The longevity-promoting factor, TCER-1, widely represses stress resistance and innate immunity.

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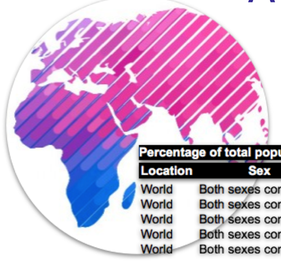
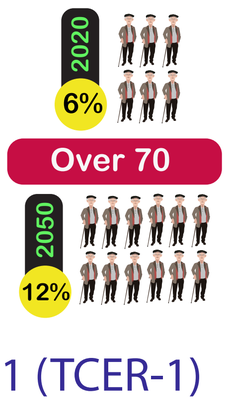
A positive correlation exists between stress resistance and longevity, but emerging evidence suggests that lifespan and stress endurance are physiologically distinct. A major challenge in aging biology has been identifying factors that play distinct roles in these closely coupled processes because genes that promote longevity often enhance stress resistance. Here, we demonstrate that TCER-1, the Caenorhabditis elegans homolog of the human transcription elongation and splicing factor, TCERG1, has discrete and opposite effects on lifespan and stress resistance. We previously identified tcer-1 as a gene that promotes longevity in germline-less C. elegans and reproductive fitness in wild-type animals. Surprisingly, tcer-1 mutants exhibited exceptional resistance against multiple biotic and abiotic stressors, including infection by the human opportunistic pathogen Pseudomonas aeruginosa. Conversely, TCER-1 overexpression increased susceptibility to infection. TCER-1 acted cell non-autonomously to both enhance longevity and repress immunity. Interestingly, TCER-1 inhibited immunity only during the fertile stages of life and not in post-reproductive adults. Elevating its levels ameliorated the fertility loss that follows infection, suggesting that TCER-1 may repress immunity to augment fecundity. Mechanistically, TCER-1 acts through the inhibition of the conserved kinase, PMK-1, as well as through repression of PMK-1-independent, novel antibacterial factors critical for innate immunity. Recent RNA-seq studies have further highlighted the role of TCER-1 in influencing immunity under pathogenic challenge. Overall, our data establish key roles for TCER-1 in coordinating immunity, longevity and fertility, and reveal the molecular mechanisms that distinguish length of life from functional aspects of aging.

A Fast Graying World



Rise in the population of older people is expected to further increase in the near future, an outcome of modern day health care.

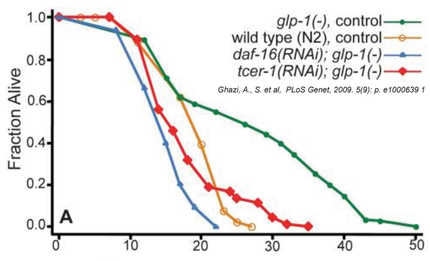


Percentage of total population by broad age group, both sexes (per 100 total population)										
Location	Sex	Age	1980	1990	2000	2010	2020	2030	2040	2050	2060
World	Both sexes combined	50+	16.0	16.6	17.6	20.6	24.2	27.3	30.7	32.8	34.3
World	Both sexes combined	60+	8.5	9.1	9.9	11.0	13.5	16.5	18.9	21.5	23.1
World	Both sexes combined	70+	3.5	3.8	4.4	5.1	5.9	7.7	9.8	11.4	13.2
World	Both sexes combined	80+	0.8	1.0	1.2	1.5	1.9	2.4	3.4	4.5	5.3
World	Both sexes combined	90+	0.0	0.1	0.1	0.2	0.3	0.4	0.5	0.8	1.2

Trancription Elongation Regulator 1 (TCER-1)

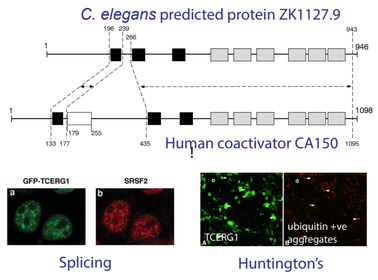
Promotes longevity

- Sterile animals (GSC-ve) have increased lifespan[1]
- TCER-1 identified as an essential factor required for this longevity[2]



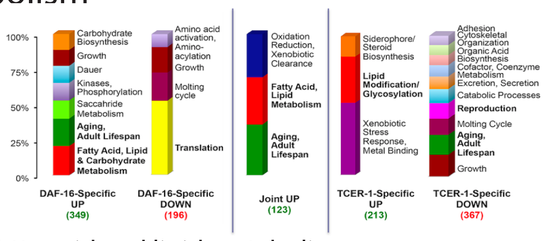
Evolutionarily Conserved

- TCER-1 is homologous to the human transcription elongation factor TCERG1[3]
- Plays an essential role in transcription and splicing[4]
- Implicated in Huntington's and HIV infection[3,5]
- Highly expressed in human oocytes, with mRNA levels declining with age[6]



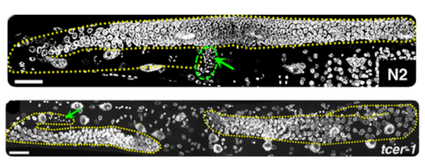
Regulates Lipid Metabolism[7]

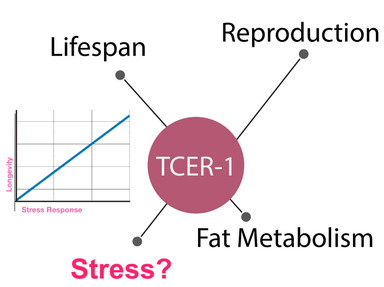
- DAVID analysis of DAF-16 and TCER-1 targets show enrichment in the three UP groups in lipid metabolic genes
- TCER-1 along with DAF-16 identified as regulators of fatty acid and lipid metabolism



Essential for Healthy Reproduction[7]

- *tcer-1* mutants display a decreased brood of ~65% and viability of ~40%
- Also have a disrupted gonad and display delay in switching from spermatogenesis to oogenesis

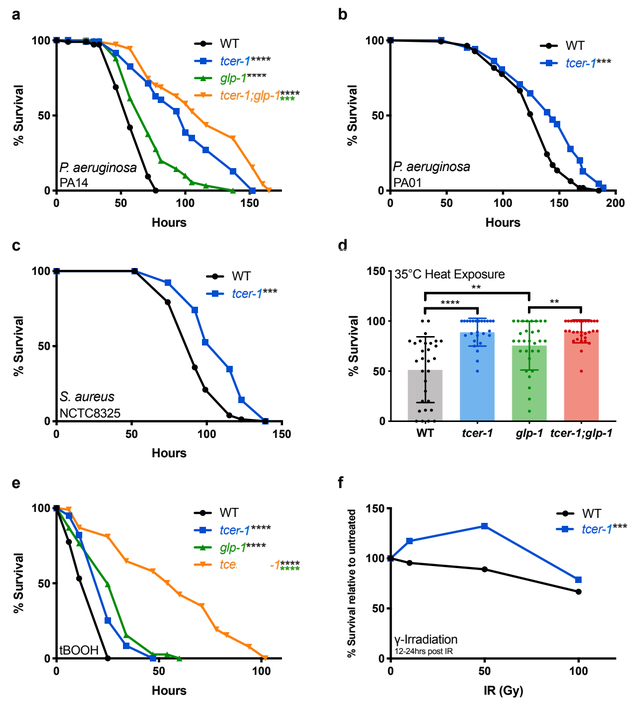




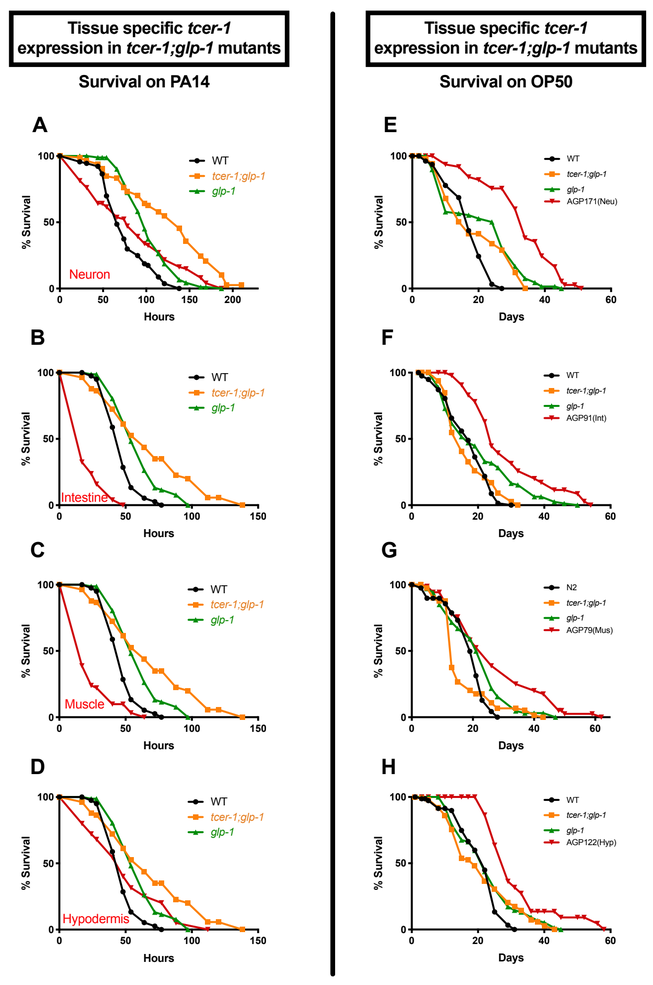
Given the importance of *tcer-1* in influencing numerous traits, we asked if *tcer-1* also played a role in stress response. Further, since the relationship between longevity and stress response are usually positively correlated we asked ....

Does *tcer-1* phenotypically couple lifespan with stress resistance?

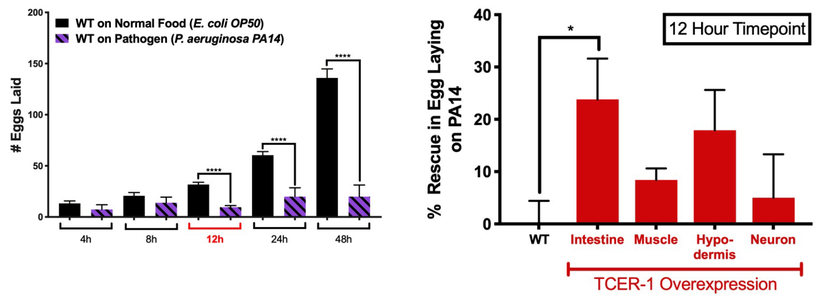
1) TCER-1 Suppresses Resilience Against Multiple Biotic and Abiotic Stressors



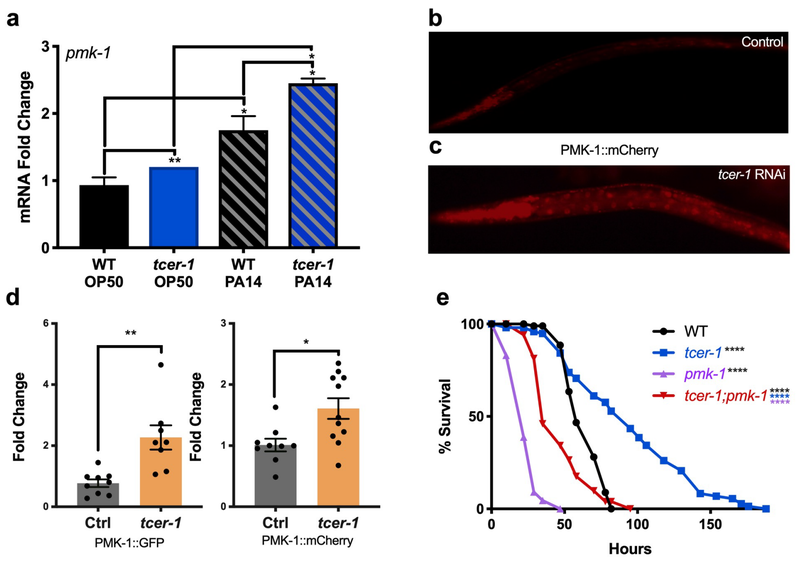
2) TCER-1 Acts Cell Non-Autonomously to Repress Stress Resistance and Enhance Longevity



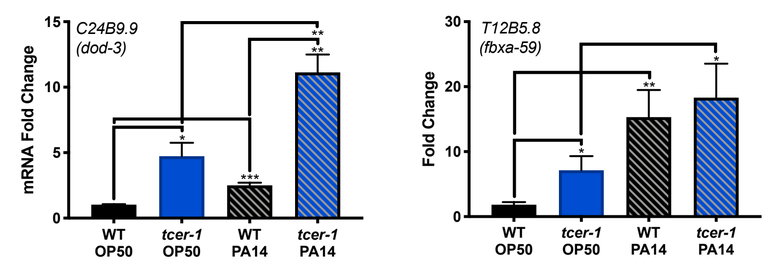
3) TCER-1 Overexpression Ameliorates the Decline in Fertility Caused by Pathogen Infection



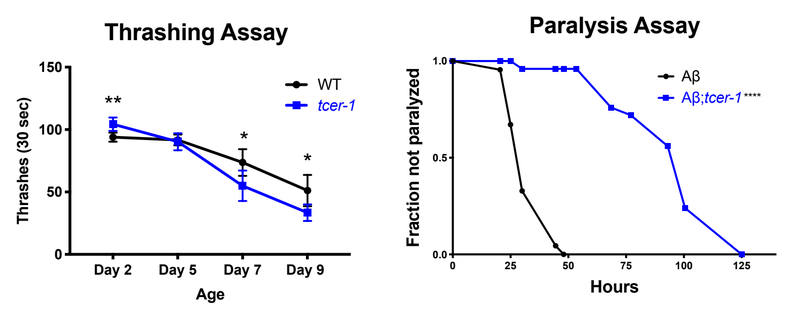
4) TCER-1 Represses the Conserved Kinase, PMK-1



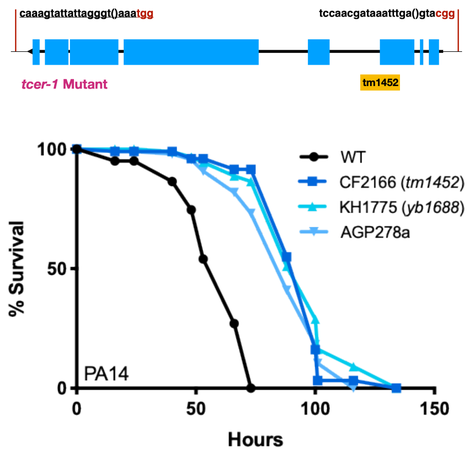
5) TCER-1 Represses Expression of PMK-1 dependent and PMK-1 Independent Immunity Factors



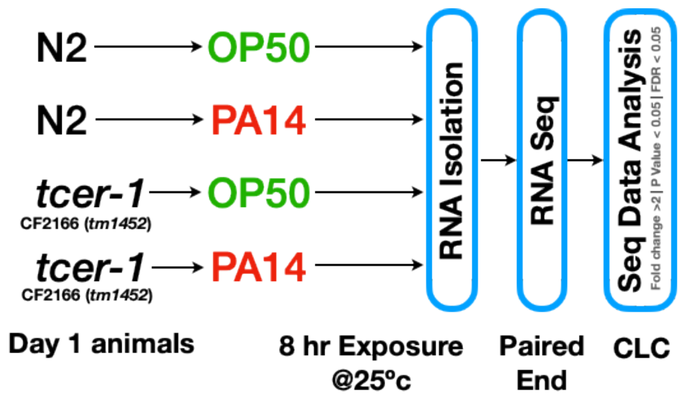
6) *tcer-1* Mutants Exhibit Improved Healthspan

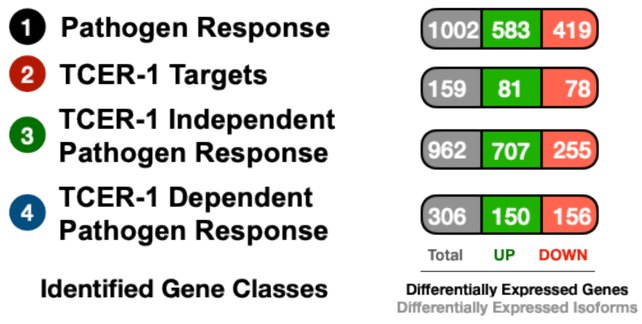


7) All *tcer-1* mutation variants Exhibit Improved tolerance to pseusomanas aeruginosa (PA14)



8) TCER-1 targets identified under normal and stressed conditions





Conclusions

- TCER-1 plays a key role in promoting longevity and fertility while inhibiting resistance to multiple biotic and abiotic stressors
- TCER-1 functions cell non-autonomously to promote longevity and repress stress
- TCER-1 functions predominantly through the fertile phase of life to inhibit immunity and not in post-reproductive animals
- TCER-1 inhibits immunoresistance by repressing PMK-1, as well as PMK-1-independent, innate immunity pathways

Future Directions

- Decipher further the function of TCER-1 and provide insights into its downstream regulators and co-factors, characterize the *tcer-1* null mutant generated using Crispr
- Explore the role of TCER-1 in genetic regulation, preliminary data suggest an exciting novel role of TCER-1 in mRNA Splicing
- Establish TCER-1 binding sites through ChIP analysis, confirm its role as a transcription elongation factor and gain further insights into its gene regulatory prowess

References – *(1) Arantes-Oliveira N, Apfeld J, Dillin A, Kenyon C. Regulation of life-span by germ-line stem cells in Caenorhabditis elegans. Science 295, 502-505 (2002); (2) Ghazi, A., S. Henis-Korenblit, and C. Kenyon, A transcription elongation factor that links signals from the reproductive system to lifespan extension in Caenorhabditis elegans . PLoS Genet, 2009. 5(9): p. e1000639; (3) Holbert S, Denghien I, Kiechle T, Rosenblatt A, Wellington C, Hayden MR, et al. The Gln-Ala repeat transcriptional activator CA150 interacts with huntingtin: neuropathologic and genetic evidence for a role in Huntington's disease pathogenesis. Proceedings of the National Academy of Sciences of the United States of America. 2001;98(4):1811-6. doi: 10.1073/pnas.041566798. PubMed PMID: 11172033; PubMed Central PMCID: PMCPMC29339; (4) Sanchez-Hernandez, N., et al. (2016). "The in vivo dynamics of TCERG1, a factor that couples transcriptional elongation with splicing." RNA; (5) Coiras, M., et al. (2013). "Transcription elongation regulator 1 (TCERG1) regulates competent RNA polymerase II-mediated elongation of HIV-1 transcription and facilitates efficient viral replication." Retrovirology 10: 124; (6) Steuerwald NM, Bermudez MG, Wells D, Munne S, Cohen J. Maternal age-related differential global expression profiles observed in human oocytes. Reprod Biomed Online. 2007;14; (7) Amrit FR, et al. DAF-16 and TCER-1 Facilitate Adaptation to Germline Loss by Restoring Lipid Homeostasis and Repressing Reproductive Physiology in C. elegans. PLoS genetics 12, e1005788 (2016); (8) Troemel ER, Chu SW, Reinke V, Lee SS, Ausubel FM, Kim DH. p38 MAPK regulates expression of immune response genes and contributes to longevity in C. elegans. PLoS genetics 2, e183 (2006); (9) Amrit, F.R.G., Naim, N., Ratnappan, R. et al. The longevity-promoting factor, TCER-1, widely represses stress resistance and innate immunity. Nat Commun 10, 3042 (2019). https://doi.org/10.1038/s41467-019-10759-z; (10) Freepix; (11) Vecteezy*