Decreased consumption of branched-chain amino acids promotes lifespan and healthspan in wild-type and progeroid mice

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The world’s aged population is growing...

FIGURE 1: YOUNG CHILDREN AND OLDER PEOPLE AS A PERCENTAGE OF THE GLOBAL POPULATION: 1950-2050

...but not very healthily
Low protein diets are associated with improved health and longevity in both mice and humans

- Low protein diets improve metabolic health and extend mouse lifespan
- Low protein diets decrease cancer and mortality incidence in non-elderly humans
- High protein diets are associated with cardiovascular mortality and diabetes

Speakman et al., Experimental Gerontology, 2016
Decreased consumption of branched-chain amino acids improves metabolic health
Inhibition of mTORC1 signaling extends lifespan

Muscle

<table>
<thead>
<tr>
<th>Protein</th>
<th>Control</th>
<th>Low AA</th>
<th>Low BCAA</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-S757 ULK1</td>
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<td>ULK1</td>
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<tr>
<td>p-S240/S244 S6</td>
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<td>S6</td>
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<td>p-S65 4E-BP1</td>
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<td>4E-BP1</td>
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Protein phosphorylation (% of Control diet)

- p-S65 4E-BP1: *
- p-S240/S244 S6: *
- p-S757 ULK1: *
Decreased circulating IGF-1 is associated with longevity

Will branched-chain amino acid restriction be effective in extending longevity?

Sofiya Milman, and Nir Barzilai Cold Spring Harb Perspect Med 2016;6:a025098

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Will a Low BCAA diet improve metabolic health and longevity in mice?

Progeroid mice
- $Lmna^{-/-}$ mice, a particularly short-lived progeria
  - high mTORC1 signaling
- $Lmna^{G609G}$ mice, a model of Hutchinson-Gilford Progeria Syndrome
  - Hardy enough for physiologic testing

Wild-type mice
- Mid-lifespan intervention (16 mos.)
- Early-lifespan intervention (weaning)

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<tbody>
<tr>
<td></td>
<td>21% of calories from amino acids (AAs)</td>
<td>BCAAs reduced by 2/3rds; NEAAs raised to maintain 21% calories from AAs</td>
<td>All AAs reduced by 2/3rds; 7% calories from AAs</td>
</tr>
</tbody>
</table>
How will a Low BCAA diet influence the health and longevity of \( Lmna^{G609G} \) mice?

- Mouse model incorporating same human mutation found in Hutchinson Gilford Progeria Syndrome, causing production of mutant protein progerin

- Both \( Lmna^{G609G/+} \) and \( Lmna^{G609G/G609G} \) mice started on Control, Low BCAA or Low AA diets at weaning
  - Physiological testing of \( Lmna^{G609G/+} \) mice
  - Lifespan tracked in \( Lmna^{G609G/G609G} \)
A Low BCAA diet extends the median lifespan of *Lmna*⁻/⁻ females.

For *Lmna*⁻/⁻ females:
- Low AA: p<0.0355, 59%
- Low BCAA: p<0.0098, 85%

For *Lmna*⁻/⁻ males:
- Low AA: p<0.0071, 37.5%
BCAA restriction reduces adiposity in wild-type and *Lmna*<sup>G609G/+</sup> mice
A Low BCAA diet improves rotarod performance in $Lmna^{G609G/+}$ females

**Females**

- Diet: $p<0.0015$
- Genotype: $p<0.0861$

**Males**

- Diet: $p<0.0449$

![Graph showing latency to fall](image-url)
\( Lmna^{G609G/+} \) males improve ejection fraction and restore cardiac output under Low BCAA feeding.
A diet decreased in all amino acids extends the lifespan of $Lmna^{G609G/G609G}$ mice

Low BCAA: $p<0.0465$
Low AA: $p<0.0248$
Will a Low BCAA diet extend lifespan of aged, wild-type mice?

- 100 aged mice from National Institute on Aging, with 25 mice per diet of each sex
  - Diets started at 16 months of age
Mice fed a Low BCAA diet do not consume less food.
Both sexes increase energy expenditure under BCAA restriction.
BCAA restriction improves glucose tolerance
A Low BCAA diet lowers age-associated increases in frailty
A Low BCAA diet does not extend lifespan when fed as a mid-lifespan intervention
A Low BCAA diet significantly extends lifespan when stratified by cancer-related incidence

Diet: $p<0.032$, 12%
An early-lifespan intervention benefits wild-type males only

Females

- Control
- Low BCAA
- Low AA

Males

- Control
- Low BCAA
- Low AA

Low BCAA: $p<0.006$; 35.2%
Low AA: $p<0.022$; 39%
Conclusions

• Decreased consumption of BCAAs improves metabolic health and decreases frailty in progeroid and wild-type mice.

• A Low BCAA or Low AA diet extends the lifespan of Lmna\(^{-/-}\) females and Lmna\(^{G609/G609}\) mice, and also extends male wild-type lifespan when started at weaning.

• A late-life intervention in wild-type females reduces both cancer incidence and extends lifespan of cancer-related deaths.

• Continuing work is in both progeroid and wild-type mice, exploring aging differences at the molecular level.