Cornell Center on the Physics of Cancer Metabolism

Claudia Fischbach-Teschl, Meinig School of Biomedical Engineering, Ithaca
Lew Cantley, Meyer Cancer Center, New York

http://psoc.engineering.cornell.edu
Organizing framework of Cornell PSOC

DelNero, Hopkins, Cantley, Fischbach, Sci. Transl. Med. 10, 2018
More than one-third of US adults are obese.
Obesity is associated with increased risk for cancer and worse prognosis.

Seo B. et al., Science Translational Medicine 2015
Obesity-associated ECM stimulates breast cancer malignancy in a mechanoresponsive manner

Seo B. et al., Science Translational Medicine 2015

Wittmann K et al., under revision
Does obesity-associated ECM affect cancer stem cells (CSCs)?

- Expression of stem cell markers (NANOG, SOX2, OCT4, ALDH)
- Self-renewal capabilities
- Therapy resistance and metastasis

Pattabiraman & Weinberg, Nat. Reviews Drug Discovery (2014)

Seo et al. Sci Transl Med. 2015
Obesity-associated ECM increases cancer stem cell characteristics in cell lines and PDX spheroids

- Stem cell maintenance
- Self-renewal
- Tumor aggressiveness
- Poor clinical outcome

Thiagarajan PS, ... Reizes O, Stem Cells. 2015

Wittmann K et al., under revision

Cornell PSOC
Physics of Cancer Metabolism
Obesity-associated ECM increases cancer stem cell characteristics in cell lines and PDX spheroids

NANOG expression (SOX-2, OCT-4):
- Stem cell maintenance
- Self-renewal
- Tumor aggressiveness
- Poor clinical outcome

Thiagarajan PS, … Reizes O, Stem Cells. 2015

Lean ECM

Obese ECM

ALDEFLUOR assay

Black: Lean ECM  
Red: Obese ECM

Wittmann K et al., under revision

CornellPSOC
Physics of Cancer Metabolism
Obese ECM modulates cancer stem cell characteristics by interfering with stiffness sensitivity.
Increased stiffness of polyacrylamide substrates decreases cancer stem cell (CSCs) characteristics.
MDA-MB231 xenografts co-implanted with obese vs. lean ASCs have more peripheral fibrosis that coincides with NANOG immunoreactivity.
Obesity-associated ECM remodeling promotes invasion

A microfluidic device for precise control of confined migration (Lammerding lab)

Mouse embryonic fibroblast expressing mCherry-Histone H4 and GFP-actin migrating through a 3 × 5 µm² constriction
Physical stress can result in transient nuclear envelope rupture and exposes genomic DNA to the cytoplasm.

MDA-MB-231 breast cancer cells expressing NLS-GFP and histone H2B-RFP.

HT1080 fibrosarcoma cell expressing NLS-GFP and cGAS-RFP.

Denais, Gilbert, Isermann et al. Science (2016)
Exposure of genomic DNA to cytoplasm activates cGAS-STING pathway and promotes metastasis

Depletion of mitotic centromere-associated kinesin (MCAK) → Formation of micronuclei, chromosomal instability → Nuclear envelope breakdown of micronucleus → Activation of cGAS-STING pathway

Non-canonical NF-κB signaling → Increased metastasis

Collaboration Cantley, Lammerding Labs

Exposure of genomic DNA to cytoplasm activates cGAS-STING pathway and promotes metastasis

Depletion of mitotic centromere-associated kinesin (MCAK) → Formation of micronuclei, chromosomal instability → Nuclear envelope breakdown of micronucleus → Activation of cGAS-STING pathway

Overexpression of lamin B2 prevents nuclear envelope rupture and reduces metastasis.

Overexpression of lamin B2 prevents nuclear envelope rupture and reduces metastasis.

Increased metastasis

Exposure of genomic DNA to cytoplasm activates cGAS-STING pathway and promotes metastasis

Depletion of mitotic centromere-associated kinesin (MCAK) → Formation of micronuclei, chromosomal instability → Nuclear envelope breakdown of micronucleus → Activation of cGAS-STING pathway → Non-canonical NF-κB signaling → Increased metastasis.

Depletion of STING prevents cGAS-STING pathway activation and reduces metastasis.

Exposure of genomic DNA to cytoplasm activates cGAS-STING pathway and promotes metastasis.

Depletion of mitotic centromere-associated kinesin (MCAK) 
Formation of micronuclei, chromosomal instability

Depletion of STING prevents cGAS-STING pathway activation and reduces metastasis.

Current and Future Directions: Developing Experimental Therapeutics

Englander Institute for Precision Medicine, Sequencing

Biobanking → Organoids

Drug screening

Image-guided tumor biopsy

Mouse models

Clinical trials

Analysis in microdevices

CornellPSOC: Physics of Cancer Metabolism