Stress and β-adrenergic signalling in metastatic processes

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Learning objectives
1. To define the physiological signaling pathways that enhance metastasis.

2. To describe how neural signaling facilitates tumor cell dissemination.

3. To explain how beta-blockers may protect against cancer progression.
Tumor microenvironment

Exposure

- infections
- psychosocial
- inflammation
- chemicals
- environment

Adapted from Antoni et al., 2006 Nature Cancer Reviews & R&D systems website
Exposure

Whole body physiology

Tumor microenvironment

Adapted from Antoni et al., 2006 Nature Cancer Reviews & R&D systems website
What is the impact of physiological SNS signaling on breast cancer?

66cl4 mouse mammary adenocarcinoma
MDA-MB-231HM TNBC
4th left mammary fat pad
In vivo bioluminescence imaging of cancer progression

Day 1
1 x 10^5 cells

Day 12

Day 20

Day 24

Day 28

Ex vivo

LN
Lung
Chronic stress impacts breast cancer progression
Chronic stress impacts breast cancer progression

Sloan et al. (2010) Cancer Research
Chronic stress impacts breast cancer progression

Sloan et al. (2010) Cancer Research
Ex vivo imaging 28 days after inoculation

- Exposome impacts TME
Which physiological signaling pathways enhance metastasis?

How does SNS signaling facilitate tumor cell escape?

Does SNS neural signaling impact other tumor types?
SNS neurotransmitters signal through β-adrenergic receptors

**Diagram:**
- β-blockade
  - X * catecholamine
  - Adenylyl cyclase
  - ATP → cAMP
  - PKA
  - Gene transcription

**Luciferase activity (photons/sec × 10^6):**
- Control
- β-blocker
- Stress
- Stress + β-blocker

**Graph:**
- Distant metastasis
- p < .0001

**Image:**
- Control
- β-blocker
- Stress
- Stress + β-blocker

Sloan et al. (2010) Cancer Research
SNS neurotransmitters signal through β-adrenergic receptors

β-blockade

β-adrenergic receptor  ATP  cAMP  PKA

Adenylyl cyclase

cAMP

PKA

CREB  ATF

Gene transcription

Metastasis-free survival

β-blocker treated, n = 43

other patients, n = 423

Powe et al., Oncotarget 2010.
Which beta-blocker to use?

Breast cancer-specific mortality

Propranolol

Atenolol

Barron, JCO, 2011 Jul 1;29(19):2635-44
Distant metastasis

Control  Saline  Non-selective β-antagonist  β1-antagonist  β2-antagonist

Stress

Metastasis x10^8 photons

Control  Stress

Ming Chai
Stress modulates primary tumor gene expression

Metastasis

Macrophage recruitment

M2 polarization

Sloan et al. (2010) Cancer Research
β-AR regulation of tumor-associated macrophages

Sloan et al. (2010) Cancer Research
β-AR regulation of tumor-associated macrophages

Control  Stress  Stress + GW2580*

*SF1R/M-CSF receptor antagonist

Sloan et al. (2010) Cancer Research
Neural signaling makes macrophages pro-metastatic

• BMDM

M2 polarization

Metastasis

Matthew Pimentel
Which physiological signaling pathways enhance metastasis?
  Neural pathways - βAR signaling
  Tumor side – M2 myeloid recruitment

How does SNS signaling facilitate tumor cell escape?
Stress impacts pathways of tumor cell dissemination

- Dependent on macrophage recruitment

Sloan et al. (2010) Cancer Research
Stress impacts pathways of tumor cell dissemination

Circulating tumor cells

![Cultured CTC](image.png)

Ming Chai, Ben Finnin
Stress impacts pathways of tumor cell dissemination

Lyve-1 immunostaining (% area)

Lymphatic vessel density

Control

Stress

Caroline Le
Stress impacts pathways of tumor cell dissemination
Stress impacts pathways of tumor cell dissemination

In vivo
Ex vivo

Control Stress Stress + Propranolol
Luciferase activity X10^7 photons/sec
Axillary lymph node metastasis

Caroline Le
Which physiological signaling pathways enhance metastasis?

- Neural pathways - βAR signaling
- Tumor side – M2 myeloid recruitment

How does SNS signaling facilitate tumor cell escape?

- Angiogenesis & lymphangiogenesis

Does SNS neural signaling impact other tumor types?
Stress accelerates pancreatic cancer progression

Control

Stress

Primary tumor

Corina Kim-Fuchs
Stress impacts pancreatic cancer

6 weeks, Panc-1

Corina Kim-Fuchs
SNS accelerates hematopoietic malignancy

Don Lamkin

14 day Nalm-6 pre-B ALL

Lamkin et al., Brain, Behav, Imm 2012
SNS accelerates hematopoietic malignancy

Don Lamkin

Control

Stress

Stress + Propranolol

14 day Nalm-6 pre-B ALL
Lamkin et al., Brain, Behav, Imm 2012
Which physiological signaling pathways enhance metastasis?

Neural pathways - βAR signaling
Tumor side – M2 myeloid recruitment

How does SNS signaling facilitate tumor cell escape?

Angiogenesis & lymphangiogenesis

Does SNS neural signaling impact other tumor types?

Other solid tumors
Hematopoietic malignancies
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