# The function of enzyme ADAR1 links it to age-related diseases via a role independent of RNA-editing during aging

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Aging and age-related disorders pose a complex challenge to the biomedical research community. To better understand how senescence is regulated is of high significance to promote healthy aging and treat age-associated disorders. In a research paper published today in *Nature Cell*

*Biology*, Rugang Zhang, Ph.D., deputy director of the Ellen and Ronald Caplan Cancer Center, Christopher M. Davis Endowed Professor, and program leader of the Immunology, Microenvironment & Metastasis Program, at The Wistar Institute, and his team revealed a novel ADAR1-SIRT1-p16INK4a axis in regulating cellular senescence and its potential implications in tissue aging.

"Understanding the basic mechanism underlying tissue aging is challenging and cellular senescence offers an angle into the complex biology that drives tissue aging. These mechanistic insights gained by studying senescence regulation during tissue aging can in turn be used to promote healthy aging and combat age-associated disorders," states Zhang.

Central to this quest is a protein called p16INK4a because its expression both increases during tissue aging and it drives senescence. Prior studies established that depletion of p16INK4a expressing cells is sufficient to delay age-associated disorders. Thus, approaches that prevent age-associated increase in p16INK4a expression may have important implications in designing intervention strategies to promote healthy aging.

The research team's findings center around a protein called ADAR1. ADAR1 is a specialized enzyme involved in RNA editing and is now revealed in senescence. Postdoctoral researcher in the Zhang lab and first author on the paper Xue Hao, Ph.D., explains that this research was largely inspired by prior independent research carried out in model organisms such as fruit flies and worms showing that depletion of the equivalent of human ADAR1 in these organisms reduces lifespan and causes age-dependent changes such as neurodegeneration.

This story also benefits from a highly collaborative Wistar Institute culture. In fact, the previous work of Kazuko Nishikura, Ph.D.,

professor in the Gene Expression & Regulation Program at Wistar's Ellen and Ronald Caplan Cancer Center—and a pioneer in ADAR1 biology—showed that stressed cells utilize ADAR1 as protection from apoptosis, programmed cell death. "As senescent cells are stressed cells and are resistant to apoptosis, the first question we set out to ask was whether ADAR1 is related to cellular senescence and secondly, how does it regulate senescence and what is its' potential implication in tissue aging," Hao explains.

The team first examined the expression of ADAR1 in vitro in human fibroblasts and in vivo in multiple tissues from young and aged mice. Then, they experimentally altered ADAR1 expression in multiple cell types in petri-dish and mouse tissues to establish ADAR1 as a critical regulator of p16INK4a expression. Intriguingly, the team discovered that ADAR1 loss promotes p16INK4a expression through SIRT1, another protein known to regulate both senescence and tissue aging. Interestingly, this function of ADAR1 does not depend on its biological role in RNA editing.

They also found that downregulation of ADAR1 by a process called autophagy (the degradation and recycling of damaged or unneeded cell components) during senescence decreased the stability of SIRT1 mRNA, which in turn upregulated the translation of p16INK4a to induce senescence. Hao elaborates, "Our study revealed a novel ADAR1-SIRT1- p16 INK4a axis that plays an important role in cellular senescence at translational level, and this newly defined function of ADAR1 is independent of its RNA editing function."

Zhang says that their "study starts to reveal the missing link between ADAR1 and tissue aging through p16INK4a expression during senescence. In addition, these findings provided a scientific rational to explore whether this newly discovered mechanism can be leveraged for therapeutic development regarding age-associated disorders."

"One of the ways to potentially restore ADAR1 expression as a means to suppress p16INK4a and senescence observed during tissue aging is by inhibiting autophagy," Hao details. She adds about next research steps, "Our study raises some interesting questions. For example, what is the relative contribution of this mechanism to p16INK4a expression during aging of different tissues? In addition, it would be interesting to determine whether intervention of this pathway can alleviate the age-associated disorders that are linked to p16INK4a expression in previous published animal models."

**More information:** Pingyu Liu, ADAR1 downregulation by autophagy drives senescence independently of RNA editing by enhancing p16INK4a levels, *Nature Cell Biology* (2022). DOI: 10.1038/s41556-022-00959-z.
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