6*). Thus GATA4 might activate the SASP through multiple mechanisms during senescence (see figure).

The findings also extend the significance of p62 in NFκB regulation. Accumulated p62 can act as a signaling hub, driving NFκB activation by promoting TRAF6 oligomerization (*7*). Kang et al. now provide an additional mechanism; degradation of p62 also leads to NFκB activation. Do these two mechanisms cooperate? Considering

that GATA4 appears to regulate senescence both in a SASP-dependent and -independent manner *(3)*, it would be helpful to know whether the senescence phenotype induced by p62-depletion is accompanied by the NFκB-SASP programme.

Kang et al. also provide evidence of *in vivo* relevance. They observed that cells expressing the senescence marker p16 also had increased expression of GATA4 in aged mouse livers and human brains. During aging the expression of some genes involved in autophagy, including p62, has been shown to decline in several organs, including mouse livers (*8, 9*). This supports a model where the reduction of basal autophagy, particularly selective autophagy, may contribute to the age-related accumulation of senescent cells through de-suppressing GATA4 activity. Indeed, p62 -/- mice exhibit an accelerated aging phenotype (*8*), whether or not a GATA4-mediated senescence program is active in these mice remains an open question.

Through this work, Kang et al. provide a molecular basis for the relationship between autophagy and the SASP (*10, 11*), and reinforce the role of p62 as a major regulator of NFκB. The nutrient sensor mTOR is a known regulator of autophagy and cap-dependent translation. While it has been recently shown that the translation arm of mTOR activity is required for the SASP (*12*), the significance of the mTOR-autophagy arm within the context of this work remains to be elucidated. This raises a potential link between nutrient sensing and the SASP wherein nutrient states may well affect the sensitivity of cells to senescence inducing triggers, in part mediated through GATA4 levels. Presently a complex picture has emerged, in which the major upstream regulators of senescence and the SASP have been described in isolation. Each is associated with a multitude of diverse effects, downstream signaling and

complex feedback loops, perhaps providing a dynamic fine-tuning mechanism for the SASP regulatory network.

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Figure Legend

SASP regulation during DNA damage induced senescence. Autophagy both opposes and promotes senescence through selective and global autophagy, respectively. Persistent DNA damage signaling mediates selective autophagy and promotes GATA4 dissociation from p62. This is necessary and sufficient to induce senescence and drive an NFκB mediated SASP. Global autophagy is required for senescence and the SASP but how it contributes to each of these remains unclear.

Blue arrows represent signaling cascades described during senescence, while green arrows represent signals that have been described in other contexts. It should be noted that some factors regulate the SASP in multiple, often opposing manners.