Investigating liver-derived secreted factors in calorically-restricted mice

Paxtyn Lawson, David E. Lee, Ph.D, and James P. White Ph.D
Duke University, Duke Molecular Physiology Institute

DUKE MOLECULAR PHYSIOLOGY INSTITUTE

Introduction

- Caloric restriction (CR) has long been considered an important tool to improve health outcomes and extend the lifespan. It has been shown to increase the maximal lifespan in species such as rodents up to 50%.[1]

Humoral factors can help explain this increase in longevity and healthspan in CR mice.

- Secreted factors play large roles in health. Although the health-promoting biology of CR has been known for decades, the mechanisms are still unclear. Blood-borne factors may hold the answer to the benefits of CR.

Methods

- A cohort of 26 16-week-old male mice were acclimated to a CR diet of 60% of their normal caloric intake. Their NIH-31M food was enriched to guarantee adequate access to nutrients.
- Mice were fed pre-weighed amounts of food each day through different time points. Data was collected at 2 weeks, 4 weeks, 8 weeks, and 12 weeks for this time course.
- Data collection included measuring body weights of mice pre- and post-CR, collecting serum samples, collecting full tissue samples to sort muscle stem cells, and isolating hepatocytes, which we will be focusing on here.

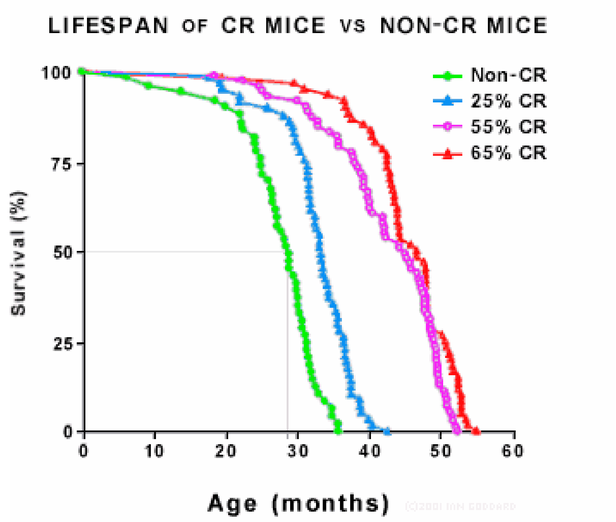


Figure 1. Lifespan of CR vs. non-CR mice adjusted to model the human lifespan.[2]

Results

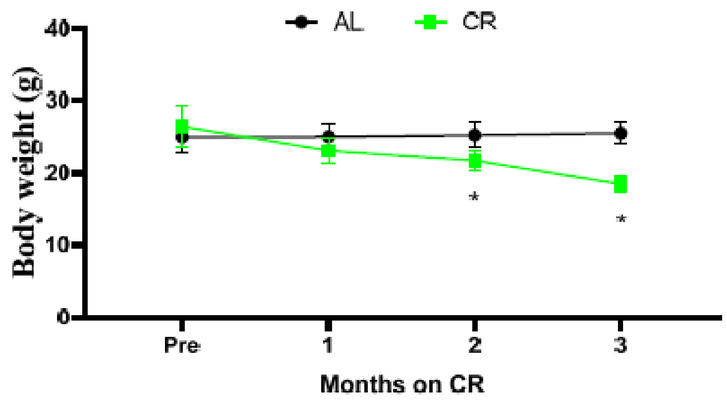
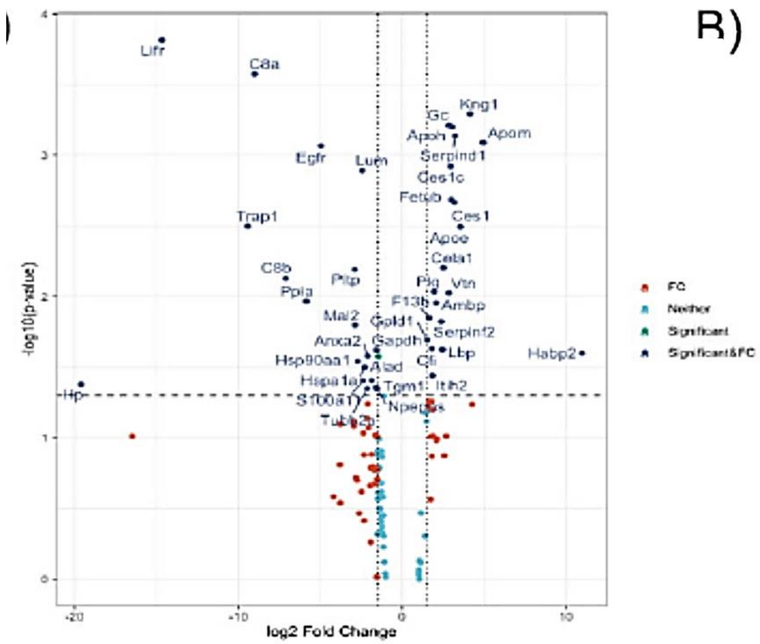


Figure 2. Body weights of ad-lib mice and CR mice across multiple timepoints.



Protein	Fold change
Plasminogen	2.3
Kininogen-1	2.1
Serpina1d	2.1
Serpina1a	2.1
Prothrombin	2.0
Serpina10	1.8
Albumin	1.3

Figure 3. Fold changes in proteins secreted by CR mice.

Conclusions

- Caloric restriction **increased the lifespan** of mice when compared to mice on an ad-libitum diet.

Calorically-restricted mice showed fold changes in multiple **important liver-derived secreted factors**, including several proteins involved in the fibrinolytic system.

- Increased levels of proteins like one or many of these proteins **may be a mechanism to** why caloric restriction is able to maximize health outcomes and increase longevity.

Future Directions

- Further research will be used to confirm and validate these proteins for their role in CR and aging biology across tissues.

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1. Pifferi, F., Terrien, J., Marchal, J. *et al.* Caloric restriction increases lifespan but affects brain integrity in grey mouse lemur primates. *Commun Biol* **1,** 30 (2018). https://doi.org/10.1038/s42003-018-0024-8
2. Weindruch R, et al. (1986). The retardation of aging in mice by dietary restriction: longevity, cancer, immunity and lifetime energy intake. Journal of Nutrition, April, 116(4), pages 641-54.