Harnessing Cellular Senescence for Cancer Immunotherapy

Marcus Ruscetti
University of Massachusetts Medical School

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Harnessing Cellular Senescence for Cancer Immunotherapy

Cancer therapy

Senescence

Immune surveillance

Cell cycle arrest

Marcus Ruscetti, Ph.D.
Assistant Professor
Molecular Cell and Cancer Biology
UMass Medical School
10-26-20
Immune Checkpoint Blockade has revolutionized treatment landscape of many cancers.

Non-small cell lung cancer

Hellmann et al NEJM 2018

Ledford et al Nature 2018
Only subset of immunologically “Hot” tumor types responsive to immunotherapy

Responsive
PD-1/PD-L1 and CTLA-4 blockade

Unresponsive

Hedge et al. Immunity 2019
Targeting tumor intrinsic mechanisms of immune evasion to potentiate immunotherapy

- Oncogene activation
- Tumor suppressor loss

Genetic Alterations
Targeting tumor intrinsic mechanisms of immune evasion to potentiate immunotherapy

- Targeted Therapy
- Oncogene activation
- Tumor suppressor loss
- Genetic Alterations
- Immune suppressive factors
Targeting tumor intrinsic mechanisms of immune evasion to potentiate immunotherapy
Targeting tumor intrinsic mechanisms of immune evasion to potentiate immunotherapy

Targeted Therapy

Oncogene activation
Tumor suppressor loss

Genetic Alterations

Immunotherapy
Cellular Senescence: a two-component program linking intrinsic and extrinsic tumor suppression

- Stable cell cycle arrest
- Modulation of the microenvironment

Physiological stress response to damage:
- Telomere shortening (replicative exhaustion)
- Genotoxic stress
- Oxidative stress
- Oncogene activation

Potent activation of secreted factors:
- Pro-inflammatory cytokines/chemokines
- Growth and stemness factors
- Matrix metalloproteinases
- Angiogenic factors

p53 and RB pathway-regulated
(gene repression)

NF-kB-regulated
(gene activation)

Senescence-inducing therapies for KRAS mutant cancers

KRAS-driven lung cancer GEMMs

Tumor volume (% change)

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KRAS-driven pancreas cancer GEMMs

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Ruscetti et al. Science 2018; Ruscetti et al. Cell 2020
Therapy-induced senescence mediates divergent immune responses in different tissues

**KRAS-driven lung cancer**

- NK cells
- Endothelium
- SASP

**KRAS-driven pancreas cancer**

- NKp46
- CD31
- CD3

**Tumor volume (% change)**

- Vehicle
- Trametinib/Palbociclib
- Trametinib
- Palbociclib
- Combo
- Combo NK1.1
- Combo CD8

**Tumor volume (T14 vs. T0)**

Ruscetti et al. Science 2018

Ruscetti et al. Cell 2020
• Which SASP factors are important for anti-tumor immune responses?
• How is the SASP transcriptionally regulated in different contexts?
• How does the resident microenvironment affect senescence and its impact on the immune system?
Uncovering tissue-specific regulation of SASP-mediated immunity in pancreas cancer

**Pancreas tumor cells in lung environment**

Pancreas *KPC* cells (*Kras^{G12D};Trp53^{-/-}*) → C57BL/6 mice

**Lung tumor cells in pancreas environment**

Lung *KP* cells (*Kras^{G12D};Trp53^{-/-}*) → C57BL/6 mice

![Graph showing NK cell percentage](image)

**RNA-seq**

Pancreas environment

- Ccl2*
- Cxcl9
- Cxcl10
- Ccl5

Lung environment

- Ccl2*
- Cxcl9
- Cxcl10
- Ccl5
EZH2 and SUZ12 are chromatin regulators that suppress SASP.

Pancreas vs. Lung TME

Encode_and_ChEA_Consensus_TFs_CHIP
Encode_TF_CHIP

CCL2
CXCL2
IL-6
CX3CL1
CXCL10
CCL5
CCL20

pg/ml

shRen
shEZH2
shSUZ12
Potentiating Immunotherapy in Pancreas Cancer Mouse Models

+ Ren shRNA
+ EZH2 shRNA
+ SUZ12 ShRNA

KPC cells
KPC organoids

C57BL/6 mice

Tramet
Palbo

High-throughput sequencing
(Senescence/SASP signatures)

Immune profiling

Tramet
Palbo
GSK126

Preclinical Pipeline
“Mouse Hospital”

p48-Cre;Kras^{G12D/+};p53^{fl/+}
(KPC) GEMM mice

Tumor growth
Metastatic Spread
Survival
Studying senescence and immune surveillance bypass in other genetic contexts and “cold” tumor types

Prostate cancer

Modeling prostate cancer in mice using in vivo electroporation

Androgen receptor (AR) pathway
PI3K pathway
WNT pathway
DNA repair
Chromatin modifiers

Transposon Vector
Transposase
CRISPR/Cas9 Vector

WT C57BL/6
EPO-GEMMs

Robinson et al Cell 2015
Leibold*, Ruscetti* et al Cancer Discovery 2020
Pipeline to identify and validate senescence-inducing compounds in tumor and genotype-specific manner

**In vitro**
- NF-KB reporter (SASP)
- p16 reporter (senescence)

Murine tumor cells with different genetic backgrounds

**In vivo**
- C57BL/6
- Nu/Nu (Nude)
- NOD-scid IL2Rγ null (NSG)

Gene expression:
- Oncogene: MYC, AR, Pik3ca
- Tumor suppressor: sg.p53, sg.Pten, sg.Rb

Oncogene Tumor suppressor

Chemical Library Screens

EPO-GEMM platform

Genetics

Immune background

Therapeutic Interventions

- Senescence-inducing therapies
- Immunotherapies

CDK4/6 i.

αPD-1

αCTLA-4
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