Harnessing Cellular Senescence for Cancer Immunotherapy

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Harnessing Cellular Senescence for Cancer Immunotherapy

Senescence

Cancer therapy

Immune surveillance

Cell cycle arrest

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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

- Oncogene activation
- Tumor suppressor loss
- Genetic Alterations
- Immune suppressive factors

Targeted Therapy
Targeting tumor intrinsic mechanisms of immune evasion to potentiate immunotherapy

- Oncogene activation
- Tumor suppressor loss
- Genetic Alterations

Targeted Therapy
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-κB-regulated (gene activation)

Senescence-inducing therapies for **KRAS** mutant cancers

**KRAS**-driven lung cancer GEMMs

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

**KRAS**-driven pancreas cancer GEMMs

- **Vehicle**
- **T/P**

**RB**-mediated senescence

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

KRAS-driven lung cancer

- Vehicle
- Trametinib/Palbociclib

KRAS-driven pancreas cancer

- NKp46
- CD31
- CD3

Ruscetti et al. Science 2018
Ruscetti et al. Cell 2020
SASP regulation in cancer: complexity and context-dependency

- 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 → NK cells (% of CD45+)

- Vehicle
- T/P

Lung tumor cells in pancreas environment

Lung KP cells ($Kras^{G12D}$; $Trp53^{-/-}$) → C57BL/6 mice → NK cells (% of CD45+)

- Vehicle
- T/P

Pancreas environment:
- Ccl2*
- Cxcl9
- Cxcl10
- Ccl5

Lung environment:
- Tramet
- Palbo

RNA-seq
EZH2 and SUZ12 are chromatin regulators that suppress SASP

Pancreas vs. Lung TME

Encode_TF_CHIP Encode_and_ChEA_Consensus_TFs_CHIP

- EZH2_B cell
- MYOD1_myocyte
- MAZ_MEL cell line
- POLR2A_cerebellum
- CTCF_C2C12
- SUZ12_CHEA
- SALL4_CHEA
- NFE2L2_CHEA
- CTCF_ENCODE

CCL2

CXCL2

IL-6

CX3CL1

CXCL10

CCL5

CCL20

KPC1 Ren
KPC1 EZH2 2124
KPC1 SUZ12 009a

0 pg/ml
500 pg/ml
1000 pg/ml
1500 pg/ml
2000 pg/ml
2500 pg/ml
3000 pg/ml
3500 pg/ml
4000 pg/ml
4500 pg/ml
5000 pg/ml

KPC1 Ren
KPC1 EZH2 2124
KPC1 SUZ12 009a

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3000 pg/ml
3500 pg/ml
4000 pg/ml
4500 pg/ml
5000 pg/ml
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

Preclinical Pipeline
“Mouse Hospital”

Tramet
Palbo
GSK126
αPD1
αCTLA4

Tumor growth
Metastatic Spread
Survival

p48-Cre;Kras\textsuperscript{G12D/+};p53\textsuperscript{fl/+}
(KPC) GEMM mice
Studying senescence and immune surveillance bypass in other genetic contexts and “cold” tumor types

Prostate cancer

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

Modeling prostate cancer in mice using *in vivo* electroporation

- 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**

- Chemical Library Screens
- HTVI
- EPO-GEMM platform

**Genetics**

- Oncogene
  - MYC
  - AR
  - Pik3ca
- Tumor suppressor
  - sg.p53
  - sg.Pten
  - sg.Rb

**Immune background**

- C57BL/6
- Nu/Nu (Nude)
- NOD-scid IL2Rγnull (NSG)

**Therapeutic Interventions**

- CDK4/6
- αCTLA-4
- αPD-1
- Senescence-inducing therapies
- Immunotherapies
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