Cancer & Accelerated Aging ADVANCING RESEARCH FOR HEALTHIER SURVIVORS

Measuring Aging And Identifying Aging Phenotypes In Cancer Survivors

Questions to Guide/Prompt Think Tank Deliberations

IDENTIFYING "AGING PHENOTYPES" AND UNDERSTANDING THE TRAJECTORY(IES) OF AGING AMONG CANCER SURVIVORS
1. What is the definition of a healthy life span or healthy aging after cancer treatment? How is health span regarded in a cancer survivorship context?
2. Does the increased prevalence in age-related comorbidities, higher inflammatory profiles, etc., in cancer survivors, compared with age-matched cancer-free individuals, represent premature ("accelerated") aging, or does it reflect specific outcomes related to cancer diagnosis and treatment toxicity, and/or side effects? a. Is it possible to elucidate unique "hallmarks of aging" within the context of cancer survivorship? b. Are we essentially interested in secondary aging? Do cancer and cancer treatment result in "injuries" to the organism that cause aging or a change in the rate of aging? Can secondary malignancies be thought of as a secondary aging outcome?[1]
3. What are the aging phenotypes in the general population?
4. How do we best measure aging?
MECHANISMS BY WHICH CANCER/CANCER TREATMENT LEAD TO ACCELERATED AGING (OR AGING PHENOTYPES)
5. What mechanisms lead to accelerated aging?
6. Recognizing that animal models (typically young-aged animals) are extensively utilized to phenocopy human cancers and test therapeutic approaches, do animal models accurately reflect the accelerated aging observed in humans? Can these models be improved to better understand and investigate accelerated aging pathways and develop novel interventions to stabilize or reverse aging processes?
7. How do aging processes influence cancer biology and progression?

8. How do aging and cancer processes interact in the inflammation/coagulation pathways?

9. How do cancer treatments impact aging? How can cancer and cancer treatment be used to further our understanding of the molecular pillars of aging?
    a. Are the primary targets of these drugs leading to accelerated aging?
    b. Are the side effects of these drugs leading to accelerated aging?
    c. Many of these drugs lead to apoptosis in the targeted cell. Is it possible that there are too many apoptotic bodies for the system to remove, and these produce aging effects?
    d. How do therapy-induced senescent cells contribute to age-related consequences of cancer treatment exposure?
    e. Which senescence-related chemotherapy side effects are due to SASP-induced immune activation? Which immune components?
    f. Which senescence-related chemotherapy side effects are due to SASP factors independent of the immune system? Which factors?
    g. Does getting cancer treatment during a specific life stage (e.g., puberty, pregnancy, or menopause) lead to increased toxicity or disrupt natural aging/development?

10. How much of the distal damage caused by tumors is due to tumor-induced immune activation? Which components?

EARLY DIAGNOSIS AND SURVEILLANCE OF ACCELERATED AGING

11. What treatment toxicity profiles can be used as early warning signs for loss of function over time?

12. Can a panel of clinical/biological tests be used to identify and monitor progression to “aging phenotypes” in cancer survivors?

13. Can the Tipping Point Theory be used to describe aging among cancer survivors?[2–4] If so, what is the tipping point, and what are the pre-symptomatic early warning signs?

14. Can we measure the loss of resilience earlier in adulthood before the occurrence of frailty?

RISK AND PROTECTIVE FACTORS

15. What risk factors result in a temporary setback or a continual decline? What changes are protective? Are the changes reversible?

16. What are the risk factors that lead to prefrail/frail states in older adults and that are predictive in younger individuals?

17. How do we protect physiological/functional reserve, protect against chronic multiple organ dysfunction, and build resilience to promote a healthy life span after cancer treatment?

18. Are there "exceptional responders," or individuals/groups whose measures of aging are not accelerated after cancer therapy? Can these individuals/groups be identified and studied?

19. Do accelerated aging trajectories differ by cancer treatment, cancer population/age group, etc.?

20. Is there a differential impact on the rate of aging that depends more on the type and stage of the cancer and less on the therapy? If so, are the effects additive, multiplicative, synergistic?

21. Do high global pro-senescence stress and a compromised immune system lead to accelerated aging?

22. Do certain cancer treatments increase survivors' vulnerability to multiple diseases? How does this intersect with aging, which also increases vulnerability to multiple diseases?

23. What are the best biomarkers, cellular and molecular characteristics that predict or protect from age-related consequences of cancer treatment exposure?

DESIGNING STUDIES OF CANCER AND ACCELERATED AGING

24. How can we study the mechanisms that lead to accelerated aging?

25. How do we obtain experimental evidence?

26. Are there existing studies (or "banks" of information) that could serve as the infrastructure to measuring aging-related phenotypes longitudinally to investigate aging-related trajectories among cancer survivors?

27. Can risk-prediction models be developed? If so, what do we need to develop models of adverse health outcomes that change the rate of aging? How granular do we need to focus to extrapolate from individual to population-level effects? What is the utility of these risk-prediction models? Should this information be incorporated into clinical decision-making (risk/benefits of certain treatments)?[5,6]

28. Can multi-level systems modeling approaches be used to understand what accelerated aging is and what the phenotype looks like beyond the measurement of one biomarker? Can they be used to: 1) identify individuals who need interventions, and 2) develop personalized cancer rehabilitation interventions?

29. Which advanced statistical analysis techniques hold potential for understanding how brain structure and function change with aging and in response to insults to the brain caused by cancer and cancer treatments?
30. Which models are most appropriate to use to study how brain structure and function change with age and by cancer treatment?
31. Which models describe the resiliency and failure of complex systems? Which are the most appropriate for guiding research related to the interactions of aging processes, cancer, and cancer treatments in determining cognitive aging?

References

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