Stress Induced Re-Programming of Metabolic Pathways in the Tumor Microenvironment: A Mechanism of Immunosuppression?

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sitc Society for Immunotherapy of Cancer
Cancer Immunotherapy CONNECT

Tumor Immune Microenvironment: A Holistic Approach
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San Diego, CA

No financial relationships or disclosures

Increased interest in chronic stress in cancer patients. Many studies from "psychoneuroimmunology" suggest a negative effect on outcome

Pain,
Social Isolation

Uncertainty of the future

Medical bills
"financial
toxicity"

Fear

Anxiety

Sleep loss

Depression

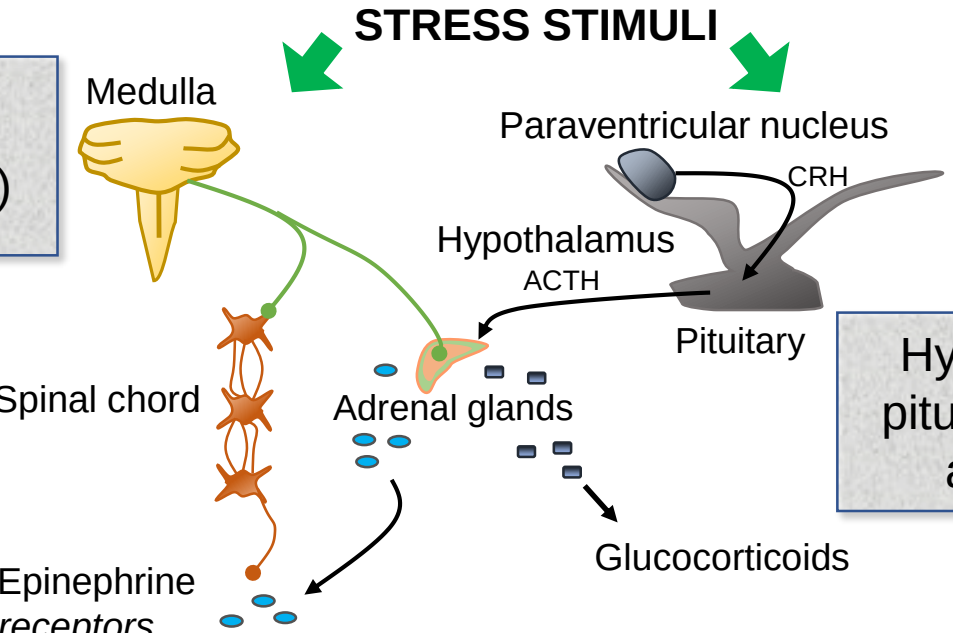
PTSD

Some examples:

Antoni & Dhabhar, 2019, Cancer (review)
Thaker et al. Anil Sood, Nature Med. 2021

Systemic stress response is regulated by two major pathways

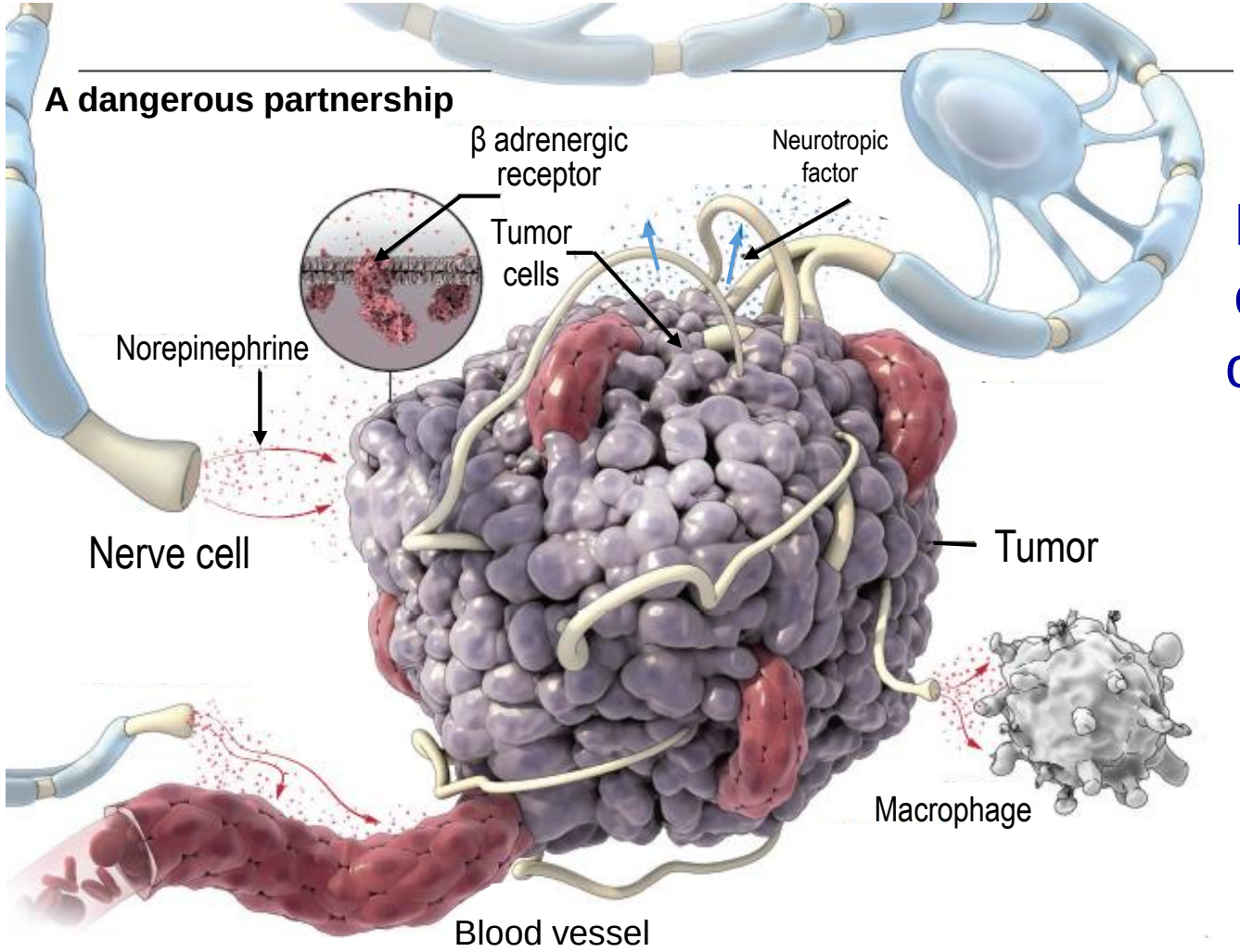
Sympathetic nervous system (SNS)



Hypothalamic–pituitary–adrenal axis (HPA)

Adapted from Verbrugghe et al, Vet Med 2012

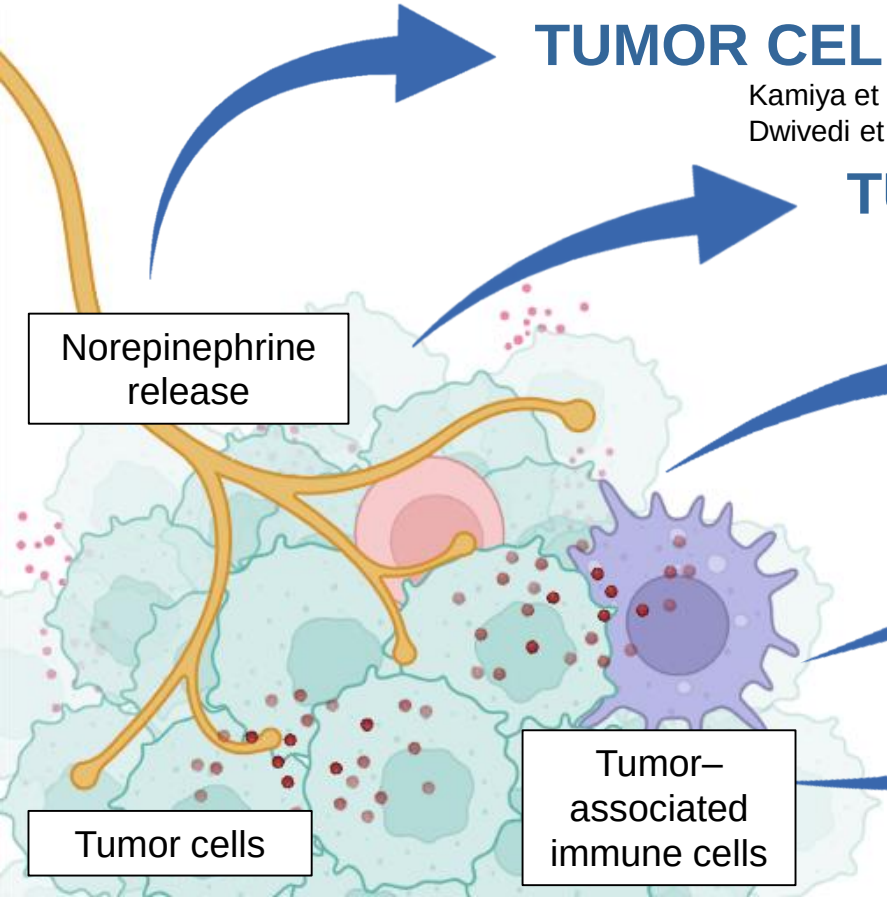
FIGHT or FLIGHT RESPONSE *and psychological forms of stress (anxiety, fear, depression) including thermal stress (heat or cold stress)*



New appreciation of the importance of nerves in tumor progression and metastasis

Servick,
"War of Nerves"
Science 2019

Pro-tumorigenic function of norepinephrine



TUMOR CELL PROLIFERATION & METASTASIS

Kamiya et al. *Nat Neurosci* 2019; Zhang et al. *Cell Death & Disease* 2019; Dwivedi et al., *Cell Death Discov*, 2021

TUMOR CELL SURVIVAL

Wang et al, *Plos One* 2009; **Eng et al. *Nat Commun* 2015**; Dash et al. *Sci Rep* 2021

THERAPY RESISTANCE

Reeder et al. *Br J Cancer* 2015; **Eng et al. *Nat Commun* 2015; MacDonald et al., *Radiat Res.* 2019**; Fjæstad et al., *Oncogene* 2021; **Gandhi et al., *Clin Cancer Res 2021***

IMMUNE ESCAPE

Wang et al, *Plos One* 2012

IMMUNOSUPPRESSION

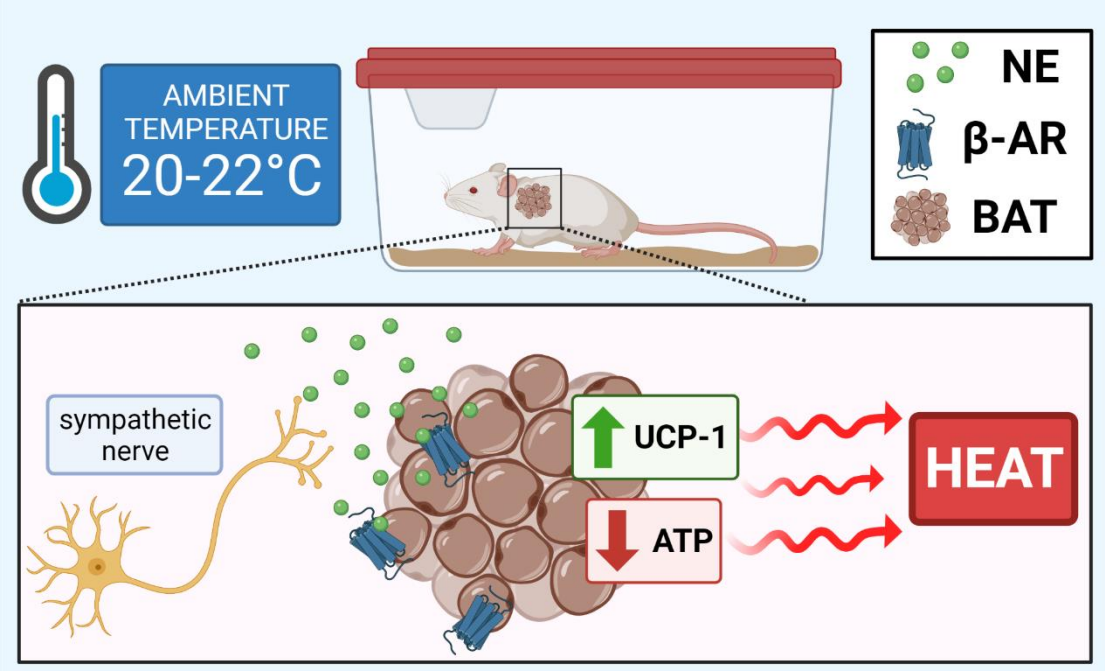
Kokolus et al 2013; Mohammadpour et al., J Clin Invest. 2019; Chen et al., *Nat Commun* 2020; Liu et al., *Nat Commun* 2021; **MacDonald et al. *Cell Immunol* 2021; Mohammadpour et al., *Cell Rep 2021;* Qiao et al. *Cancer Immunol Res., 2021;*** Fjæstad et al., *Oncogene* 2022

Standard ambient temperature (ST) of laboratory animals: a model of chronic β-adrenergic-mediated stress

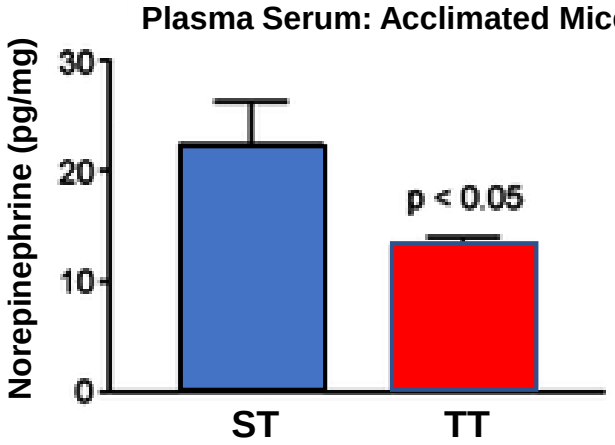
Thermoneutral temperature (TT) is defined by the ambient temperature ($\mathbf{T_a}$) that does not require *additional* metabolic heat production or evaporative processes to regulate core body temperature – for laboratory mice, TT = ~30°C.

Fischer et al. *Molecular Metabolism.* 2017; Bucsek et al., *Cancer Research*, 2017

Standard ambient temperature (ST) of laboratory animals: a model of chronic β-adrenergic-mediated stress



↑ serum norepinephrine (NE) in mice housed at standard temperature (ST) (Eng et al., 2015)



The metabolic drain from adaptive thermogenesis is highly significant!

Eng et al., Nature Comm. 2015; Fischer et al. *Molecular Metabolism.* 2017; Bucsek et al., *Cancer Research*, 2017

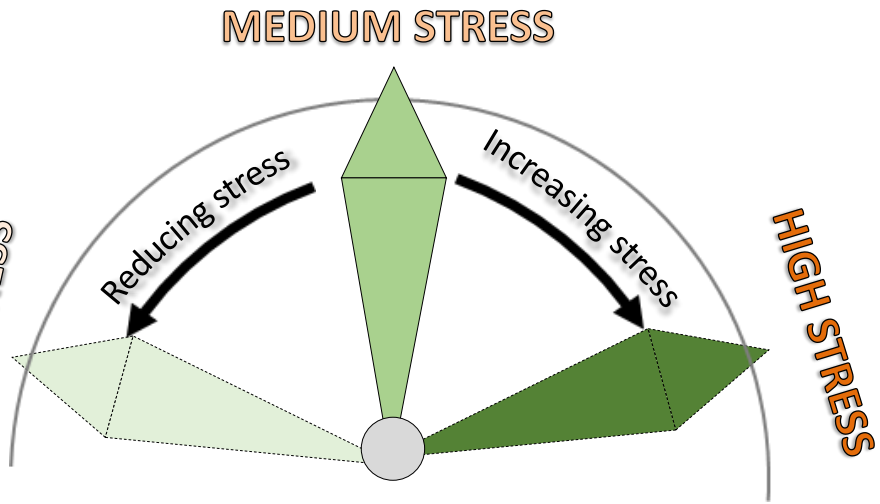
Using standard housing temperature as a model of chronic adrenergic stress

Standard Control Mice are chronically cold stressed (22˚C)

Methods to Reduce Stress

Thermoneutrality 30˚C OR using β-blockers block signaling in mice at 22˚C

Environmental Enrichment



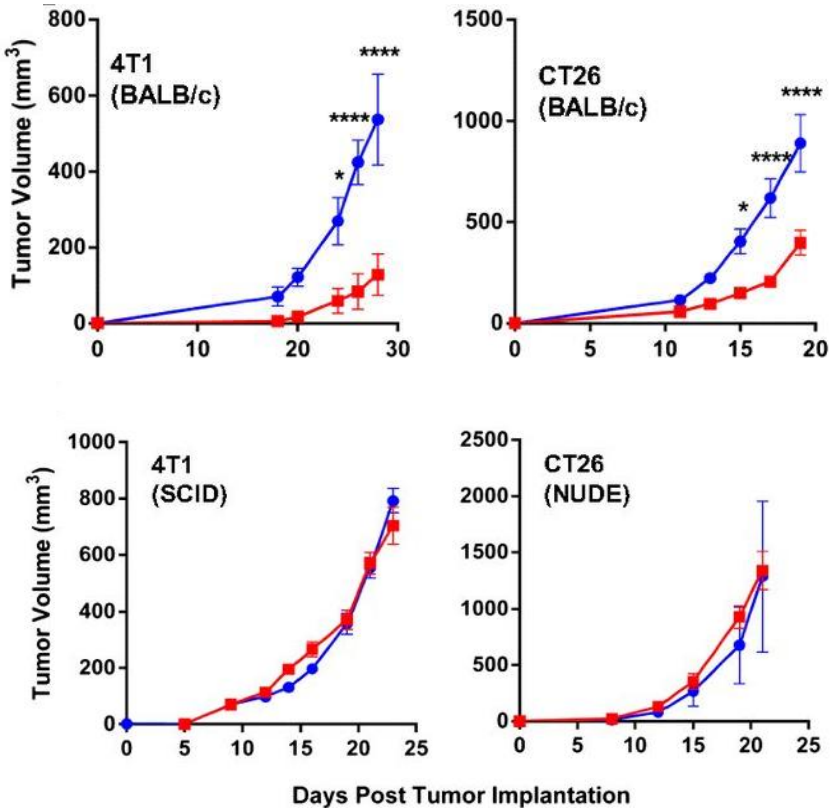
Methods to Increase Stress (acute?)

Restraint: 1-2 hr episodes per day 7-28 days
Social Isolation: house singly
Fear: predator odor, scream
β-AR agonists: isoproterenol- 1-2x/day, 21-54 days
Catecholamine: NE by osmotic pump.

Models impose stress on mice at 22˚C

Hylander, Gordon and Repasky, J. Immunol., 2019

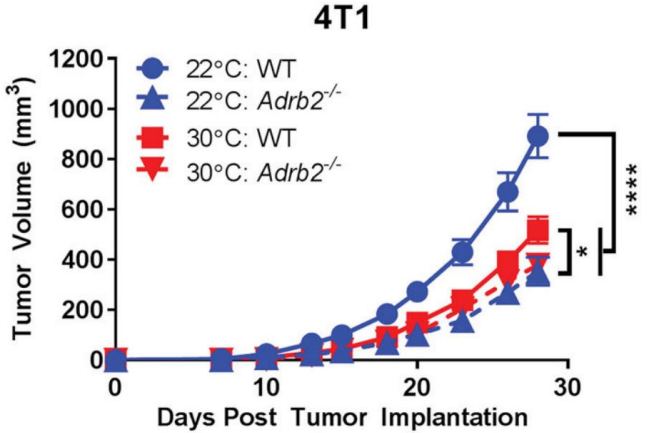
Thermoneutral temperatures (TT) reduce tumor growth



ST (22°C)

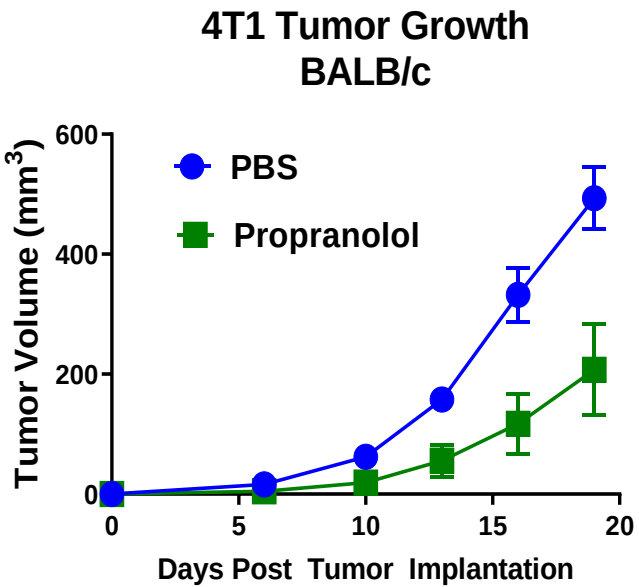
TT (30°C)

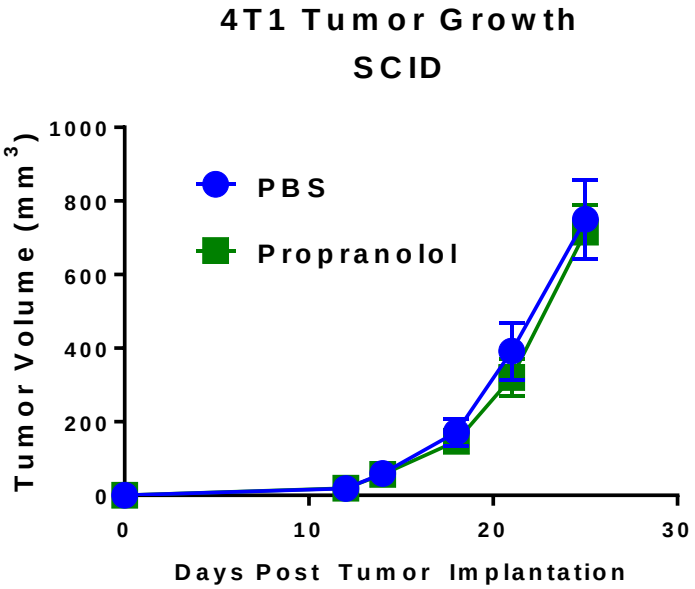
Reduced tumor growth at TT is **immune and β2-AR-dependent**



Kokolus et al. *PNAS*. 2013; Bucsek et al. *Cancer Res*. 2017

Adrenergic signaling blockade in mice housed at ST slows tumor growth: depends on adaptive immune system

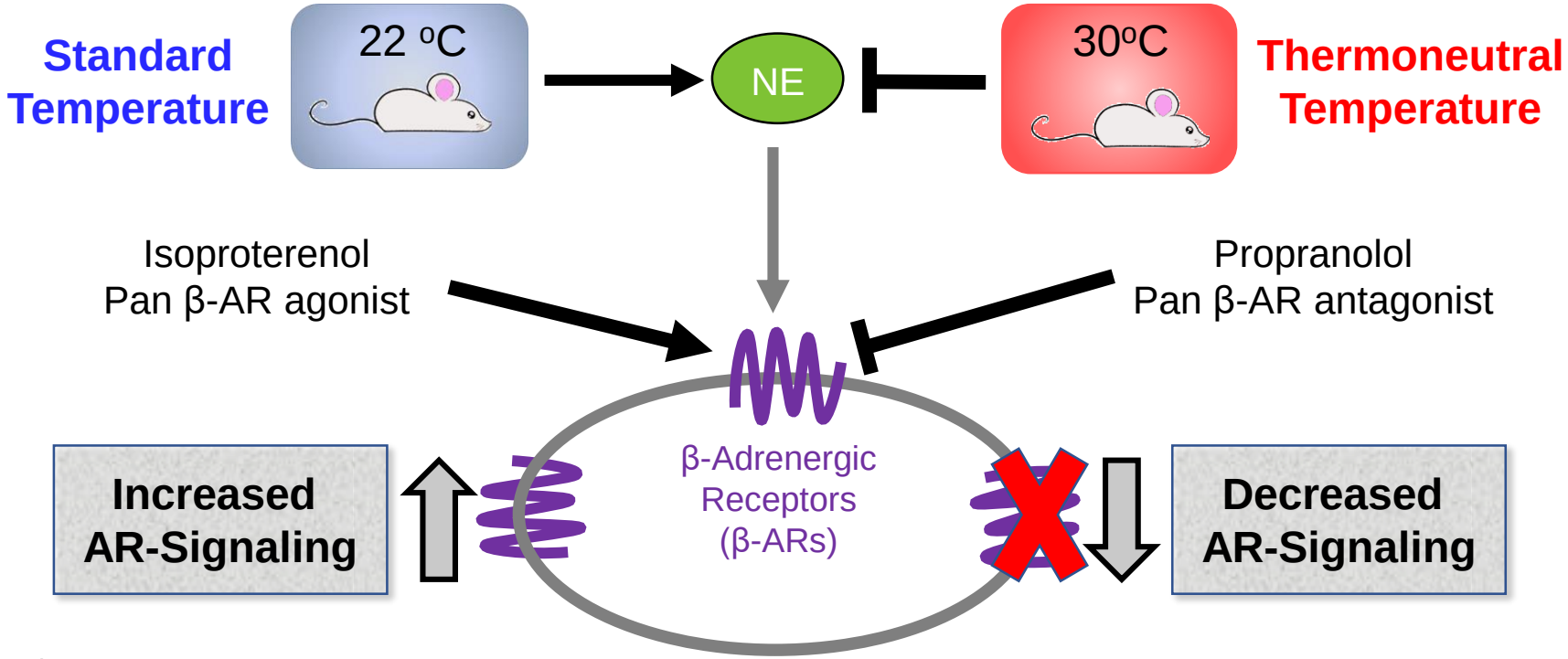




Propranolol: pan- β-AR antagonist

Eng et al., Nature Comm. 2015 Bucsek, Qiao et al, Cancer Research, 2017

Our models for studying the impact of adrenergic stress in on the immune system and the TME

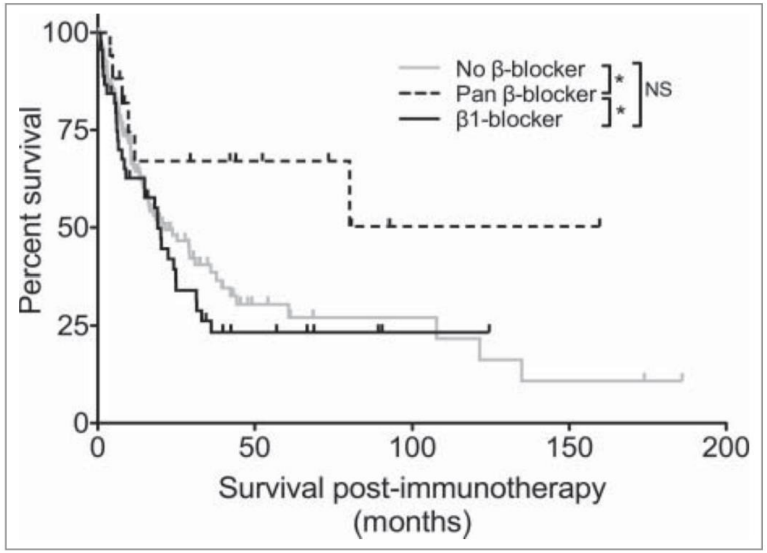


Eng et al., Nat. Comm. 2015;
Leigh/Kokolus et al., J. Immunol. 2015
Mohammadpour et al., J. Immunol. 2017;
Hylander et al., J. Immunol. 2019

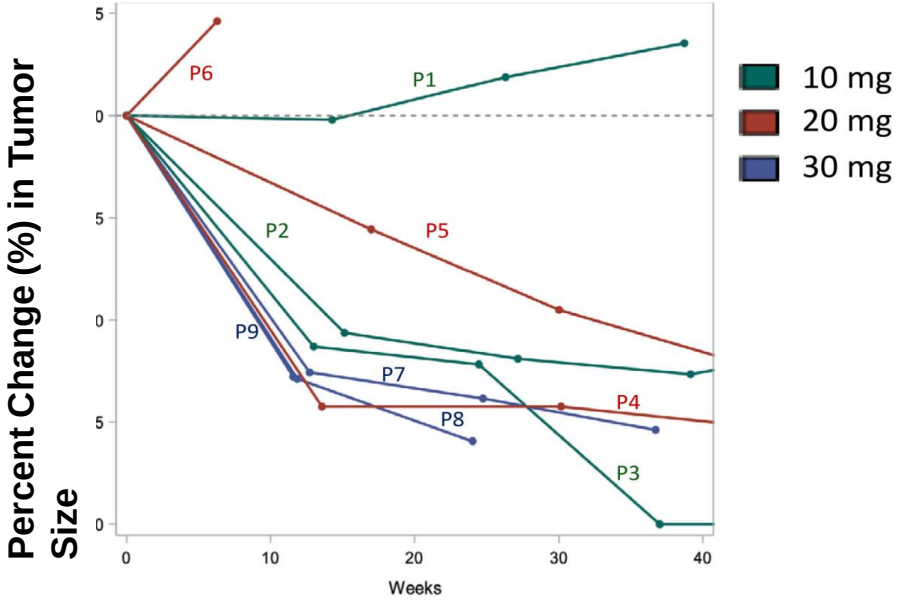
β2-AR KO mice

Balb/c (from Dr. David Farrar)
C57Bl/6 (generated in-house)

Beta-blockers improve patients' response to immunotherapy



Retrospective study: Survival is significantly increased in melanoma patients who received at least one immunotherapy (IL-2, αCTLA-4, αPD-1) and a β-blocker K. Kokolus et al. *OncoImmunology*. 2018

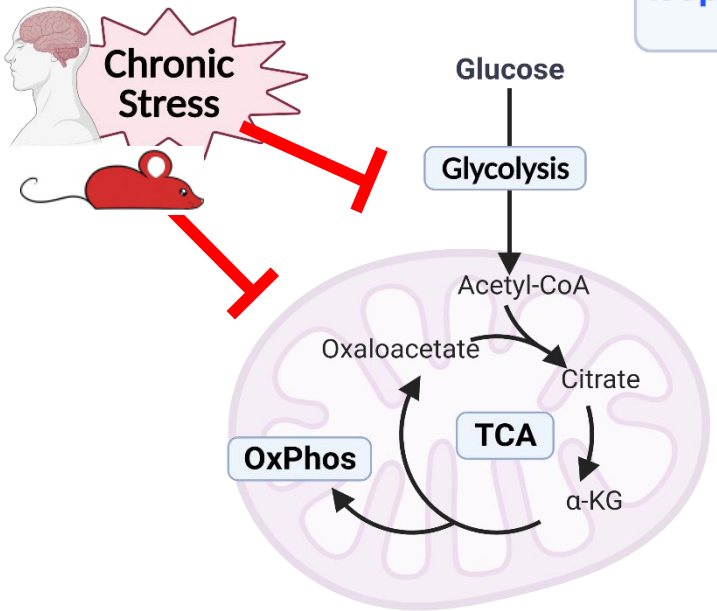


Phase I clinical trial: treatment-naïve patients with unresectable stage III or IV melanoma → pembrolizumab (**αPD-1**) and propranolol (**pan β-blocker**); Objective response rate was 78%; phase II currently ongoing and new trials underway in breast, lung and esophagus cancers. S. Gandhi et al. Clin Cancer Res. 2021

Hypothesis:

Chronic adrenergic stress suppresses anti-tumor immunity/efficacy of immunotherapy through its regulation of metabolic pathways in the tumor microenvironment.

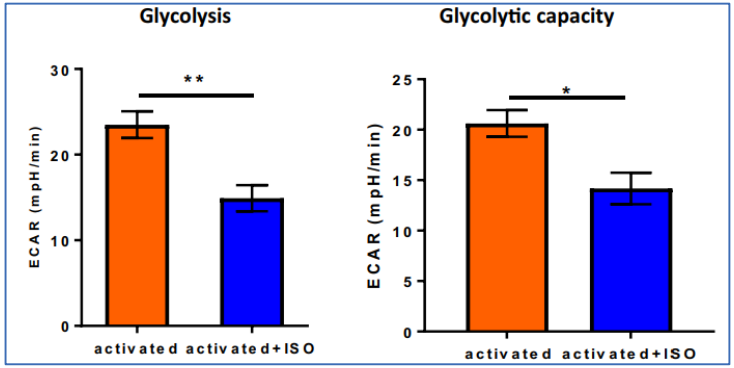
β-AR signaling impairs T cell metabolic reprogramming

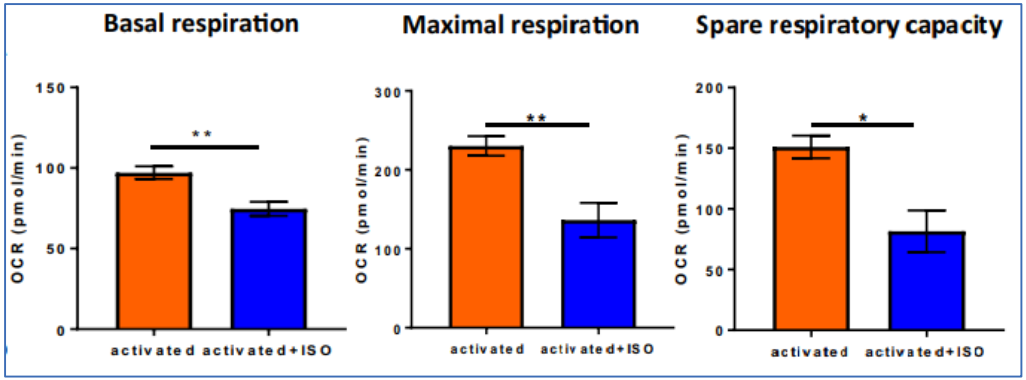


Isoproterenol (iso) → β-AR

Activated

Activated + ISO

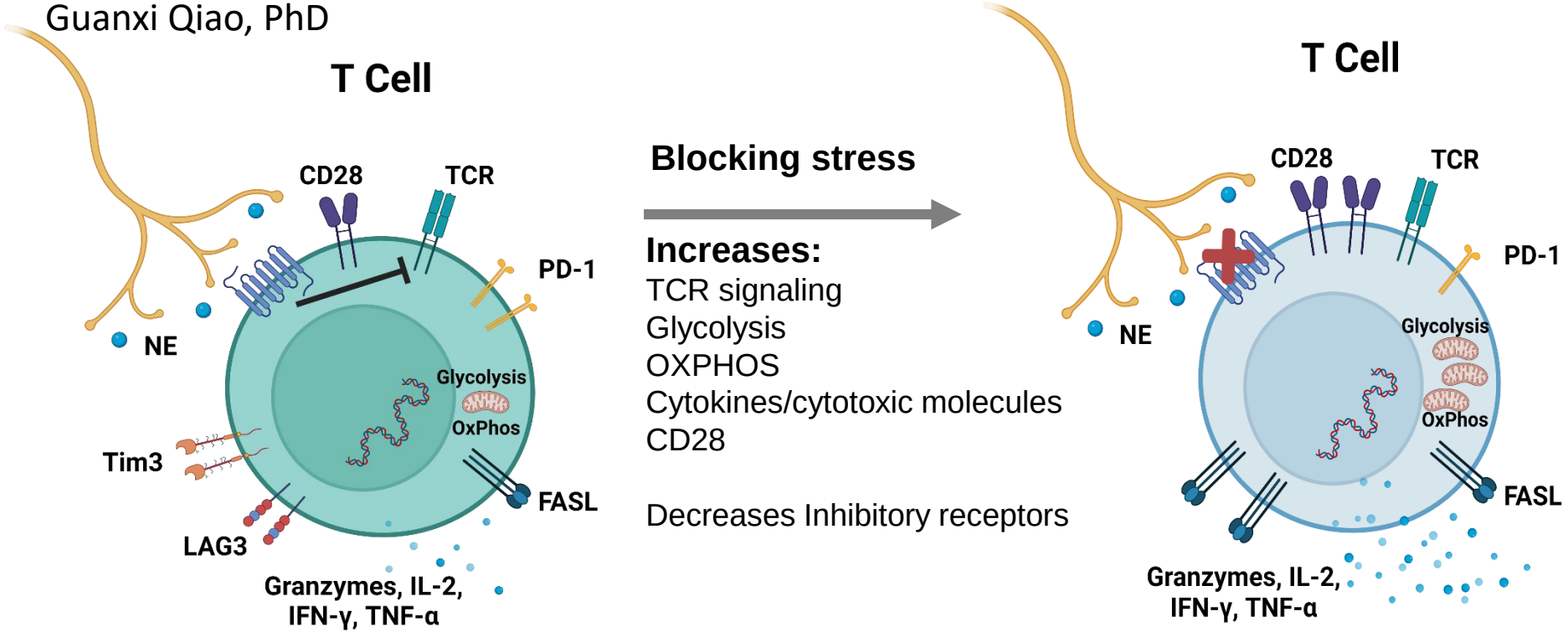




Qiao et al., *Cancer Immunol Immunother.*, 2019;

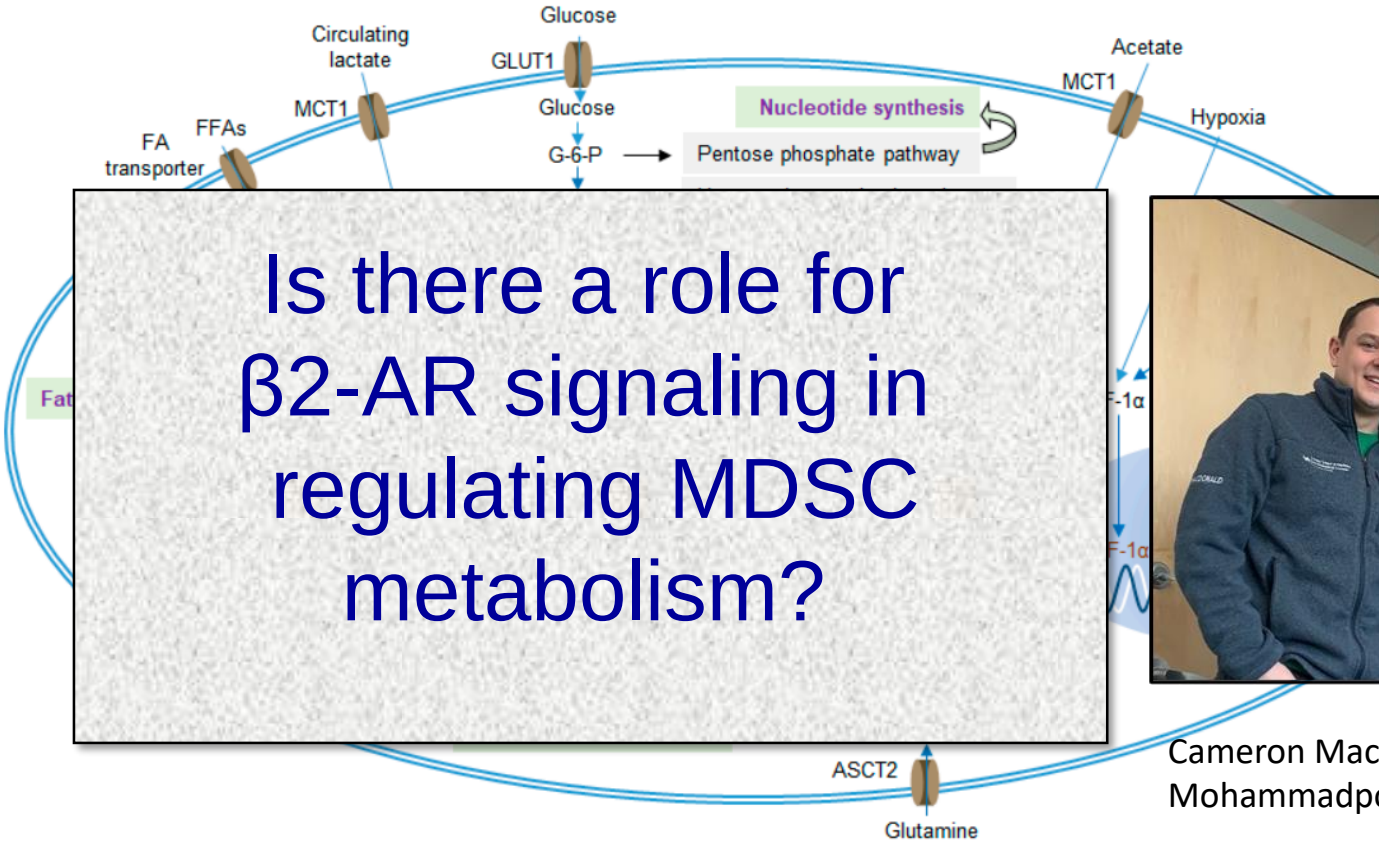
Adrenergic stress suppresses metabolic reprograming and drives exhausted phenotype in CD8^{+} T cells in the TME

Guanxi Qiao, PhD



Qiao G, Cancer Immunol Res. 2021

The metabolic fitness of MDSCs is key to their function

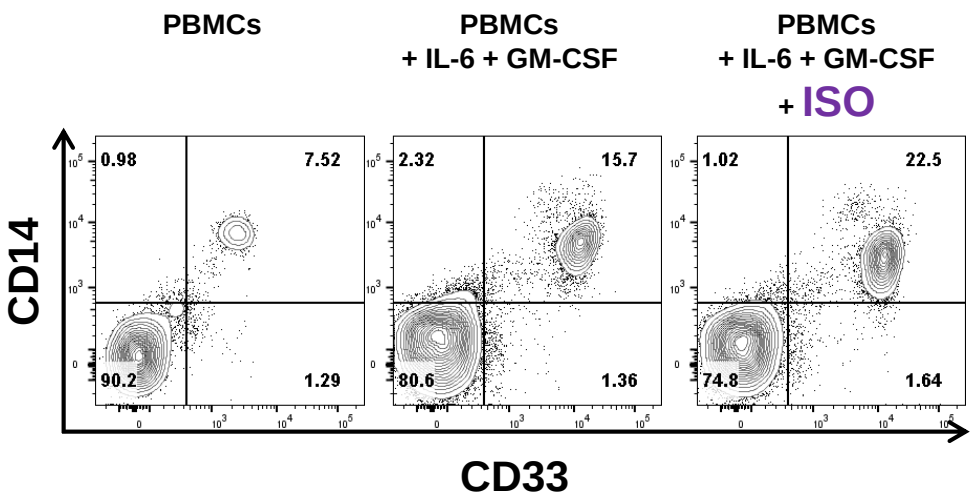


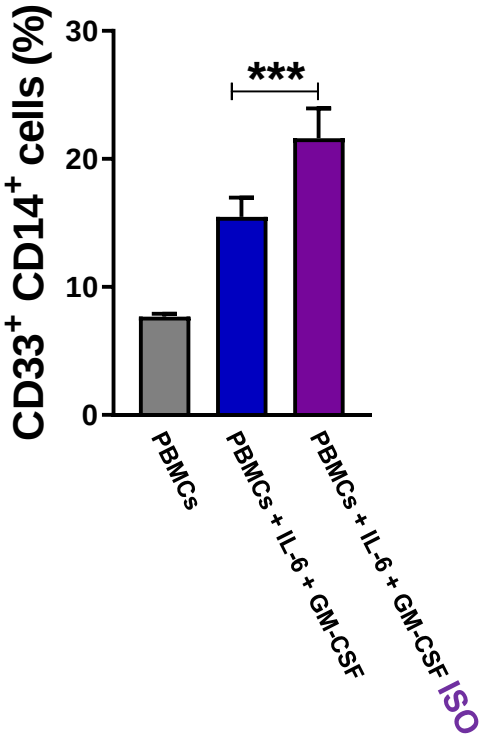
Is there a role for β2-AR signaling in regulating MDSC metabolism?

Cameron MacDonald and Hemn Mohammadpour, VDM, PhD

Wang et al., Cells, 2020

β-AR signaling in human PBMCs promotes MDSC generation



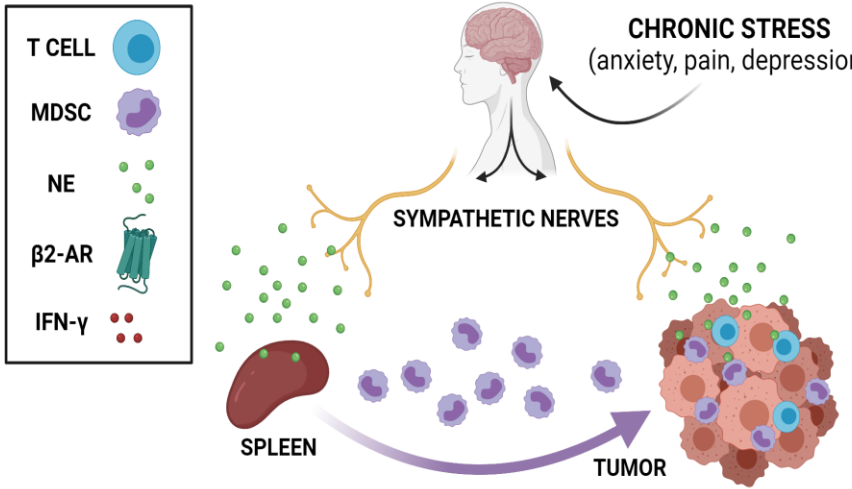


Mohammadpour et al., JCI 2019

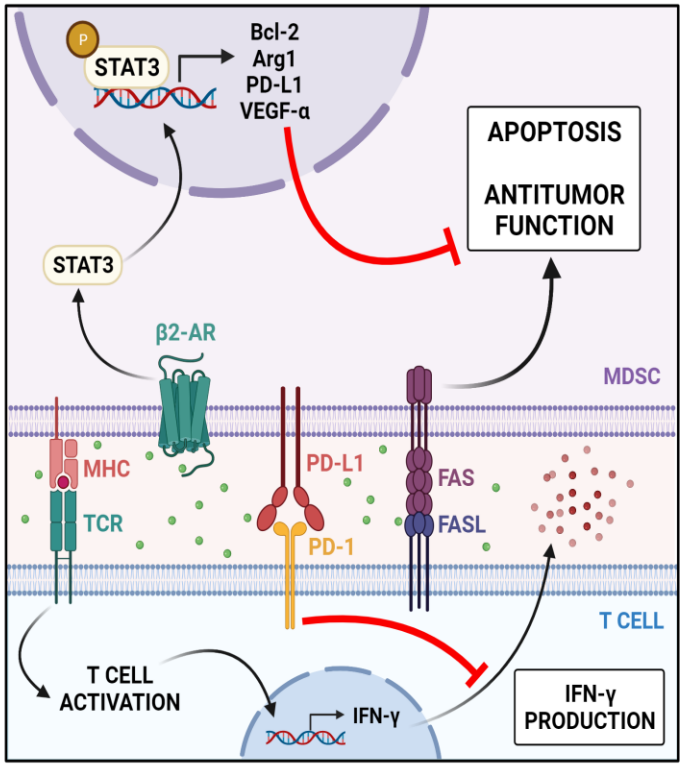
β2 adrenergic receptor–mediated signaling regulates the immunosuppressive potential of myeloid-derived suppressor cells

The Journal of Clinical Investigation

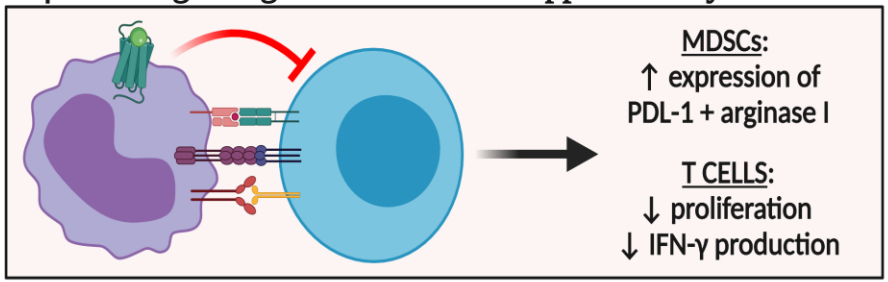
Hemn Mohammadpour,[1] Cameron R. MacDonald,[1] Guanxi Qiao,[1] Minhui Chen,[1] Bowen Dong,[1] Bonnie L. Hylander,[1] Philip L. McCarthy,[2] Scott I. Abrams,[1] and Elizabeth A. Repasky[1]
[1]Department of Immunology, and [2]Department of Medicine, Roswell Park Comprehensive Cancer Center, Buffalo, New York, USA.



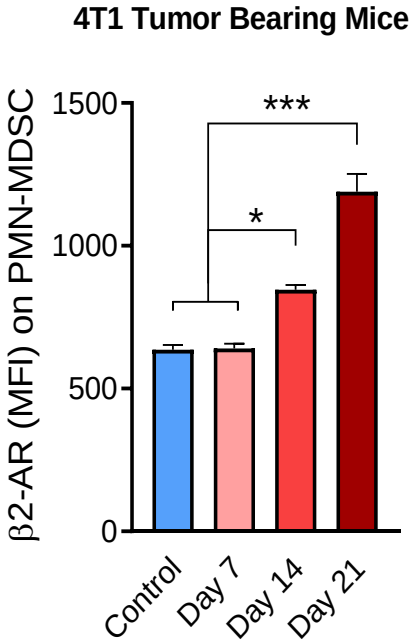
β2-AR signaling promotes MDSC survival & protumorigenic function

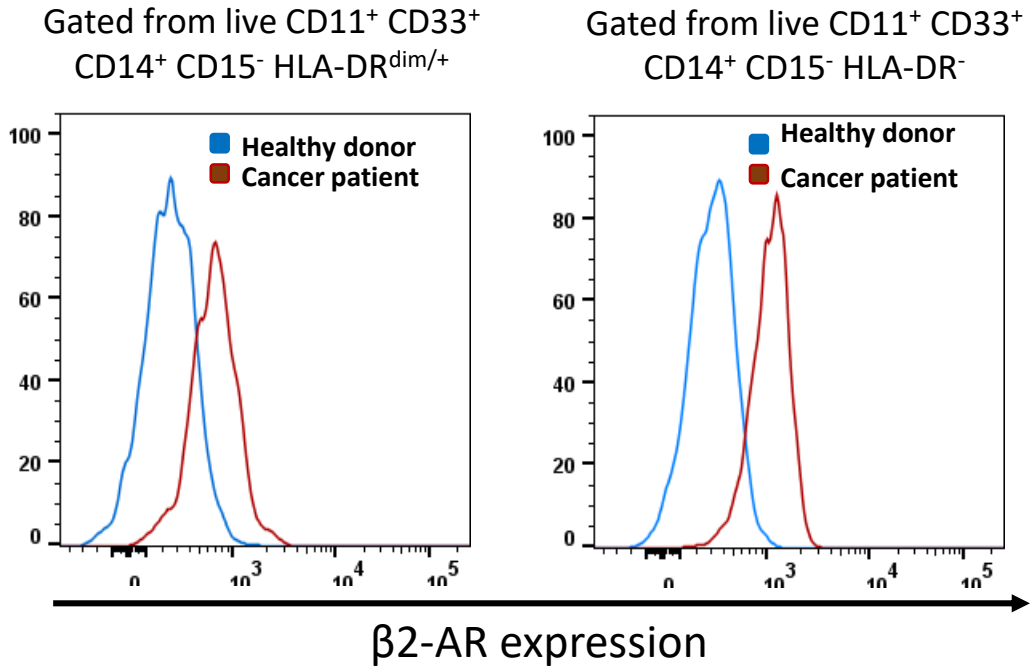


β2-AR signaling increases imunosuppression by MDSCs



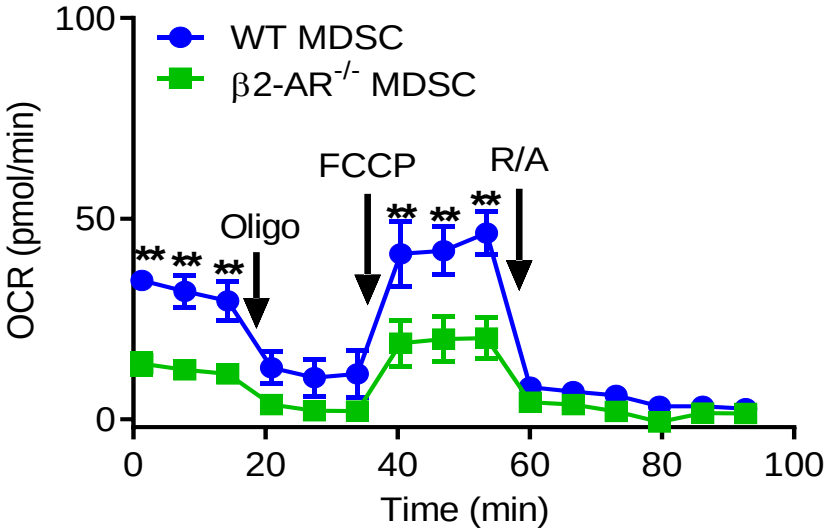
The expression of β2-AR on MDSCs increases in human patients with cancer

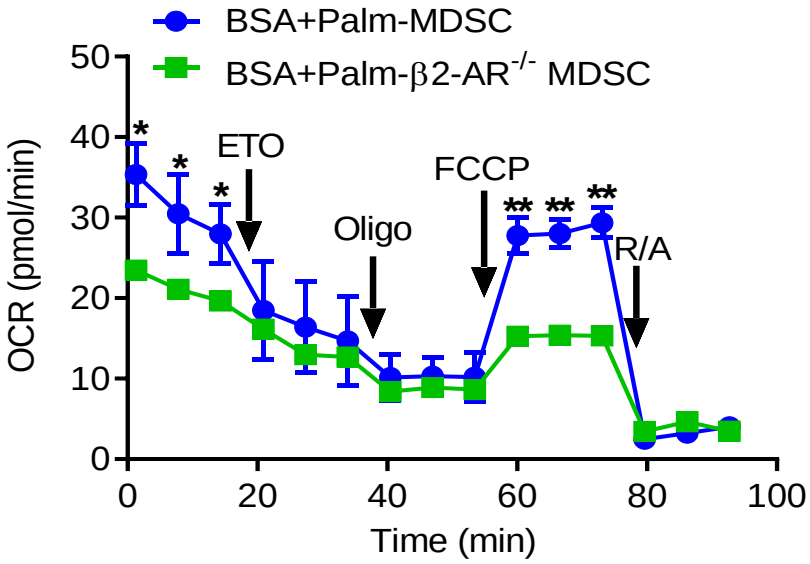




Mohammadpour et al., Cell Reports, 2021

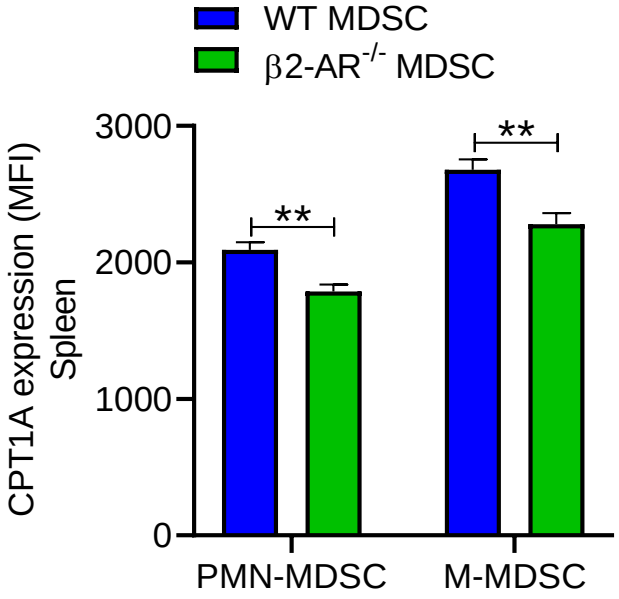
The absence of β2-AR signaling decreases oxidative phosphorylation and fatty acid oxidation in MDSCs



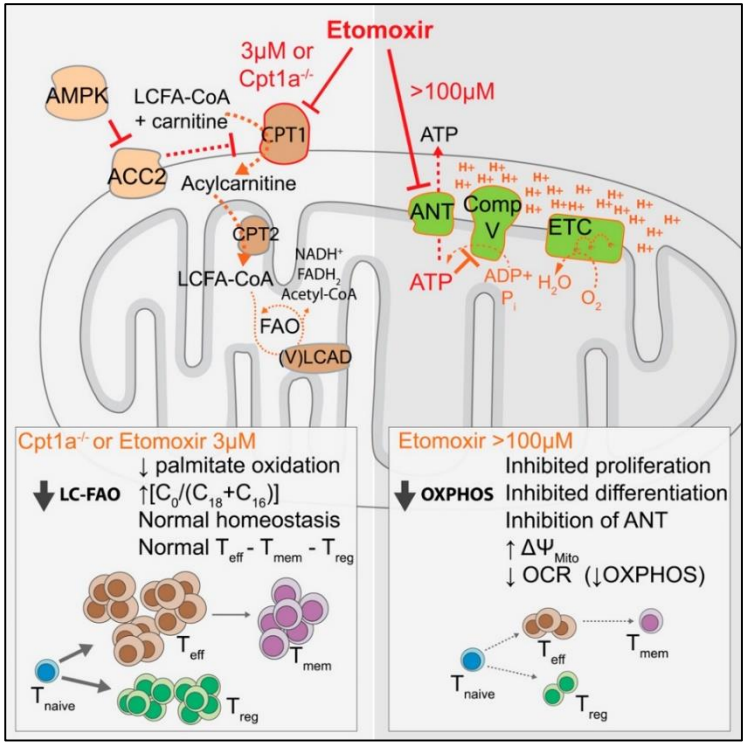


Mohammadpour et al., Cell Reports, 2021

The absence of β2-AR signaling decreases CPT1A expression

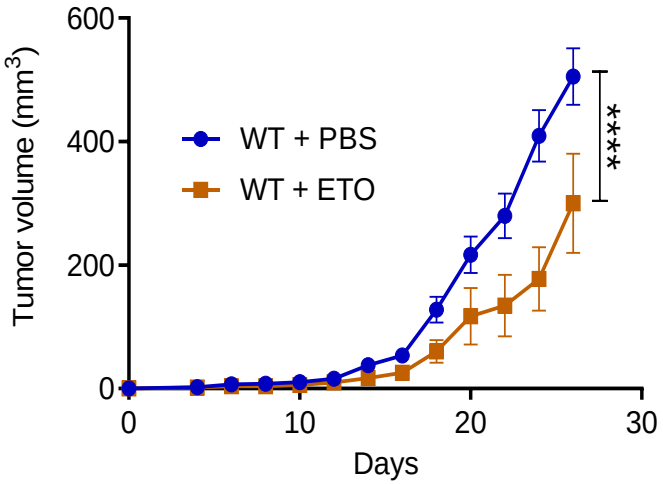


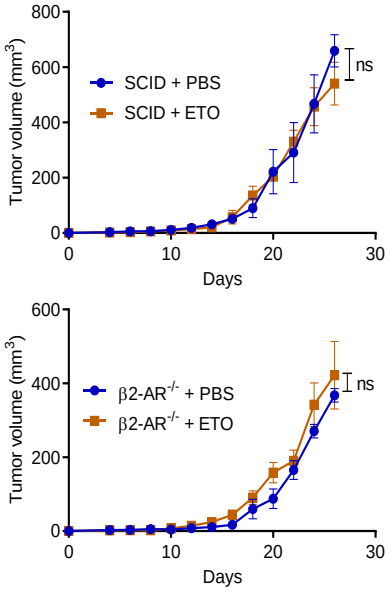
Mohammadpour et al., Cell Reports, 2021

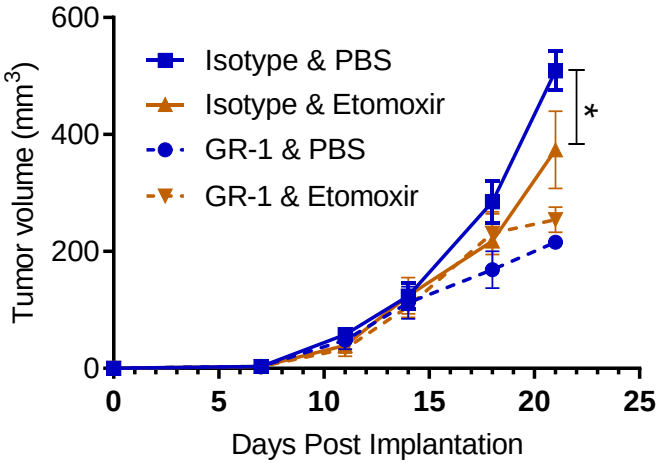


Raud et al., Cell Metabolism 2018

β2-AR signaling enhances FAO and is associated with increased tumor growth



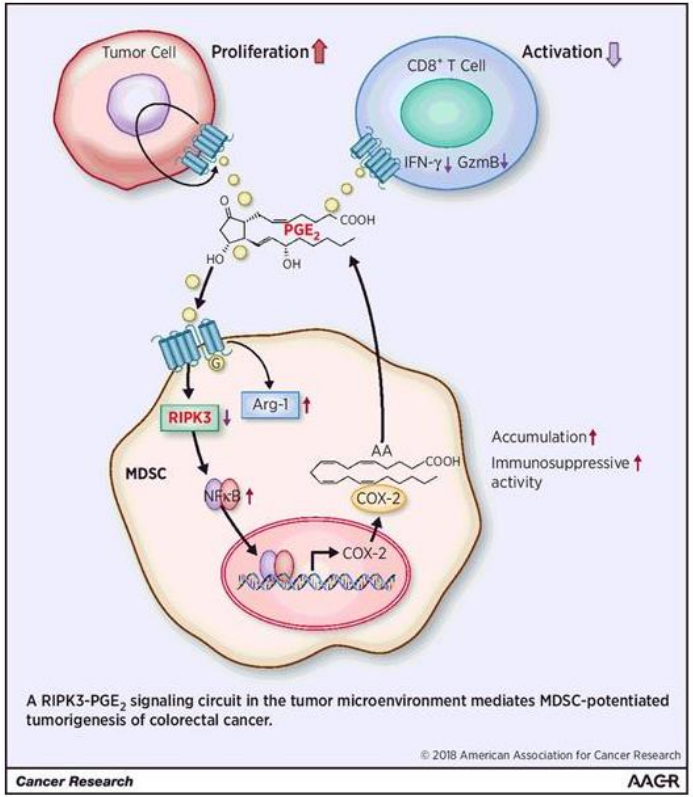




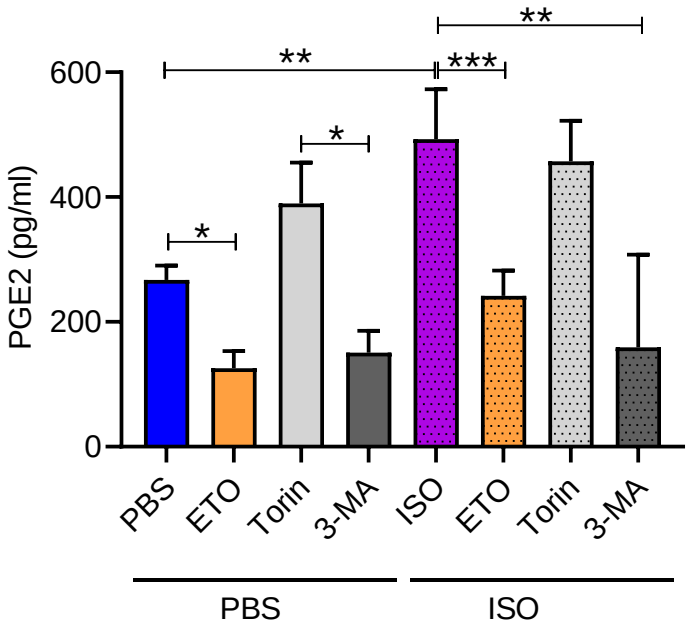
Etomoxir dose:10 mg/kg (10-15μM)

Mohammadpour et al., Cell Reports, 2021

Fatty acid oxidation in MDSCs increases PGE2 production



Veglia et al., Nature 2019
Yan et al., Cancer research 2018
Adeshakin., Cellular Immunology 2021



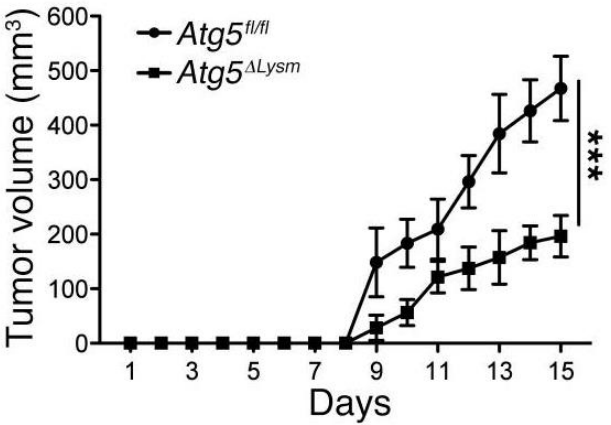
ETO – CPT1A inhibitor

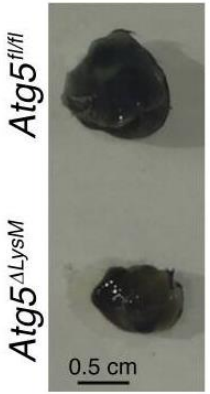
Torin – Autophagy activator

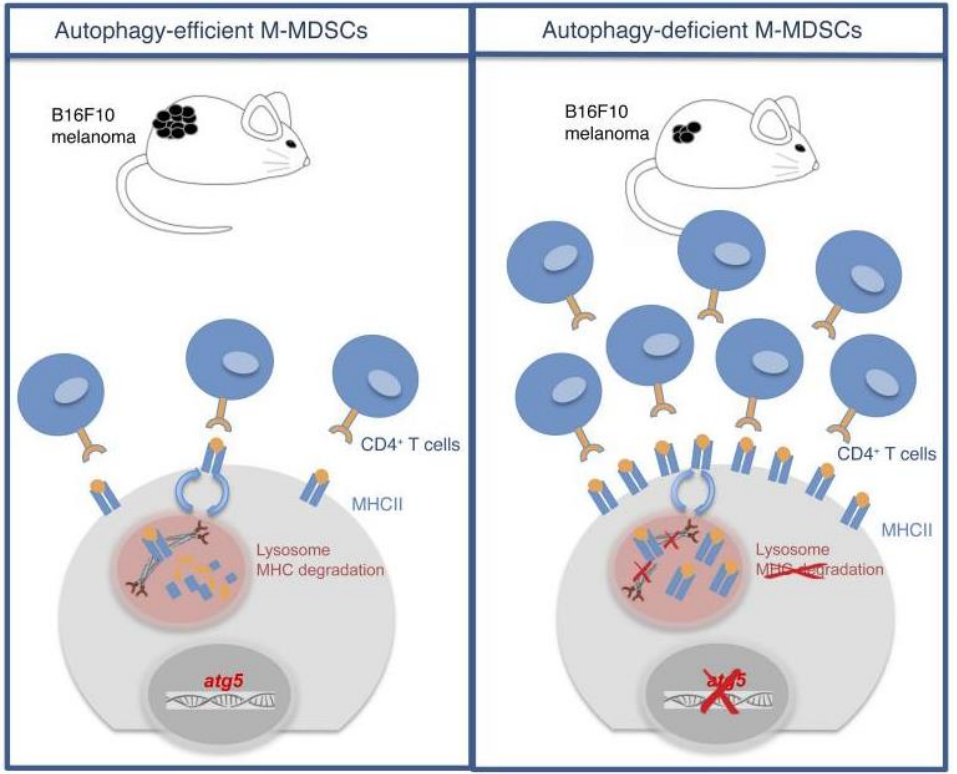
3-MA – Autophagy inhibitor

Mohammadpour et al., Cell Reports, 2021

Autophagy promotes MDSC suppressor functions

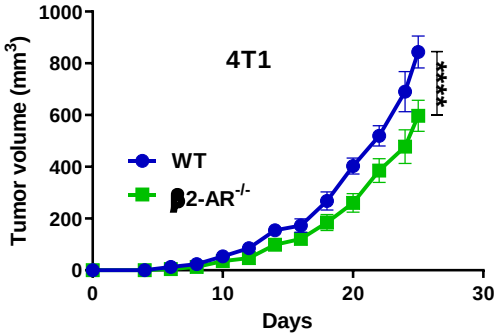


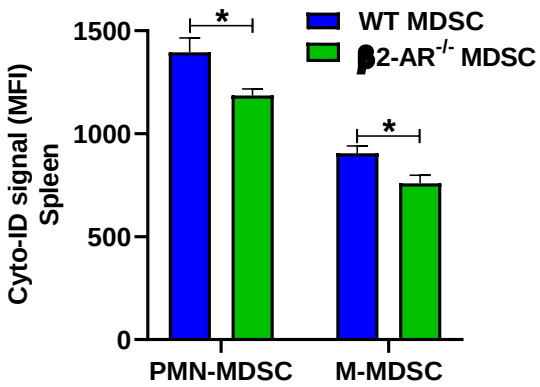


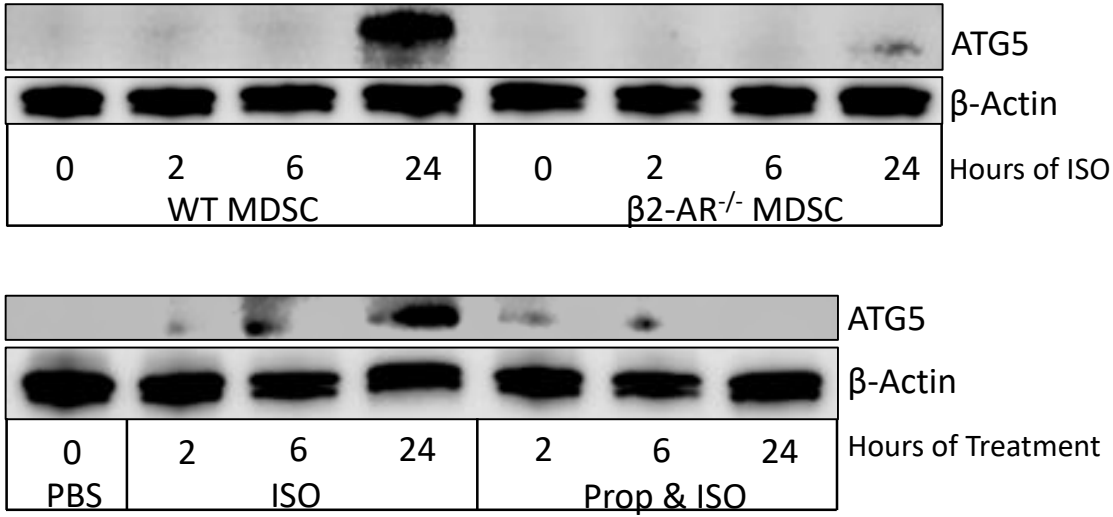


Alissafi and Hatzioannou et al., JCI, 2018

β2-AR signaling increases autophagy



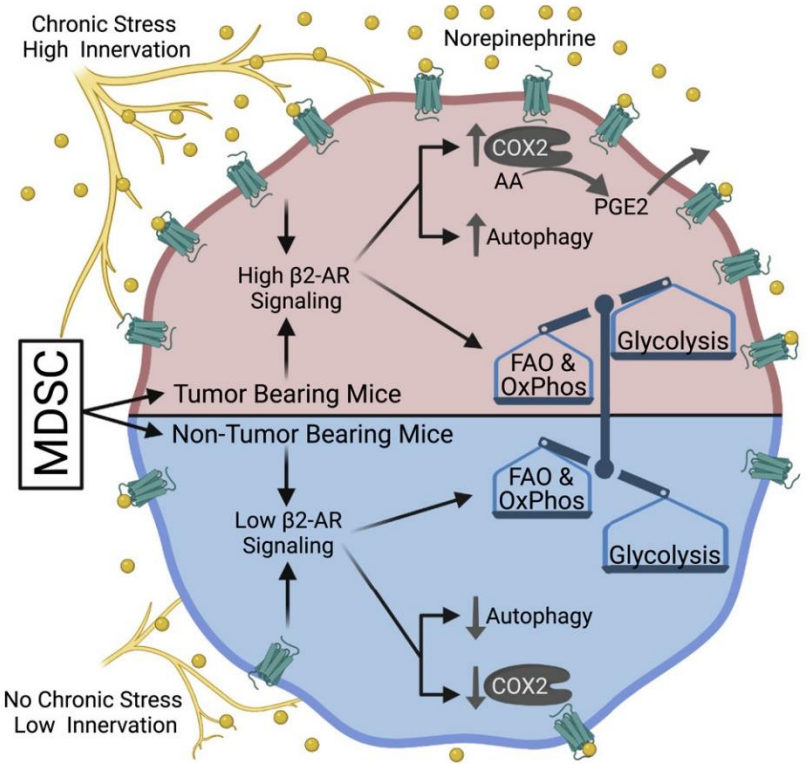




Mohammadpour et al., Cell Reports, 2021

Summary of myeloid derived suppressor cell data

- Tumor progression increases the expression of β2-AR on MDSCs.
- Activation of β2-Adrenergic signaling increases fatty acid oxidation and oxidative phosphorylation.
- Activation of β2-Adrenergic signaling in MDSCs increases autophagy-mediated PGE2 production.



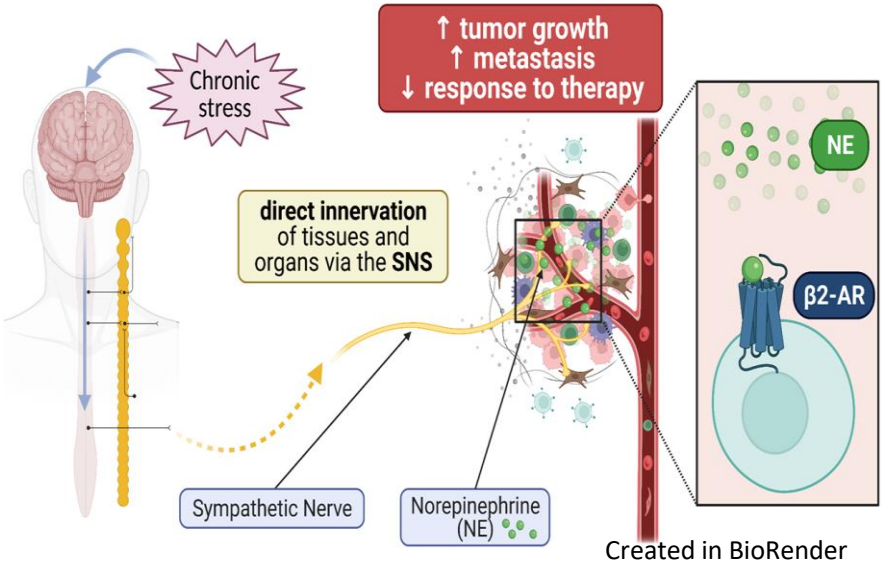
Mohammadpour et al., Cell Reports, 2021

Implications/Discussion Points

- Chronic stress, through the activity of nerves, acts to suppress immune control of tumors through stress-induced T cell exhaustion and enhanced MDSC function in the TME. *Metabolic pathways in immune cells are targeted!*

- *These effects are consistent with an evolutionarily conserved need to conserve energy during the flight or flight response.*

- Chronic forms of stress increase in patients following a cancer diagnosis. Is this negatively affecting their response to therapies because of immune suppression and metabolic changes in the TME?



Return to psychoneuroimmunology! Can we utilize biomarkers associated with stress/norepinephrine activity in the TME as a more precise marker for patients at risk for immune suppression and in need of pharmacological or behavioral stress reduction?

Whatever we accomplish is due to the combined effort.” Walt Disney

Hemn Mohammadpour, VDM, PhD**
Guanxi (Christina) Qiao, PhD
Cameron MacDonald, MSTP program
Sarah Choi, MSTP program
Caitlin James, PhD student
Bonnie Hylander, PhD
Jeanne Prendergast, BS
Minhui (Kate) Chen, PhD (Postdoc)
Alumni:
Maegan Capitano, PhD
Chen-ting (Kelly) Lee, PhD
Katie Kokolus, PhD
Jason Eng, MD, PhD
Mark Bucsek, MD, PhD
Tom Mace, PhD

Scott Abrams, PhD
Phil McCarthy, MD
Scott Olejniczak, PhD

Shipra Gandhi, MD
Manu Pandey, MD
Marc Ernstoff, MD (NIH)
Anurag Singh, MD
Igor Puzanov, MD

Herd of Hope!
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