Blocking the longevity gene S6K1 extends lifespan in mice by reducing inflammation

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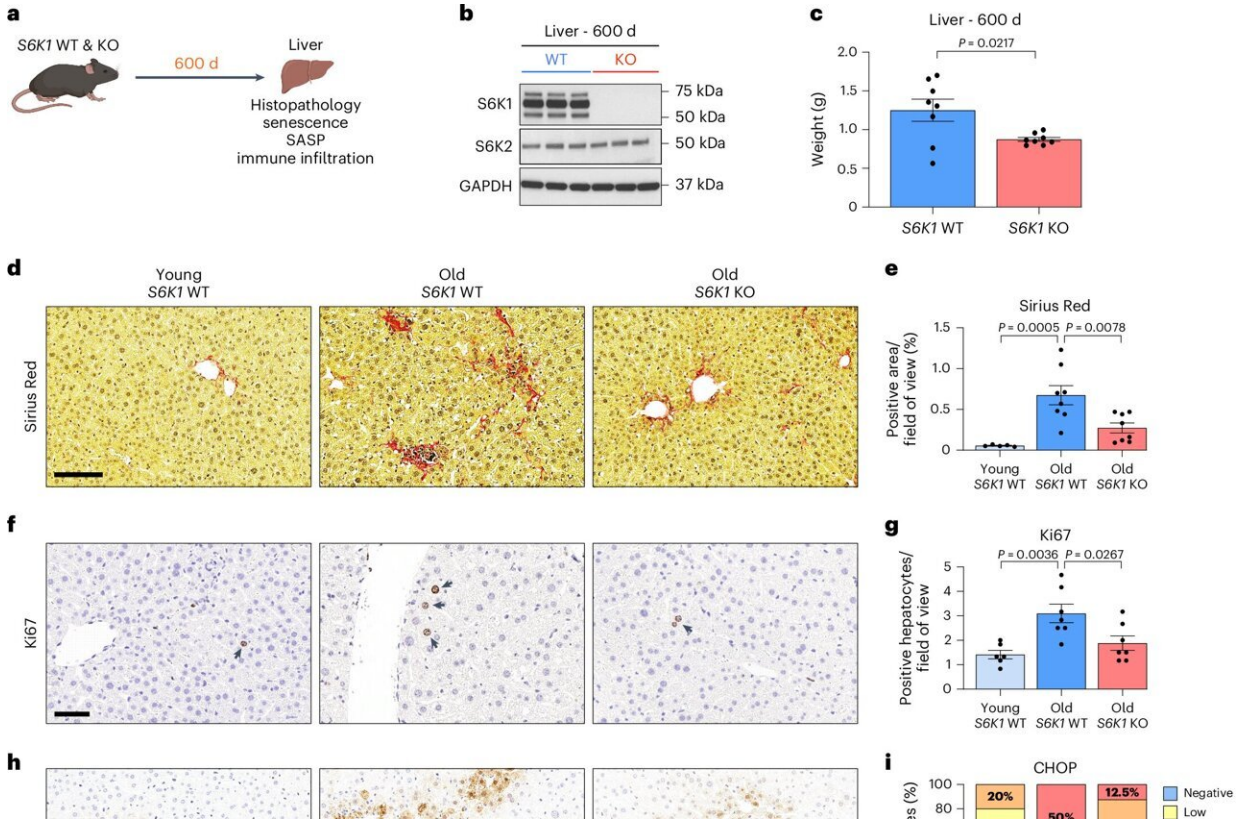

S6K1 deletion attenuates age-related liver pathology. **a**, Experimental scheme. *S6K1* WT and KO mice were aged for 600 d to assess senescence. **b**, Immunoblot images of S6K1, S6K2 and GAPDH protein expression in whole liver lysates of 600-day-old *S6K1* WT (left; $n = 3$) and KO (right; $n = 3$) mice. GAPDH acted as a loading control for S6K1. S6K2 was run on a separate blot (and, therefore, GAPDH is a sample preparation control for that blot). **c**, Liver weight (grams) at 600 d from *S6K1* WT ($n = 8$) and KO ($n = 8$) mice. **d**,**e**, Sirius Red staining (**d**) and quantification (**e**) in livers in young *S6K1* WT (90 d; $n = 5$),

old *S6K1* WT (600 d; *n* = 8) and old *S6K1* KO (600 d; *n* = 8) mice. **f**,**g**, Ki67 staining (**f**) and quantification (**g**) in livers in young *S6K1* WT (90 d; *n* = 6), old *S6K1* WT (600 d; *n* = 7) and old *S6K1* KO (600 d; *n* = 7) mice. **h**,**i**, CHOP staining (**h**) and quantification (**i**) in livers in young *S6K1* WT (90 d; *n* = 5), old *S6K1* WT (600 d; *n* = 8) and old *S6K1* KO (600 d; *n* = 8) mice. **j**,**k**, BiP staining (**j**) and quantification (**k**) in livers in young *S6K1* WT (90 d; *n* = 5), old *S6K1* WT (600 d; *n* = 8) and old *S6K1* KO (600 d; *n* = 8) mice. Data are expressed as mean ± s.e.m. Statistical significance was calculated using either a two-tailed Student's *t*-test (**c**) or one-way ANOVA with Tukey's multiple comparison test (**e**,**g**). *n* denotes individual mice. Scale bar, 100 μm (**d**,**h**,**j**) or 50 μm (**f**). Credit: *Nature Aging* (2024). DOI: 10.1038/s43587-024-00695-z

S6K1 is a protein involved in the regulation of aging and age-related diseases. Blocking this protein in mice makes them live longer and mimics the health benefits of reducing calorie intake, such as reduced body fat, stronger bones and resistance to diabetes, though the underlying mechanisms were not previously understood.

S6K1 is a key target of the mTOR signaling pathway, which regulates growth and metabolism in response to nutrients and stress. The pathway also influences cellular senescence. As we age, senescent cells accumulate and release high levels of inflammatory proteins—a phenomenon known as the senescence-associated secretory phenotype (SASP).

Elucidating the relationship between S6K1, senescence and the SASP will advance our understanding of aging and holds potential for treating age-related diseases.

In research published in *Nature Aging*, scientists at the LMS and the University of Tübingen have shown that deleting the S6K1 gene in aged mouse livers reduces inflammation by suppressing the production of

inflammatory proteins released as part of the SASP, rather than by affecting senescence, as originally hypothesized by the research teams.

Excitingly, this work now provides a biological mechanism for the beneficial effects of removing S6K1 upon aging and health span in mice first demonstrated by Professor Dominic Withers, Head of the Metabolic Signaling Group and published in *Science* in 2009.

Uncovering converging pathways

While initially surprising, the findings corroborate those of other studies published this year, building an emerging picture of the interrelated role that inflammation, metabolism and senescence play in aging and disease—all of which are strategic areas of research focus for the LMS.

This includes complementary work in fruit flies showing that the S6K protein controls inflammation, a study showing that simulating an excess of nutrients in mice increased inflammation and shortened lifespan, as well as work from Professor Stuart Cook, Head of the Cardiovascular Disease Mechanisms Group at the LMS, showing that inhibiting an inflammatory protein, IL-11, led to health benefits and increased lifespan.

Now that the principles of S6K1 deletion have been established in liver tissue, the team plans to carry out follow-up studies to determine whether the same thing is happening in other tissues in the body.

Potential new strategies for treating age-related diseases

While inflammation plays an important role in helping your body respond to injury and infection, it is a significant driver of aging and

many diseases. Enriching our knowledge of how inflammation contributes to aging and disease opens up avenues for developing new strategies to treat aging and age-related diseases.

Professor Withers, senior author, commented, "This work was a tour de force exploring the physiological, cellular and molecular mechanisms that underlie the long-lived phenotype in mice lacking S6K1. It is becoming increasingly clear that inflammatory processes are a key component of age-related diseases and there is great potential for interventions that could modulate this process."

Professor Jesús Gil, Head of the Senescence Group and senior author, commented, "Enhancing our understanding of the interaction between metabolism, senescence and inflammation is a key first step to designing rational synergistic therapies that could be used to treat diseases of aging."

This work was led by Dr. Suchira Gallage, a former Ph.D. student at the LMS, under the supervision of Professor Withers and Professor Gil, and in collaboration with Professor Mathias Heikenwälder at the University of Tübingen, where Dr. Gallage is now a group leader.

More information: Suchira Gallage et al, Ribosomal S6 kinase 1 regulates inflammaging via the senescence secretome, *Nature Aging* (2024). DOI: 10.1038/s43587-024-00695-z

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