Aging and Cancer: Targets for New Drug Development

Harvey Jay Cohen, MD
SIOG
Berlin, Germany

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Goals of Research: Cancer vs Aging

- Both – Seek basic understanding, then application

Target

- Cancer Research – Ways to prevent, cure or ameliorate cancer
- Aging Research – Extend longevity
  - Prevent functional decline
  - Prevent/Ameliorate diseases of aging
Central Premise

Cancer ← Tissue Renewal and Repair → Aging & Functional Decline
Antagonistic Pleiotropy

Mechanisms evolved to have beneficial effects at young (reproductive) age, may have deleterious effects at older (post reproductive) age

eg: Mechanisms to control excessive proliferation to prevent cancer in earlier life (largely successful) may result in decreased cell and tissue repair (aging) in later life

or

Aging is the price we pay to control cancer.
Are Cancer and Aging Different Sides of the Same Coin?

POTENTIAL TARGETS

- DNA Damage
- Mitochondrial Function
- IGF$_1$ Pathway
- FOXO Pathway
- p53
- p16$^{INKa}$
- Immune Function
  - IL6
  - PPARs
DNA Damage Responses in Tumor Suppression and Aging

Excision Repair in Cancer And Aging

Global-Genome Nucleotide Excision Repair (GG-NER)

- HHR23B
- DDB2
- XPC
- XPE
- UV
- ???

Damage recognition

Transcription-coupled Excision Repair (TCER)

- UV
- RNApolII
- CSB
- CSA
- XAB2
- UVS
- CSA

Helix-unwinding and damage verification

- TFIHH
- XPG
- RPA
- XPD
- ATP
- TTD
- XPA

Excision

- ERCC1/XPF
- XPF
- XPG
- XPG

DNA synthesis and ligation

- DNApol &
- PCNA, RFC
- DNA ligase

TCER defects lead to progeria (e.g. Cockayne syndrome)

GG-NER defects lead to eroderma pigmentosum

Generation of Reactive Oxygen Species

Dual Function Agents Deliver an ROS Scavenging Payload into Mitochondria

Other Possible Targets for Intervention

Endocrine Signals and DNA Damage

FOXO Factors in Aging and Cancer

FOXO Factors in Aging and Cancer

Other Possible Targets for Intervention

Dual Activities of p16^{INK4a} during Aging

IL-6 in Hepatocarcinogenesis

Peroxisome Proliferation-Activated Receptors (PPARs)

- Ligand activated transcription factors ($\alpha, \beta/\delta, \gamma$)
- Regulate cell proliferation and differentiation
- Inhibit expression of inflammatory genes (cytokines, matrix metalloproteases)
- Involved in age-related upregulation of NF-κB
- PPARγ ligand reduces carcinogen induced tumor incidence in mice
Age and Cancer Incidence

Conclusions

While being mindful of the dangers of messing with Mother Nature, targeting the biological interface of Aging and Cancer is fertile ground for improvements in our approach to both Cancer and the consequences of Aging.