Comment on "Brain IRS2 Signaling Coordinates Life Span and Nutrient Homeostasis"
Colin Selman, et al.
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Comment on “Brain IRS2 Signaling Coordinates Life Span and Nutrient Homeostasis”

Colin Selman,1 Steven Lingard,1 David Gems,2 Linda Partridge,2 Dominic J. Withers1*

Taguchi et al. (Reports, 20 July 2007, p. 369) reported that mice heterozygous for a null mutation in insulin receptor substrate–2 (Irs2) display a 17% increase in median life span. However, using the same mouse model, we find no evidence for life-span extension and suggest that the findings of Taguchi et al. were due to atypical life-span profiles in their study animals.

Taguchi et al. (1) demonstrated a 17% increase in median and maximum life span in Irs2+/− compared with wild-type (WT) mice on a C57BL/6J background. Although time-consuming and expensive, mouse longevity studies require replication to confirm that findings are robust and reproducible across laboratories and hence of broad applicability to mammalian aging. We made a parallel study of Irs2+/− mice (2) using the same model (3, 4) but, in contrast to Taguchi et al., we did not see life-span extension (2).

Using Irs2+/− parents, we bred WT and Irs2+/− mice and aged them in a specific-pathogen–free facility in individually ventilated cages under our standard husbandry conditions (2, 5). We studied 51 WT and 87 Irs2−/− mice, which is close to the expected Mendelian ratio of progeny genotypes. Kaplan-Meier survival curves were indistinguishable between the two genotypes (Fig. 1A), with no significant differences in cumulative mortality rate (log-rank test: X² = 1.79, P > 0.05). Parental identity, sex, genotype, and birth date had no significant influence on life span (Cox regression analysis, table S1).

We sought explanations for the discrepancy by examining the respective study designs and directly comparing the published longevity data (1, 2). Both studies used the same gene-targeted animal (3, 4) on a C57BL/6J background and similar husbandry conditions, although Taguchi et al. used a relatively high-fat diet (9% fat) compared with our study (5% fat). Differences in dietary composition might influence longevity (6–8). Taguchi et al. reported data from 30 WT and 31 Irs2−/− mice, a 1:1 ratio, which implies that not all progeny from their Irs2+/− × Irs2−/− intercrosses used to generate the study groups (and which should give a 1:2 ratio of WT:Irs2−/− animals) were entered into the study. One possibility is that a potential failure to study all the available Irs2+/− progeny from these crosses in the life-span trials introduced an uncontrolled variable (e.g., parental identity or recruitment date), which increased the life span of the Irs2+/− population. Indeed, these factors appeared to influence the longevity of offspring independent of genotype in the Taguchi et al. study (1). A difference in the number of backcrosses onto the C57BL/6J background (6 for Taguchi et al. and 10 for our animals) and potential differences in colony health status and stocking density may also explain the observed differences.

Comparison of the longevity profiles of the WT control animals in the two studies (1, 2) shows similar cumulative mortality risk profiles and median life span (Table 1; X² = 1.62, P > 0.05). However, Kaplan-Meier survival curves constructed using Taguchi et al.’s life-span data demonstrated a later onset of deaths and a more precipitous fall in survival in WT mice from their Irs2+/− study compared with those from our study, resulting in a truncated period over which all WT deaths occurred in their study (Fig. 1B). Importantly, the life-span profiles of the same-strain control mice for the brain-specific Irs2 mutant described by Taguchi et al. did not resemble those from their Irs2+/− study and instead were similar to the WT data from our Irs2+/− study (Fig. 1 and Table 1). Furthermore, there were significant differences between mean age of death of the oldest 10% and youngest 10% WT animals from Taguchi et al.’s Irs2+/− study, compared with both our and Taguchi et al.’s brain-specific Irs2 mutant study (X² = 22.14, P < 0.001 and X² = 11.03, P < 0.01 for the oldest and youngest 10% of each population, respectively), and the range of ages at time of death was also markedly different in this study (Table 1). Thus, the survival curves of the control mice from Taguchi et al.’s Irs2+/− study are very different from our study (Fig. 1 and Table 1) and their own brain-specific Irs2 mutant study (Fig. 1B and Table 1) and do not appear to resemble those of others who have studied life span in C57BL/6 mice [e.g., (9–14)]. In addition, although Taguchi et al. reported a significant increase in median life span in Irs2−/− mice, the 10th decile of survivorship, which is generally accepted to be an indication that the aging process has been altered (11, 12), was not significantly different (X² = 0.290, P > 0.05) from our Irs2−/− animals (Table 1). Therefore, the WT life-span data supporting Taguchi et al.’s conclusion of increased longevity in Irs2−/− mice is atypical for this mouse strain, and robust conclusions about the role of systemic IRS2 in longevity cannot be made.

In contrast, our studies, using large numbers of WT and Irs2+/− animals that showed typical mortality curves for C57BL/6 mice, did not

Fig. 1. Life span of systemic Irs2+/− mice and WT mice from (2) and a comparison of WT mice from the studies of Selman et al. (2) and Taguchi et al. (1). (A) Kaplan-Meier survival curves are shown for WT and Irs2+/− mice for combined sexes of the Irs2 strain from (2). Cumulative mortality risk profiles, as determined by log-rank analysis, were not significantly different in Irs2+/− mice compared with WT mice (X² = 1.79, P > 0.05). Survival was assessed from 138 mice (87 Irs2+/−; 51 Irs2−/−). Green indicates Irs2+/− mice and blue indicates WT mice. (B) Kaplan-Meier survival curves are shown for WT mice for combined sexes of the Irs2 strain from either Selman et al. or Taguchi et al. Cumulative mortality risk profiles, as determined by log-rank analysis, were not significantly different in WT mice compared across the studies (X² = 1.62, P > 0.05). Survival was assessed from 174 mice. Blue indicates WT mice from the systemic Irs2 of Selman et al. (n = 51), black indicates WT mice from the systemic Irs2 comparison of Taguchi et al. (n = 30), and red indicates WT mice from the brain-specific Irs2 comparison of Taguchi et al. (n = 93).
implicate systemic IRS2 signaling in the regulation of longevity. Indeed, in separate studies, we found that double heterozygote Irs1+/−:Irs2+/− mice had no increase in life span (X² = 3.39, P > 0.05) (figure S1 and table S2) and no alterations in the life span of the oldest 10% and youngest 10% of mice (oldest 10%: X² = 0.511, P > 0.05, and youngest 10%: X² = 0.802, P > 0.05), with no recruitment, sex, or parental effects (table S3). These findings strongly suggest that partial loss of function in this pathway does not increase life span in mammals. We recently presented data that provisionally suggests that global deletion of Irs1 increases life span (2), indicating that appropriate manipulation of systemic IRS signaling has the potential to extend longevity. Therefore, we are able both to generate typical life-span profiles for C57BL/6J mice and to detect life-span extension under our husbandry conditions, which suggests that the absence of life-span extension in our Irs2+/− mice is unlikely to be attributable to our study conditions. Moreover, deletion of Irs1 delayed a range of age-related changes (2), suggesting that aging was genuinely retarded in Irs1−/− mice. Such evidence is lacking for Irs2+/− mice. We therefore conclude that the atypical mouse survival profiles (which may have resulted from experimental design, husbandry, or environmental factors) probably account for the apparent life-span extension in Irs2+/− mice reported by Taguchi et al. The discrepancies in the findings underscore the value of replication of mouse life-span measurements in different laboratories before categorical statements about the role of specific factors in the regulation of mammalian life span can be made.

Table 1. Comparative survival characteristics of systemic Irs2+/− and WT mice from Selman et al. (2) and Taguchi et al. (1). Life span is reported in days (±SEM, where appropriate) for WT and Irs2+/− mice. Oldest 10% and youngest 10% were calculated as the mean life span of the longest (or shortest) living 10% of animals within a genotype. n = sample size.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Median</th>
<th>Mean ± SEM</th>
<th>Range</th>
<th>Oldest 10%</th>
<th>Youngest 10%</th>
<th>n</th>
</tr>
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<td>WT</td>
<td>785</td>
<td>755 ± 22</td>
<td>203–1019</td>
<td>967 ± 15</td>
<td>442 ± 65</td>
<td>51</td>
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<tr>
<td>Irs2+/−</td>
<td>800</td>
<td>788 ± 17</td>
<td>135–1105</td>
<td>1011 ± 17</td>
<td>480 ± 57</td>
<td>87</td>
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<td>Selman et al. (2)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>WT</td>
<td>877</td>
<td>775 ± 10</td>
<td>655–898</td>
<td>868 ± 15</td>
<td>681 ± 13</td>
<td>30</td>
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<tr>
<td>WT†</td>
<td>722</td>
<td>730 ± 18</td>
<td>205–1054</td>
<td>975 ± 11</td>
<td>403 ± 31</td>
<td>93</td>
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<tr>
<td>Irs2+/−</td>
<td>924</td>
<td>905 ± 22</td>
<td>402–1042</td>
<td>1037 ± 4</td>
<td>634 ± 116</td>
<td>31</td>
</tr>
</tbody>
</table>

*WT mice are control mice from the systemic Irs2 comparison of Taguchi et al. †WT mice are control mice from the brain-specific Irs2 comparison of Taguchi et al.

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Supporting Online Material
www.sciencemag.org/cgi/content/full/320/5879/1012b/DC1
Fig. S1
Tables S1 to S3
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