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COMMENTARY

PERSPECTIVES

MOLECULAR BIOLOGY

Longevity steps on the cGAS

A DNA repair function in a cytosolic sensor demonstrates a potential role in naked mole-rat longevity

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The first line of defense that cells have against foreign pathogens is an innate immune response. Cyclic guanosine monophosphate–adenosine monophosphate synthase (cGAS) plays a crucial role in this response by detecting pathogen-derived DNA or RNA in the cytosol of the host cell and initiating a signaling cascade that causes the transcription of genes encoding type I interferons (*1*). Increased inflammation is a hallmark of aging (*2*), and dysregulation of cGAS signaling during aging can drive debilitating inflammatory processes (*3*, *4*). Therefore, cGAS was proposed as a therapeutic target. However, although present in the cytosol, cGAS is predominantly bound to chromatin, and its role in the nucleus is unclear (*5*). On page 150 of this issue, Chen *et al.* (*6*) report that cGAS from the naked mole-rat has a distinct set of four mutations on its N terminus that promote DNA repair—a mechanism crucial to the organism's extreme longevity.

The naked mole-rat has a maximum life span of nearly 40 years, making it the longest-lived rodent, and is resistant to a wide range of age-related diseases, including cancer, neurodegeneration, and arthritis. Chen *et al.* assessed differences in cGAS activity between naked mole-rat, mouse, and human cells in culture. They showed that upon DNA damage, amino acid substitutions in naked mole-rat cGAS allow it to undergo reduced ubiquitination and degradation relative to mouse and human isoforms. This increased abundance of cGAS enhanced the interaction between the DNA repair factors FANCI and RAD50, which promoted homologous recombination. Homologous recombination is essential for the repair of double-strand breaks in DNA. The authors also found that depletion of naked mole-rat cGAS in cultured cells results in increased DNA damage. These results suggest that the observed amino acid differences in naked mole-rat cGAS enhance the chromatin binding capabilities of the protein, ultimately resulting in higher rates of DNA repair. Notably, this strengthened tethering of cGAS within the nucleus would be expected to result in dampened inflammation, which would be interesting to explore in future studies. Additionally, Chen *et al.* demonstrated that fruit flies (*Drosophila melanogaster*) that express a form of human cGAS bearing the four naked

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The naked mole rat (*Heterocephalus glaber*) is the longest-lived rodent, with a maximum life span of nearly 40 years.

mole-rat mutations lived longer compared with flies that express human cGAS without the mutations. This result suggests that cGAS plays a role in the longevity of the naked mole-rat.

It is unclear what species other than the naked mole-rat gain from using cGAS in the nucleus. Previous studies in human and mouse cells have suggested that cGAS inhibits DNA repair and replication (*7*, *8*). This is consistent with cGAS playing a role in chromatin maintenance, whereas the removal of cGAS may unleash uncontrolled recombination or replication. Preliminary data from genetically modified mice lacking cGAS show derepression of transposable elements—“jumping genes” that can move from one location of the genome to another—that ultimately leads to increased inflammatory signaling and a shortened life span (*9*). Similar to the findings from Chen *et al.*, these findings indicate that cGAS is important in regulating chromatin organization and maintenance by protecting genomic integrity.

If naked mole-rat cGAS has been modified in a way that confers resistance to DNA damage, do other long-lived organisms alter their cGAS in a similar way? Several bat species also have enhanced longevity relative to mammals their size. Furthermore, in contrast to most mammals, these bats have an immune system that tolerates viruses (*10*)—the result of lineage-specific evolutionary adaptations on hundreds of proteins. These adaptations include a single-residue mutation in a phosphorylation site on stimulator of interferon genes (*STING*), which encodes a transmembrane protein that is downstream of cGAS and is important for initiating interferon production, as well as the complete loss of the *PYHIN* family of genes, which encode cytosolic sensors that recognize the same double-stranded nucleic acid substrates as cGAS (*11*, *12*).

But how is *cGAS* modified in bats? The *cGAS* gene is present in bats, and the evolutionary retention of the protein over the *PYHIN* sensors would suggest that *cGAS* may serve additional noncanonical roles outside of immune sensing or that it may serve as a more important immune regulator than the *PYHIN* sensors. Indeed, expanded phylogenetic analysis corroborates the importance of *cGAS*—there are homologs in both invertebrates and bacteria (*13*). However, analysis of amino acid differences between bat *cGAS* and that of other mammals uncovered a high rate of changes, including a region of extremely high divergence in the N terminus of cGAS (essential for innate immune activation) in Old World fruit bats (pteropodids), some of which exhibit enhanced longevity (*14*). Notably, these bats also have amino acid mutations within two of the three loops in cGAS that were previously identified as important for binding to nucleosomes, which are the basic building block of chromatin (*15*). The mutations have the potential to increase the interaction of cGAS and chromatin. Notably, one of the four amino acid mutations that was shown by Chen *et al.* to be necessary for naked mole-rat cGAS to enhance DNA repair (and is absent from both mouse and human cGAS), $\mathrm{Glu}^{511}\rightarrow\mathrm{Lys}$, is also shared with pteropodids. Thus, evolutionary forces resulting in chromatin binding of cGAS, potentially through differing sets of mutations, could be a characteristic of long-lived species as a mechanism to facilitate DNA repair or avoid autoimmunity—a major component of the increased inflammation associated with aging.

The findings from Chen *et al.* describe an unexpected role for naked mole-rat cGAS in the nucleus that influences longevity. Further research will be required to establish the roles that cGAS may play in the nucleus in other organisms, both short- and long-lived, but the answer may be substantially more complex than originally predicted. □

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ACKNOWLEDGMENTS

The authors acknowledge support by grants from the US National Institute on Aging, the Impetus Grant, and the Hevolution Foundation.

10.1126/science.aeb6125

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