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COMMENTARY

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Caloric restriction safeguards genome stability in a tissue- and region-specific manner

Siyao Wang[1,2,*] **and Jiongming Lu**[3,*]

[1]Institute of Molecular Biology, Mainz 55128, Germany

[2]Institute for Genome Stability in Ageing and Disease, Cologne 50931, Germany

[3]Shanghai Institute of Nutrition and Health, Chinese Academy of Sciences, Shanghai 200031, China

*Correspondence: S.Wang@imb-mainz.de (S.W.); jmlu@sinh.ac.cn (J.L.)

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Caloric restriction (CR), a reduction in food intake without malnutrition, is one of the most robust interventions to extend healthspan and lifespan in multiple species. It has been linked with broad improvements in proteostasis, mitochondrial function, metabolic health, cellular senescence, stem-cell maintenance, and inflammatory regulation in aging. However, whether CR systematically preserves the more fundamental genome stability is less clear. Studies have shown that CR can lower mutation frequency in certain reporter systems, but these methods were constrained to a specific locus, cell type, or marker system. Thus, it remains unknown whether CR alters somatic mutation accumulation on the whole genome level, whether such effect is tissues-specific, and whether this aligns with CR lifespan effects. Recently, Grońska-Pęski et al. have applied high-fidelity duplex DNA sequencing to profile somatic mutations in liver, kidney, hepatocytes, and cerebellar neurons from male mice subjected to ad libitum (AL) and two different CR regimens, reporting that CR diminishes somatic mutation burden in a tissue- and genomic-region-dependent way, while the two CR regimens show no obvious differences.[1] Here, we discuss its technical strengths, tissue-specific results, limitations, and future directions for nutrition-based genome stability geroscience and precision dietary intervention (Figure 1).

A significant novelty of this study is the use of NanoSeq to address whether CR could reduce genome-wide mutation burden in mice. This approach is much more sensitive to low-frequency mutations and avoids the requirement of clonal expansion or whole-genome amplification, making it particularly useful for analyzing bulky tissue and post-mitotic cell types. And it has been successfully applied to human and mouse tissues, including in differentiated blood/colon cells, neurons and smooth muscle, arterial tissue and cerebral cortex samples carrying POLE/POLD1 proofreading mutations.[2] Previous studies have used reporter-based assays, such as the endogenous Hprt locus and transgenic lacZ reporters, to provide important early evidence that CR may affect mutagenesis. Nevertheless, these methods only cover a small fraction of the genome and fail to detect the diversity of genomic regions, sequence contexts, or mutational types. By contrast, this study applies NanoSeq and separates different classes of somatic mutations, showing that CR lowers both substitution and indel burdens. This is particularly important since substitutions and indels can be generated through different mechanisms, including replication-associated errors, DNA damage, repair pathway activity, and local sequence features. The quantification of these mutations genome-widely therefore provides mechanistic insights for how CR may reshape the balance between DNA damage and repair.

Moreover, the authors focused on the substitution and indel signatures and identified a major single base substitute (SBS) signature, SBS5-like signature. Consistent with a previous aging study in normal mammalian tissues, in which SBS1, SBS5-like, and SBS18-like signatures accumulate with age,[3] this study further reveals that CR can significantly reduce the SBS5 signatures across the tested samples, suggesting that the aging-associated signature can be mitigated via dietary interventions. SBS5 is a mutation signature without a known biological cause. It has been reported that SBS5-like pattern is linked to bladder cancer samples with ERCC2 mutations, which correlate with nucleotide excision repair (NER) deficiency. NER is responsible for removing endogenous and exogenous bulky and helix-distorting lesions, which may occur in both genic and intergenic regions. A further particular interesting finding is that the CR-associated mutation reduction is strongest in intergenic and low-transcription regions. The intergenic regions are normally more compact with limited transcription and repair machineries' accessibility. The reduction of mutation burden may indicate an increased capacity of DNA repair in the intergenic region. Alternatively, it indicates a global reduction in DNA lesion formation, without an improvement in the transcription-couple repair (TCR) capacity, consistent with a previous report that CR can tripled the median and maximal remaining lifespans of TCR-deficient progeroid mice.

Another significant improvement is that it analyzed mutational spectra in different tissues and cell-types. Profiling bulk liver, bulk kidney, purified hepatocytes, and cerebellar neurons, it illustrates that the impact of CR differs by organ and cell type, with greater reductions in livers and hepatocytes, and minor benefits in cerebellar neurons. This pattern suggests that CR-mediated genome protection may be determined by tissue-specific characteristics, and is in line with tissue-specific benefits of CR. Therefore, the study demonstrates not only that CR can reduce somatic mutation burden but also that this protective effect is genome-region- and tissue-dependent.

Although this study presents several advances, it also shows limitations. First, NanoSeq has its own constraints. As a short-read duplex sequencing approach, NanoSeq is very powerful to detect rare single-nucleotide mutations with exceptional accuracy, but it is not designed to identify structural variants and large chromosomal abnormalities. This is particularly relevant because previous work has shown that large genomic alterations and mosaic structure variants are associated with aging. Thus, NanoSeq only captures one dimension of genome instability and cannot fully represent the broader landscape of age-related genome instability.

Second, the experimental design of this study itself has inherent constraints. The samples were obtained from a previous study aimed to investigate the longevity effects of CR with or without fasting,[4] rather than one to examine the accumulation somatic mutation during aging. Therefore, several key designs were not optimized for mutational analysis. A major limitation is the lack of a true baseline measurement at the start of dietary intervention. Two newborn mouse samples were analyzed, but the CR began only after 14 weeks (6-week-old mice subjected to 2 weeks adaptation and followed by additional 6 weeks AL feeding) - this critical baseline was not profiled directly. If mutation had already begun to accumulate at that point, the beneficial effect of CR may have been underestimated. Another limitation is that the mutation analysis was conducted at only one time point, at age of 19 months. Sampling at additional earlier and later ages may have indicated whether CR modulates the rate of accumulation over time and whether it produces pronounced effects in older animals. This is also relevant for understanding the temporal effects of CR on reducing the load of mutations.

Third, the number of tissues and cell types examined in this study is relatively small. The accumulation of somatic mutation is highly tissue- and cell-type-specific, and depends on differences in proliferation capacity, metabolic status, DNA repair ability, and environmental exposure. While liver (hepatocytes), kidney and cerebellar neurons provide some tissue contexts, they do not recapitulate the organism-wide effect of CR. This is particularly relevant in light of the finding that CR with fasting led a stronger lifespan extension than CR without fasting, yet no significant difference between the two protocols in mutation reduction was observed. One possible reason for this confusion is that the key tissues responsible for the additional longevity benefit of

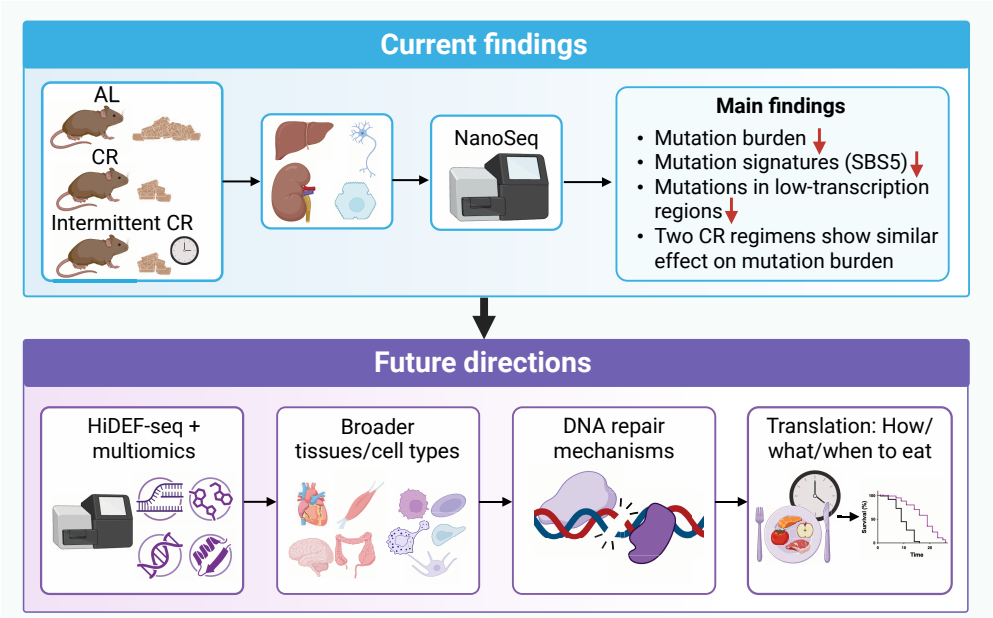


Figure 1. Caloric restriction reduces somatic mutation burden and provides new directions for nutritional geroscience NanoSeq was used to analyze somatic mutations in liver, kidney, hepatocytes, and cerebellar neurons from aged male mice subjected to either AL or CR. CR decreased genome-wide somatic mutation burden, including both substitutions and indels, and suppressed an SBS5 mutational signature. These effects varied with tissue and genomic region. Future work should extend mutation profiling to cancer-prone tissues to link genome stability with tumor prevention and lifespan extension, investigate the molecular mechanisms, and compare CR with other geroprotective dietary interventions to guide precision nutrition.

fasting were not included in the present analysis. Thus, more comprehensive tissue coverage will be critical to determine whether CR alters somatic mutagenesis in a highly tissue-specific manner and, if so, whether such effects are linked to longevity.

Future work should explain how CR maintains genome stability during aging. As already noted by the author, to elucidate the mechanism underlying this observation, a new method that distinguish DNA lesion formation from the enhanced repair can be applied, for example, hairpin duplex enhanced fidelity sequencing (HiDEF-seq) may help to resolve this problem. In addition, CR has been reported to preserve the capacity of base excision repair (BER). However, in this work, no BER-associated mutation signature such as SBS18, SBS30, or SBS36 was detected. This may be due to limitations in the sequencing technique or the types of tissues and cells examined. Furthermore, combining mutational profiling with other omics analysis, such as transcriptomics and proteomics, could enable a more mechanistic assessment. In line with this, it is also crucial to examine whether the observed somatic mutations are causal drivers of aging or merely downstream consequences.

A second direction is to increase the coverage of tissue, especially in cancer-prone tissues. In natural aging, sex- and strain-dependent tumor development is highly tissue-specific, and hematopoietic and lymphoid tissues, liver, lung, mammary gland, pituitary gland, and gastrointestinal tract are those most involved. CR has been known for a long time to suppress many age-related neoplasms, including lymphomas, mammary tumors, liver tumors, and pituitary tumors, through its protective effects vary across tissues.[5] Thus, future work should focus on the cancer-prone tissues in which both spontaneous tumor incidence and CR-mediated tumor suppression have been well established, to provide more direct links between CR, somatic mutation burden, cancer prevention, and ultimately lifespan of animals.

Finally, the comparison of CR with other geroprotective dietary interventions is an important future direction. It remains unknown whether fasting without reduced total energy intake or protein/amino-acid restriction without CR can also decrease somatic mutations, and if so, whether they show different tissue-specific effects. Addressing these questions would clarify whether mutation suppression is driven by reduced energy intake per se, fasting physiology, or specific macronutrient signals. Furthermore, it will be important to determine whether CR mimetics, such as rapamycin and metformin, exert similar effects on the maintenance of genome stability. Such work would also enhance the translational and commercial relevance of dietary interventions, facilitating the development of precision nutrition strategies for preventive age-related diseases.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this work, the authors used ChatGPT5.5 (OpenAI) in order to check grammar and polish language. After using this tool, the authors reviewed and edited the content as needed and took full responsibility for the content of the publication.

REFERENCES

1. Gronska-Peski M., Acosta-Rodriguez V., Srinivasa A., et al. (2026). Caloric restriction modulates genome-wide somatic mutation in mice. *Cell* **189**:6922-6932.e11. DOI:10.1016/j.cell.2026.08.013
2. Abascal F., Harvey L.M.R., Mitchell E., et al. (2021). Somatic mutation landscapes at single-molecule resolution. *Nature* **593**:405–410. DOI:10.1038/s41586-021-03477-4
3. Cagan A., Baez-Ortega A., Brzozowska N., et al. (2022). Somatic mutation rates scale with lifespan across mammals. *Nature* **604**:517–524. DOI:10.1038/s41586-022-04618-z
4. Acosta-Rodriguez V., Rijo-Ferreira F., Izumo M., et al. (2022). Circadian alignment of early onset caloric restriction promotes longevity in male C57BL/6J mice. *Science* **376**:1192–1202. DOI:10.1126/science.abk0297
5. Hursting S.D., Smith S.M., Lashinger L.M., et al. (2010). Calories and carcinogenesis: Lessons learned from 30 years of calorie restriction research. *Carcinogenesis* **31**:83–89. DOI:10.1093/carcin/bgp280

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AUTHOR CONTRIBUTIONS

S.W. and J.L. conceptualized the core ideas, drafted the initial manuscript, and performed the editing and revision work. All authors contributed to and approved the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.