Emerging Role of Senescence in Cardiotoxicity

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Disclosures

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None relevant to this presentation
What is cellular senescence?

The process by which damaged cells permanently exit the cell cycle

Schmitt CA, Nature Reviews Cancer 2003
Shared pathways leading to senescence

Aging

DNA damage
Telomere attrition
↓ NAD⁺/SIRT
Oxidative stress
Inflammation
Mitochondrial dysfunction

Chemotherapy

Cardiovascular Disease
Chemotherapy induces senescence in tumor cells

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism</th>
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<tbody>
<tr>
<td>Aphidocolin</td>
<td>DNA polymerase inhibitor</td>
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<tr>
<td>Bleomycin</td>
<td>DNA damage</td>
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<tr>
<td>Camptothecin</td>
<td>DNA damage</td>
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<tr>
<td>Carboplatin + docetaxel</td>
<td>DNA damage</td>
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<tr>
<td>Cisplatin</td>
<td>DNA damage</td>
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<tr>
<td>Cyclophosphamide + doxorubicin</td>
<td>DNA damage</td>
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<tr>
<td>5-Fluorouracil</td>
<td>DNA damage</td>
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<tr>
<td>Diaziquone/AZQ</td>
<td>DNA damage</td>
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<tr>
<td>Doxorubicin</td>
<td>DNA damage</td>
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<tr>
<td>Epigallocatechin gallate</td>
<td>Telomerase inhibition</td>
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<tr>
<td>Etoposide</td>
<td>DNA damage</td>
</tr>
<tr>
<td>Gamma irradiation</td>
<td>DNA damage</td>
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<tr>
<td>Hydroxyurea</td>
<td>ROS</td>
</tr>
<tr>
<td>K858</td>
<td>KIF11</td>
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<tr>
<td>Lovastatin</td>
<td>HMG-CoA-reductase inhibitor</td>
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<tr>
<td>Mitoxantrone</td>
<td>DNA damage</td>
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<tr>
<td>MLN4924</td>
<td>Cul1 SCF subunit inhibitor</td>
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<tr>
<td>MLN8054</td>
<td>Aurora kinase A inhibitor</td>
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<tr>
<td>Pyrithione</td>
<td>Zinc/calcium regulation, ROS</td>
</tr>
<tr>
<td>Resveratrol</td>
<td>ROS</td>
</tr>
</tbody>
</table>

Ewald JA, J Natl Cancer Inst 2003
Roberson RS, Cancer Res 2005
Does senescence occur in the heart?

Aging → miR-34a → PNUTS → DNA damage response
              Telomere attrition
              Decline in cardiac function

Boon RA, Nature 2013
Does senescence occur in the heart of patients with cancer?

Aging → miR-34a → PNUTS → DNA damage response

Telomere attrition
Decline in cardiac function

Chemotherapy

- Anthracyclines
- Alkylating agents
- Taxanes
- Cisplatin

Freres P et al., J Cell Physiol 2014

Correlation between upregulation of plasma miR-34a and troponin T

\[ p < 0.05, r = 0.47, n = 25 \]
Senolysis protects the heart against doxorubicin

Induction of $p16^{INK4a}$ and $p21$ in the heart*

Rescue of cardiac function with gancyclovir

*Endothelial cells and fibroblasts

Demaria M, Cancer Discovery 2017
Other chemotherapies induce senescence in non-cancerous tissues

Demaria M, Cancer Discovery 2017
What is the effect of senolysis on cancer outcomes?

Demaria M, Cancer Discovery 2017
Therapies targeting senescence could be beneficial in patients at risk for cancer treatment-associated heart toxicity.

Unmet needs for future research include:

- Molecular markers that are more specific for cellular senescence
- Clarification of the cardiovascular cell type(s) most affected by cancer therapy-induced senescence
- Preclinical platforms that enable evaluation of the effects of senolytic therapies on the cardiovascular system and tumor within the same model