Understanding how chronic stress modulates immune activity in the tumor microenvironment

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Stress Tests and Biomarkers of Resilience
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No Disclosures
Increased chronic stress in cancer patients

- Pain, Social Isolation
- Medical bills “financial toxicity”
- Anxiety
- Depression
- PTSD
- Sleep loss
- Uncertainty of the future
- Fear
Systemic stress response is regulated by two major pathways

1. Sympathetic nervous system (SNS)
   - Norepinephrine/Epinephrine bind adrenergic receptors
   - Spinal chord

2. Hypothalamic–pituitary–adrenal axis (HPA)
   - CRH
   - ACTH
   - Glucocorticoids
   - Medulla
   - Paraventricular nucleus
   - Hypothalamus
   - Pituitary
   - Adrenal glands

FIGHT or FLIGHT RESPONSE and psychological forms of stress (anxiety, fear, depression) including thermal stress (hot or cold)
Housing temperature: A useful model system to study the impact of *chronic* adrenergic stress on immuno-oncology

- Kokolus et al., PNAS 2013
- Eng et al., Nat Comm 2015
- Bucsek et al., Can Res 2017
- Mohammadpour et al., JCI 2019
- Chen et al., Nat Comm 2020
- Qiao et al., Can Imm Res 2021
- Mohammadpour et al., Cell Reports 2021

Figure from MacDonald/Choi et al./Repasky
*Trends in Molec. Med.* 2023
Standard housing temperatures induce chronic β-adrenergic stress

Thermoneutral housing (30°C) decreases circulating norepinephrine but does not change core body temperature!

We use several ways to manipulate β-AR signaling in mice

- **Isoproterenol (ISO, 10μM)**
- **Thermoneutral Temperature (TT 30°C)**
- **Standard Temperature (ST 22°C)**
- **Propranolol (PROP, 200μg, i.p.)**
- **Genetic knock out**
Tumor growth is slower in mice housed at 30 °C

Kokolus et al/ Repasky
PNAS, 2013

N = 5 - 6; * p < 0.05, ** p < 0.01, *** p < 0.001, **** p < 0.0001
Mice Housed at TT Develop Fewer Metastatic Tumors

4T1 mouse model
Triple Negative BreCa

Kokolus et al, Repasky
PNAS 2013
Relief from cold stress slows tumor growth rate: This effect is lost in SCID mice.

Kokolus et al, Repasky PNAS 2013
Adrenergic signaling blockade improves tumor growth control at ST: depends on adaptive immune system

Propranolol: pan-β-AR antagonist

Eng et al., Nature Comm. 2015  Bucsek, Qiao et al, Cancer Research, 2017
T-cells isolated from tumors of mice housed at TT have a more “activated” phenotype

Kokolus et al, Repasky PNAS 2013
β-AR stress signaling drives CD8⁺ T cell exhaustion in the tumor microenvironment

Guanxi Qiao, PhD

Qiao et al., Cancer Immunol Res, 2021
Qiao et al., Cancer Immunol Immunother 2019
Inhibition of T cell function by adrenergic signaling is combined with enhanced MDSC survival and function.
Ongoing clinical translation using propranolol in combination with immuno- and/or radio-chemotherapies

Clinical Translation

New Trials
Melanoma: Phase I Trial Gandhi (TII) PI Clin Can Res 2020
Multi-center Phase II Shipra Gandhi, PI
M Myeloma: Phase I/II Trial, Hillengass (PI)
Esophagus: Phase Ib/II Singh, PI;
Esophagus: Phase II Mukherjee, PI

Breast Cancer:
CPI refractory population: Pilot to Phase II (Gandhi, PI) seeking collaborators and funding.

Canine and Human Sarcoma: Phase II, with Cornell Univ Veterinary Hospital (in development

ICI- Bucsek et al., Cancer Res. 2017
Radiation- Chen et al., Nat. Comm, 2019
Chemotherapies- Eng et al., Nature Comm. 2015
SUMMARY: Chronic stress negatively influences cancer treatment outcomes through:

- Suppression of anti-tumor immune activity

These data may contribute to our understanding of how chronic stress leads to more aggressive cancers in patients and to the identification of novel biomarkers in patients in need of greater stress-reducing interventions.

Question? How does chronic stress affect anti-tumor immune function in older individuals compared to those who are younger?
Whatever we accomplish is due to the combined effort.” – Walt Disney

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β2 adrenergic receptor–mediated signaling regulates the immunosuppressive potential of myeloid-derived suppressor cells

The Journal of Clinical Investigation

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**β2-AR signaling increases immunosuppression by MDSCs**

**β2-AR signaling promotes MDSC survival & protumorigenic function**

**T CELL**

**MDSC**

**NE**

**β2-AR**

**IFN-γ**

**CHRONIC STRESS**

(anxiety, pain, depression)

**SYMPATHETIC NERVES**

**SPLEEN**

**TUMOR**

**MDSCs:**

↑ expression of PDL-1 + arginase I

**T CELLS:**

↓ proliferation

↓ IFN-γ production

**APOPTOSIS**

**ANTITUMOR FUNCTION**

**STAT3**

**Bcl-2**

**Arg1**

**PD-L1**

**VEGF-α**

**β2-AR**

**MHC**

**TCR**

**PD-L1**

**FAS**

**FASL**

**MDSC**

**T CELL**

**IFN-γ PRODUCTION**