# The role of the extracellular matrix in cancer metastasis

Ramray Bhat, Fellow, Indian Alliance DBT Wellcome Trust EMBO Global Investigator Developmental Biology and Genetics Bioengineering Indian Institute of Science

> Flags, Landscapes and Signalling IMSc Chennai

> > May 8<sup>th</sup> 2024

ramray@iisc.ac.in

@ramrayB

### Cancer and tissue specificity and architecture







invasive cancerous

non-transformed

non-invasive cancerous

Loss of pattern or transformation of pattern? -

Bhat and Bissell, *WiRES Dev Biol*, 2014 Pally and Bhat, *J Biosci*, 2016



Early migration from primary focus





Intravasation into endothelial/mesothelial environments







Intravasation into endothelial/mesothelial environments What novel rules of cell-ECM interactions govern the kinetics of metastasis?



Migration within fluid environments

Pally et al *Phys Biol*, 2022



Early migration from primary focus

Front Physiol Biophys, 2019; J Clin Med, 2019; Angew Chem, 2020; ACS Central Sci, 2021; J Theor Biol, 2021; Anal Chim Acta, 2021; ACS Chem Biol 2022; Comp Sys Oncol, 2023; Biophys J, 2024; patent 2021





Patent, 2024

Intravasation into endothelial/mesothelial environments





How do spheroids survive confined travel?

# Morphological heterogeneity in cancer



Jimpi Langthasa

### Grape-like structure of early (24 hours) OVCAR3 spheroids



### Smooth outer surface of mature (1 week) OVCAR3 spheroids



### Relocalisation of matrix proteins was observed in blastuloid spheroids





Langthasa et al, Life Sci All, 2021

### Moruloid spheroids express fibronectin





### Blastuloid spheroids are more stable in structure than moruloid spheroids



### Basement matrix helps in maintaining blastuloid spheroids

# B

Collagenase treatment leads to loss of lumen

Removal of collagenase leads to restoration of lumen



## How do spheroids form?



Jimpi Langthasa

# Why heterogeneity in spheroid formation?

### Cancer ecological tradeoffs



Moruloid spheroids adhere faster onto peritoneal surfaces

### Moruloids are viscoplastic; blastuloids are elastic





P=0.01



Dutt et al BioRxiv, under revision Lif Sci All



What determines colonization of cancer cells in new stromal locales?





Spheroid settling on mesothelial cells

### Presence of senescent mesothelia encourages ovarian cancer attachment and growth

150**-**

100-

50-

SKOV-3 cells/field

P = 0.0020

cont.

sen.





-3/Me<sup>-</sup> SKOV





Thapa et al, Cell Mol Lif Sci, 2023

### 19

### SKOV-3 on cont. MeT-5A



### SKOV-3 on sen. MeT-5A



Ovarian cancer cells preferentially attach closer to senescent mesothelia and extrude it



### Computer models predict proximity and higher adhesion for mesothelial extrusion







Higher adhesion of cancer cells close to senescent mesothelia is mediated through its ECM



Thapa et al, Cell Mol Lif Sci, 2023



Bi





(at 20ug/mL RGD peptide conc.)



Early migration from primary focus

ECM degradation and adhesion required for collective invasion

Colonization

Ageing stroma secretes an ECM that increases adhesion and migration of incoming cancer cells





Intravasation into endothelial/mesothelial environments

Chronic inflammation related discarbonyl crosslink ECM increasing cancer migration



Migration within fluid environments

Spheroidal ECM enhances its elasticity and durability in travel

## **Acknowledgments**

Dharma Pally Jimpi Langthasa Satyarthi Mishra Mallar Banerjee Shruthi Narayanan Tavishi Dutt Bharat Vivan Thapa

Deepak K Saini, Prosenjit Sen, Mohit K Jolly (IISc) Annapurna Vadaparty (Sri Shankara Cancer Hospital, Bangalore) Tilmann Glimm (Western Washington University)









