thereby decreasing disease-associated aggregates. Prior work in rodents and C. elegans has shown expression levels of the small heat shock protein 25 (HSP25) correlates with maximum lifespan potential. Increased levels of HSP25 extends lifespan in a transgenic C. elegans model. This lifespan extension is dependent on skn-1 with evidence suggesting an enrichment in several skn-1-related pathways, such as lysosomal genes. Concomitantly, proteasome activity declines while autolysosome activity increases. This observation might suggest a switch from proteasome degradation to autophagy as the main driver of protein degradation in C. elegans in this transgenic model. To investigate if a reduction of proteasome function and elevated lysosomal gene activation during aging and under proteotoxic stress are modulated by HSP25 we have crossed our HSP25-transgenic worm with an aggregating and non-aggregating tau worm model. This work will elucidate a possible mechanism that explains the change in the protein degradation response pathways potentially modulated by HSP25 during increased protein misfolding.

INDICES OF RESILIENCY IN CELLS FROM UM-HET3 MICE MAY CORRELATE WITH INDIVIDUAL FUTURE HEALTH OUTCOMES

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The ability of an organism to respond to physical stresses and return to homeostasis (i.e. resilience) has been suggested to correlate with longevity. Here, we investigated whether this extends to resilience at a cellular level using primary fibroblasts isolated from tail skin of genetically heterogeneous young adult UM-HET3 mice. Cells isolated from each individual mouse (cell line) were tested in their response to concentrations of agents or conditions predicted to induce a cellular challenge, including paraquat, hydrogen peroxide, antimycin a, cadmium chloride, mdivi-1, thapsigargin, and nutrient starvation. Cell viability was monitored in real-time using an incucyte S3 live cell analysis system and we addressed the response following challenge as a marker of resilience. Cellular uptake of ethidium homodimer-1 was used to determine the loss of viability. Cellular bioenergetics were assessed using a seahorse XF24. We found that cell lines that were resistant to paraquat were also resistant to antimycin a, and hydrogen peroxide. Cell lines that were resistant to nutrient starvation were also resistant to mdivi-1. Indices of cellular bioenergetics status including ATP production rate and cell respiratory control ratio, revealed potential relationships with resiliency. Taken together, our data indicate that skin fibroblasts retain individual physiological programs that may in part explain the patterns of resiliency or sensitivity to a stressor at the organismal level. Since the cell lines tested in this study were obtained from living mice, future work will investigate whether these patterns of resiliency change with age and elucidate their utility in predicting future health outcome.

THE ENDOPLASMIC RETICULUM PROTEIN QUALITY CONTROL ADAPTATION IN A LONG-LIVED C. ELEGANS PROTEASOMAL MUTANT

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Protein degradation mechanisms are integral to protein homeostasis. Their reduced efficiency during aging leads to accumulation of misfolded and aggregated proteins which potentiate proteotoxic disorders. Paradoxically, our lab reported that the Caenorhabditis elegans rpn-10(ok1865) proteasome mutant possesses enhanced proteostasis and extended lifespan. RPN-10/PSMD4 is a ubiquitin receptor of the 26S proteasome that targets polyubiquitinated substrates to its catalytic core for degradation. Proteasome dysfunction of the rpn-10 mutant is characterized by reduced, not inhibited, ubiquitin fusion degradation. We ascertained that upregulated autophagy and SKN-1/Nrf-mediated responses partially contribute to the robust rpn-10 mutant phenotype. Further investigation of its underlying mechanism revealed that several ERQC genes are transcriptionally upregulated in the rpn-10 mutant. Thus, we hypothesized that the rpn-10 mutant exhibits improved ER proteostasis which mediates its elevated cellular stress resistance. Accordingly, the rpn-10 mutant shows increased ER stress resistance and altered ER homeostasis. Complementarily, attenuated expression of the aggregation-prone α-1 antitrypsin (ATZ) reporter proves that ER proteostasis is ameliorated in the rpn-10 mutant. Via a genetic screen for suppressors of decreased ATZ aggregation in the rpn-10 mutant, we identified novel player H04D03.3, which is a homolog of the proteasome adaptor ECM29. This suggests that assembly of the rpn-10 mutant proteasome itself critically regulates its ER proteostasis. Moreover, we observed that cytosolic proteostasis and longevity depend on ER master chaperone hsp-3/-4(BiP) and ER ATPase cdc-48.2(p97/VCP), further highlighting ERQC significance in the rpn-10 mutant. Altogether, it appears that mild proteasomal dysfunction induces ERQC adaptation that underlies proteostasis and longevity benefits of the rpn-10 mutant.

THE LONGEVITY ASSOCIATED ALLELE OF FOXO3 PROTECTS AGAINST TELOMERE ATTRITION DURING AGING

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Telomere attrition in proliferative tissues is a hallmark feature of human aging. To date, the genetic influence on the rate of telomere attrition is poorly understood. Previously we discovered a variant of the FOXO3 gene that is strongly associated with human longevity, an observation that has been now reproduced in over a dozen independent studies. In the present study, we sought to assess the effect of the longevity associated variant of FOXO3 (rs2802292 - G allele) on the rate of telomere attrition during aging. The results from a cohort of Okinawan-Japanese (N=121), ranging in age from 25 – 94 years, demonstrates carriers of 1 or 2 copies of the longevity-associated G allele of FOXO3 showed markedly reduced rates of telomere loss in peripheral blood leucocytes