



Seminartalk

Cancer development

Jacqueline Thy Walther

18th June 2019

Nanoanalytics by Prof. Rheinlaender

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Introduction

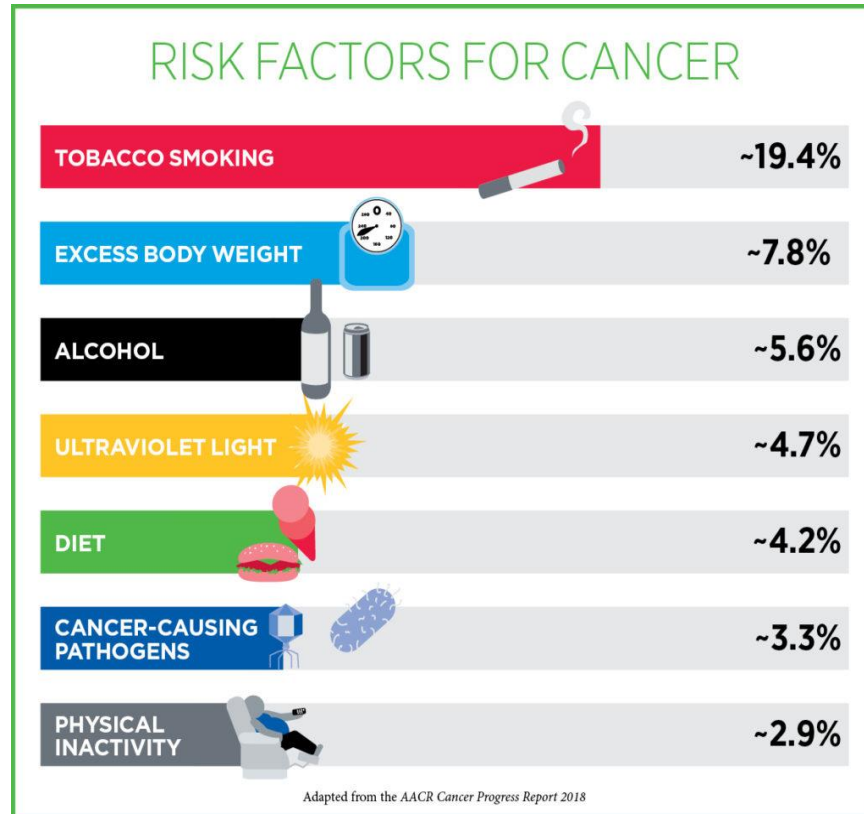
According to a study by the World Health Organization (WHO)
7.6 million people worldwide died of cancer during 2005 alone. WHO estimates that **mortality rates** due to cancer will **continue to rise worldwide**, with **9 million cancer deaths by 2015** and **11.4 million by 2030**.

Suresh, Subra (2007), Acta biomaterialia 3 (4), S. 413-438.

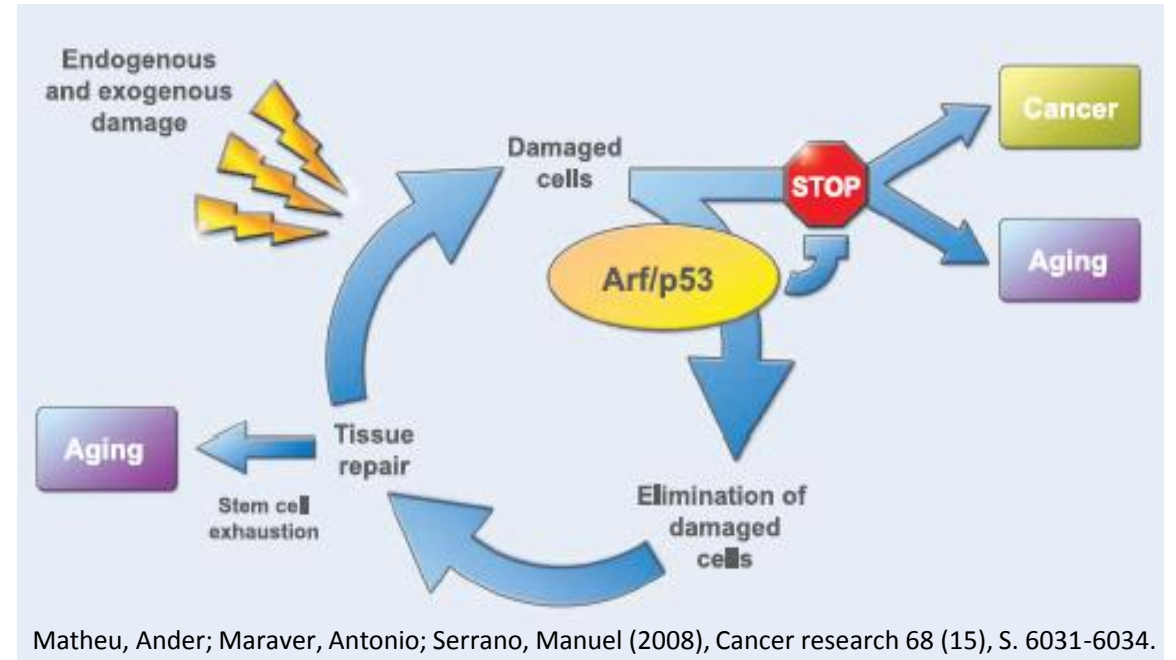
Introduction

How does the cell interaction between cancer cells functions and which physical/ mechanical mechanisms take place, e. g. in the formation of metastases?

Cause of cancer development



<https://blog.aacr.org/wp-content/uploads/2019/01/Risk-Factors-graphic-768x680.jpg>

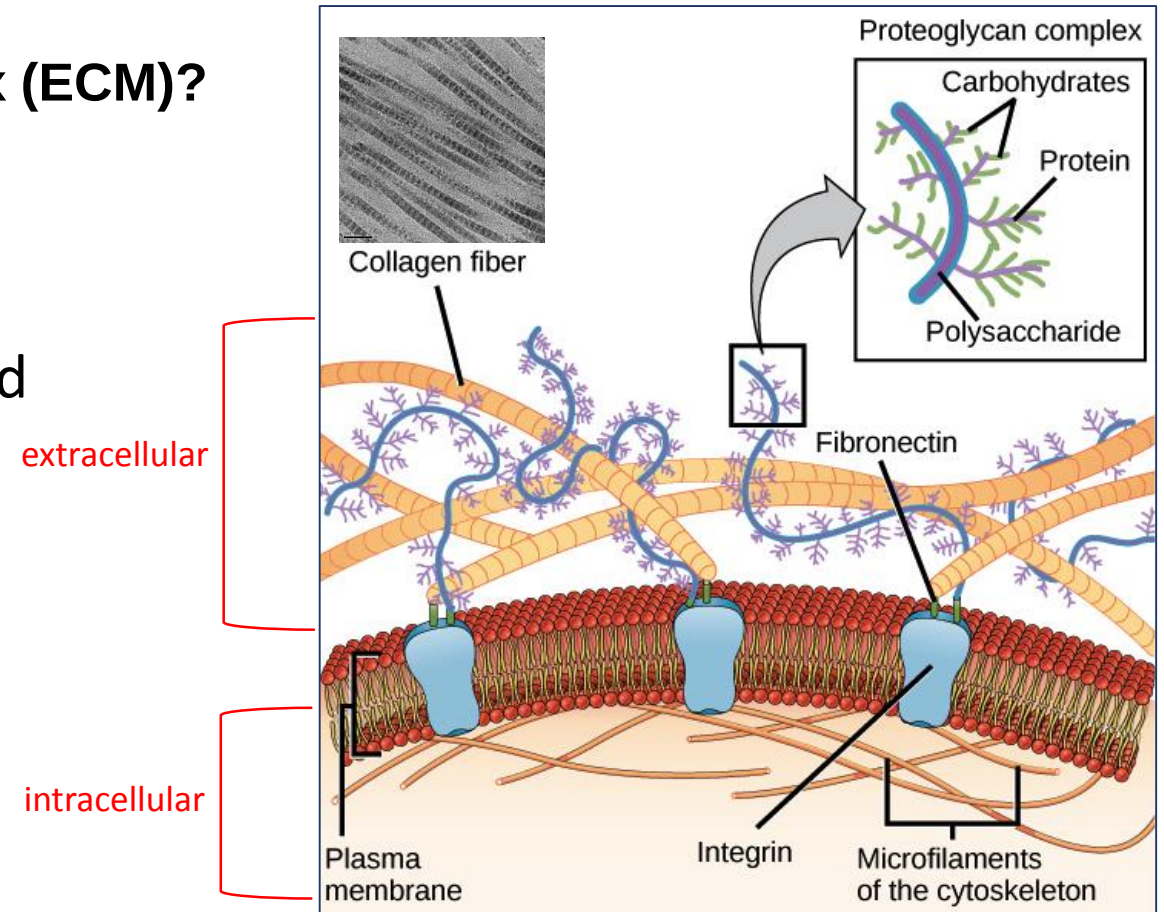


- genomic alterations
- uncontrolled cell growth
- activation of oncogenes and/or the deactivation of tumor suppression genes

Cell-matrix interaction

What is the role of the extracellular matrix (ECM)?

- Supports tissue
- Provides substrate for cell adhesion and migration
- Constantly being remodeled

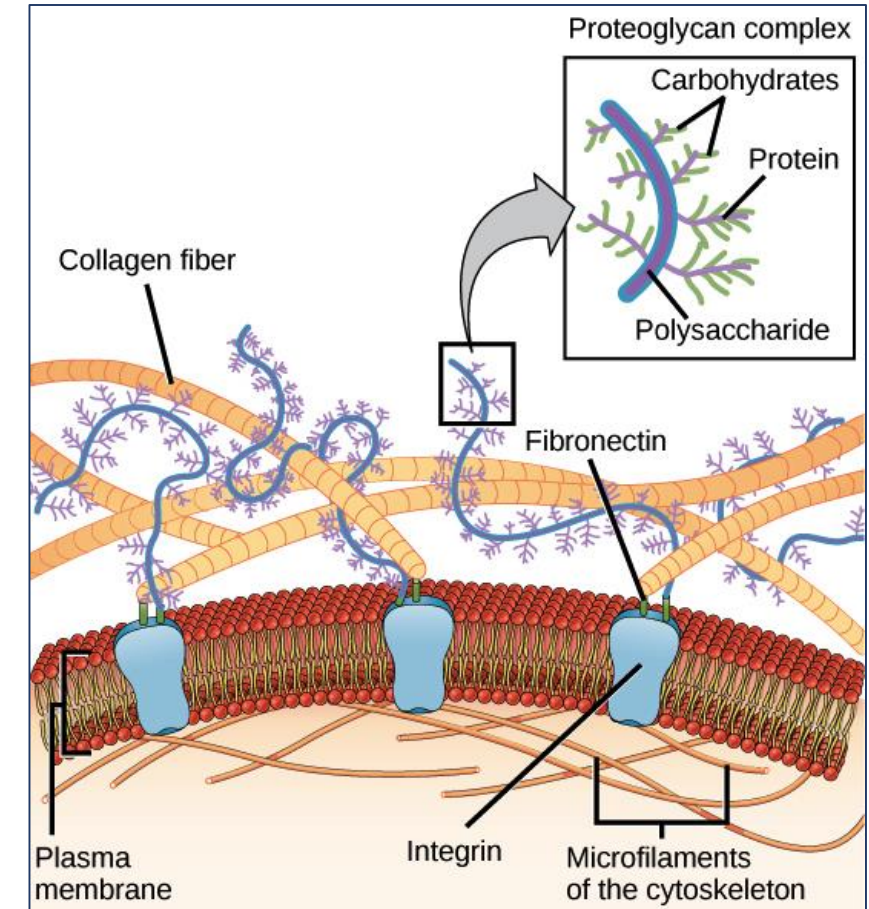


<https://cdn.kastatic.org/ka-perseus-images/2743d345dabf839cffe83a7474260f3c23730d91.png>

Sever, Richard; Brugge, Joan S. (2015), Cold Spring Harbor perspectives in medicine 5 (4).

What is the role of the extracellular matrix (ECM)?

- The ECM changes as cancer progresses
- stiffens due to deposition of **cancer-associated fibroblasts (CAF)**
→ **Tumour growth promotor**
- collagen fibers become more cross-linked by **lysyl oxidases (LOX)**



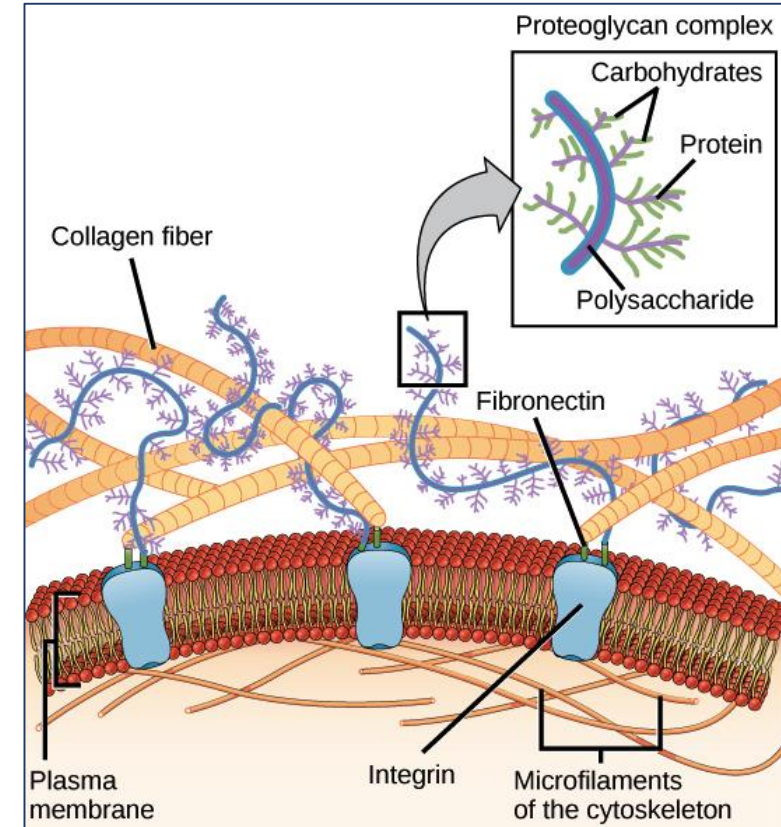
<https://cdn.kastatic.org/ka-perseus-images/2743d345dabf839cffe83a7474260f3c23730d91.png>

Sever, Richard; Brugge, Joan S. (2015): Signal transduction in cancer. DOI: 10.1101/cshperspect.a006098.



What is the role of the integrins?

- transmembrane glycoproteins
- Heterodimer : α and β subunits
- bind components of ECM specifically

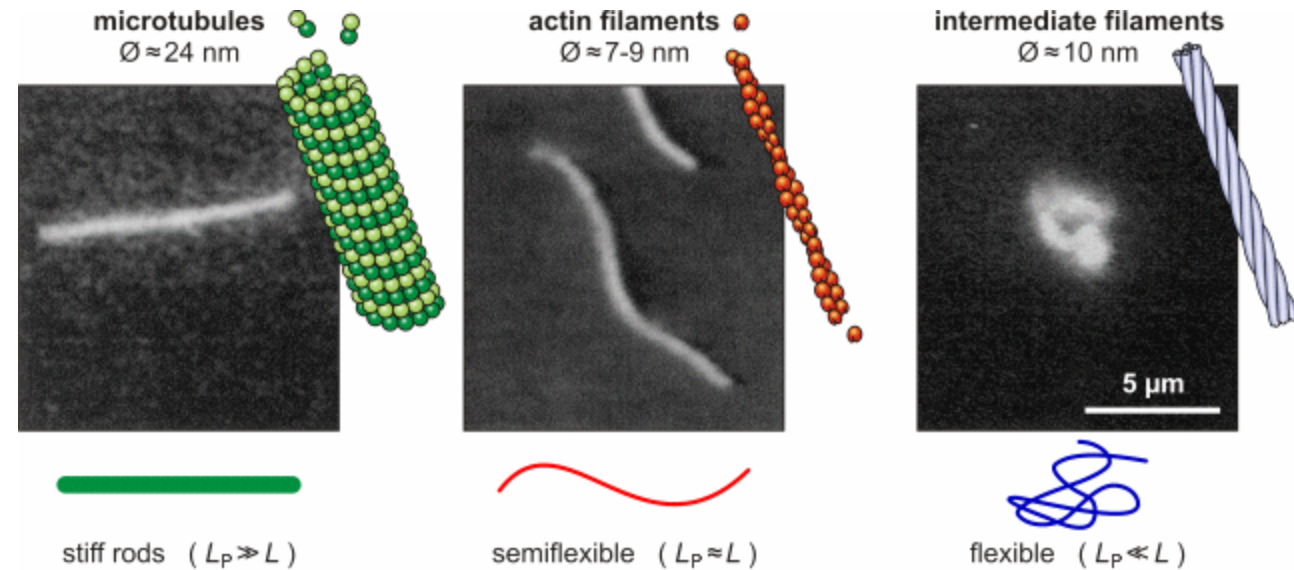


<https://cdn.kastatic.org/ka-perseus-images/2743d345dabf839cffe83a7474260f3c23730d91.png>

Sarkar et al. (2013), International journal of molecular sciences 14 (10), S. 21087-21113.

Cytoskeleton

- F-actin
- intermediate filaments
- Microtubules

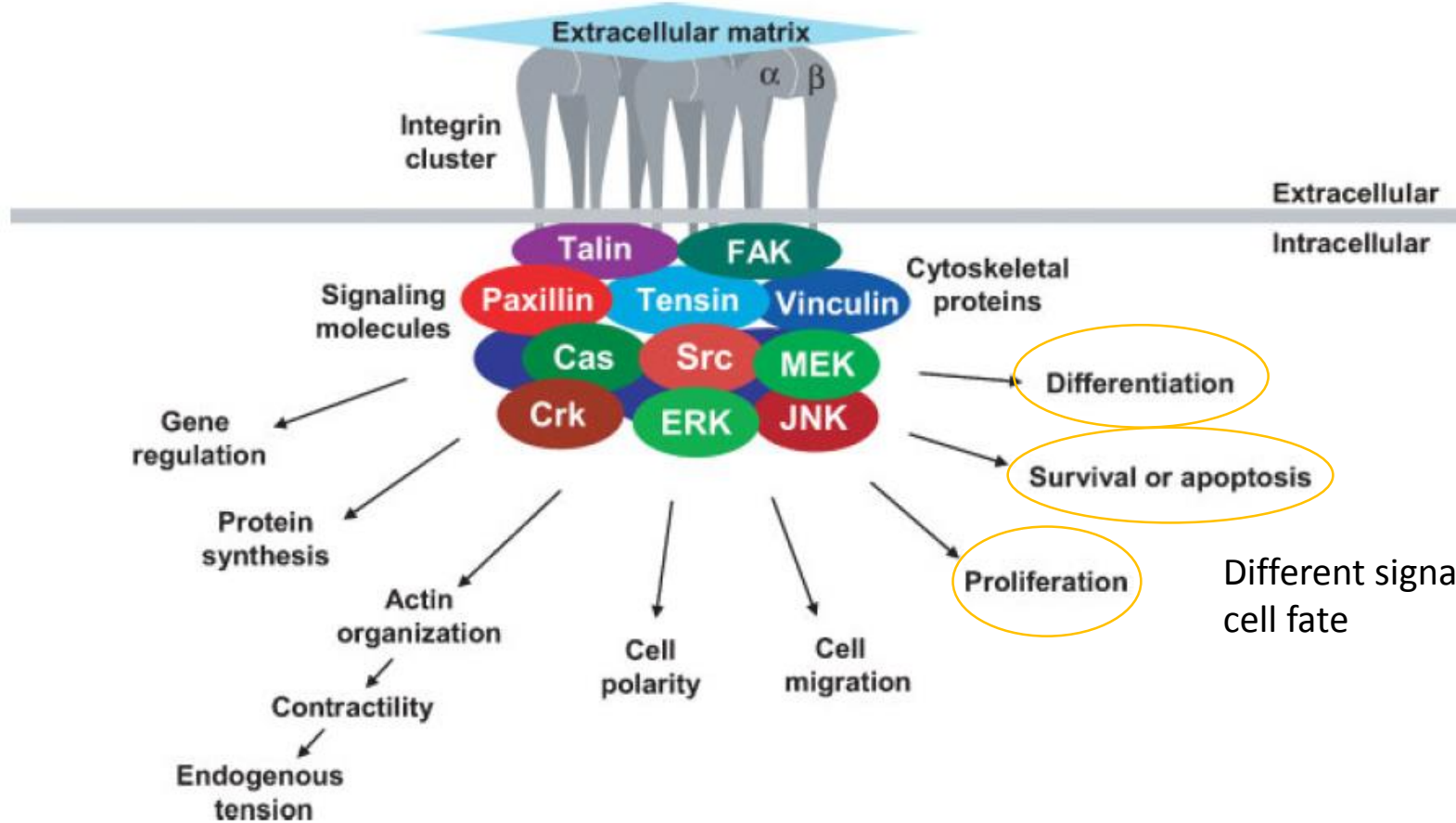


http://home.uni-leipzig.de/pwm/web/img/intro_cytoskeleton_filaments.png

→ Determines deformability and mechanical response of the cell

→ coordinated crosstalk enables cell migration and tissue remodelling

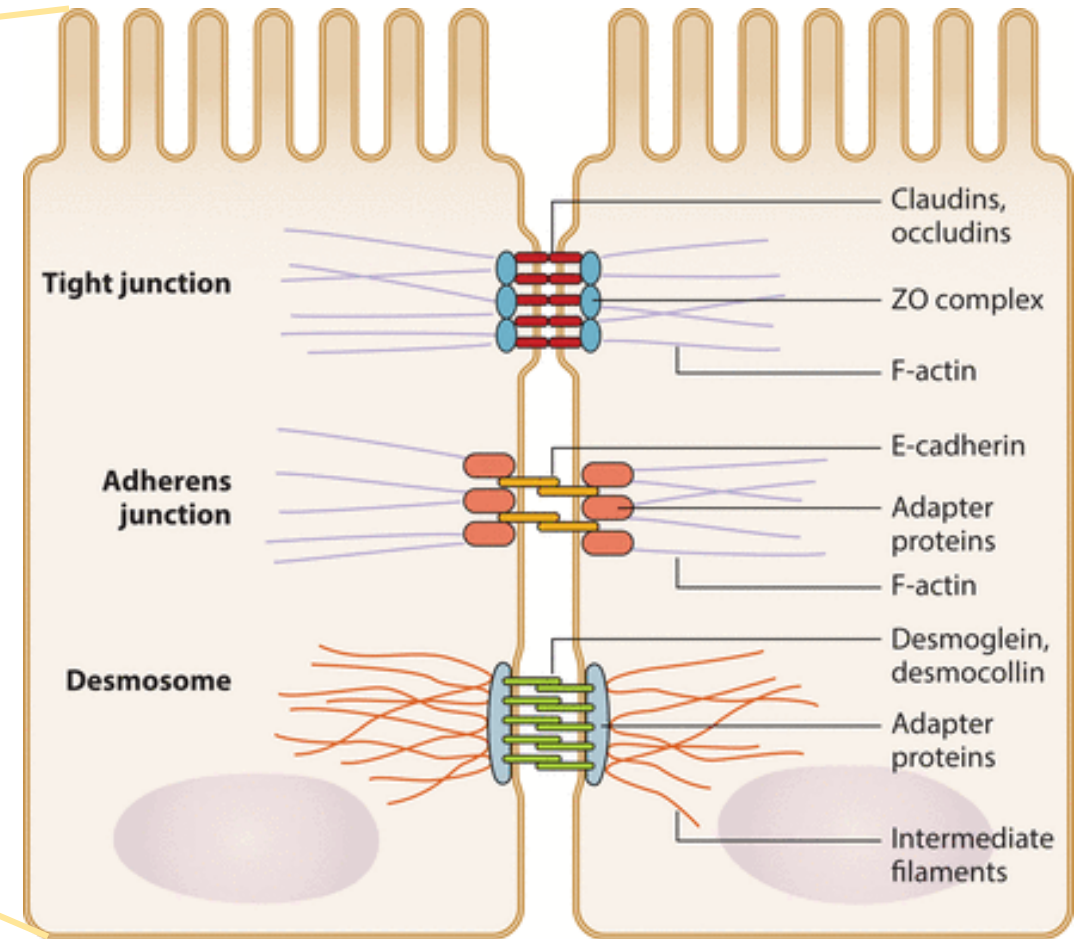
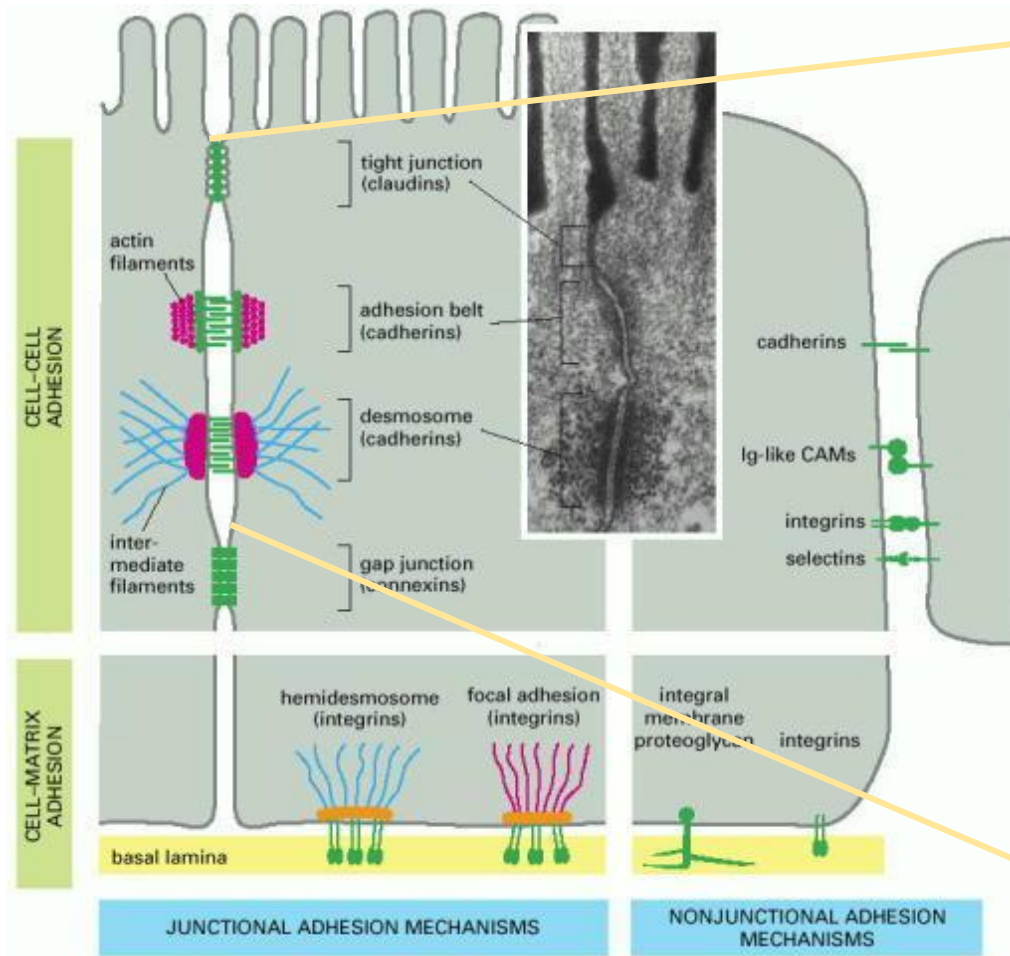
Cell-matrix interaction



Different signaling cascades determine the cell fate

Berrier, Allison L.; Yamada, Kenneth M. (2007). *Journal of cellular physiology* 213 (3), S. 565–573.

Cell-cell interaction

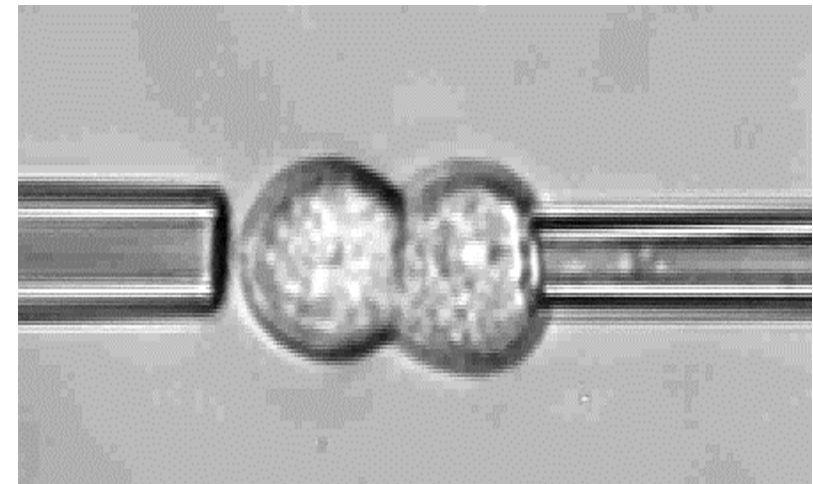
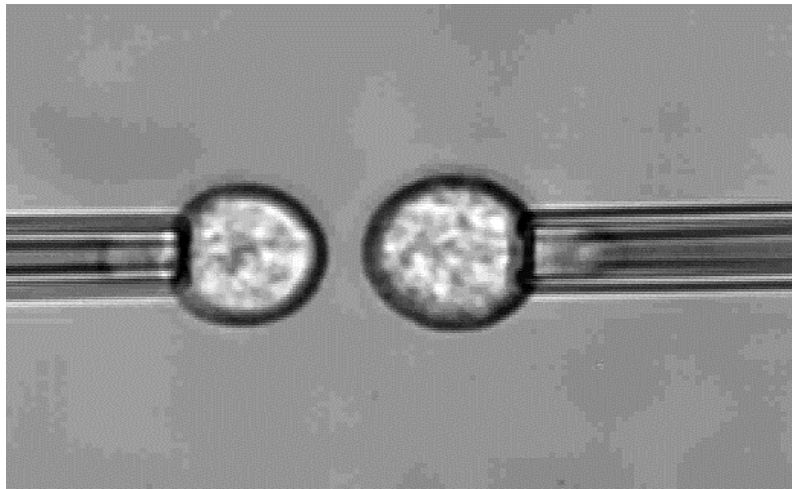


Alberts B, Johnson A, Lewis J, et al. Molecular Biology of the Cell. 4th edition. New York: Garland Science; 2002. Cell-Cell Adhesion. Available from <https://www.ncbi.nlm.nih.gov/books/NBK26937/>

<https://cmr.asm.org/content/cmr/30/1/191/F7.medium.gif>



Cell-cell interaction – E-cadherins



<http://jcb.rupress.org/content/167/6/1183/tab-figures-data>



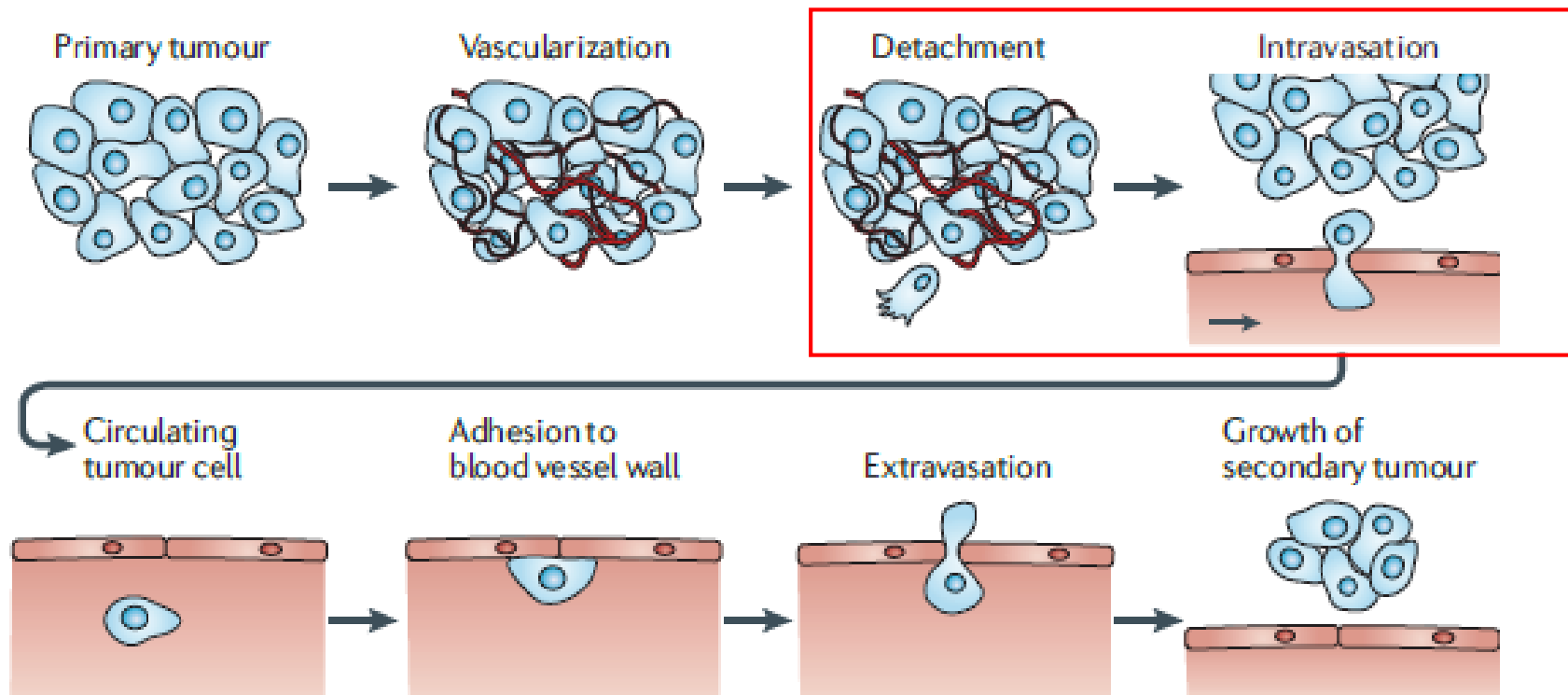
Physics of cancer cells

- Cancer cell dissemination is a result of the **invasion-metastasis cascade** that includes:
 - I. escape of cancer cells from the primary tumor and invasion of the basement membrane
 - II. migration in the tissue stroma
 - III. intravasation into blood and lymph vessels
 - IV. spreading through circulation
 - V. arrest at distant organ sites and extravasation
 - VI. survival in distant organs
 - VII. metastatic outgrowth

Gloushankova et al. (2017), *Tissue barriers*

Physics of cancer cells

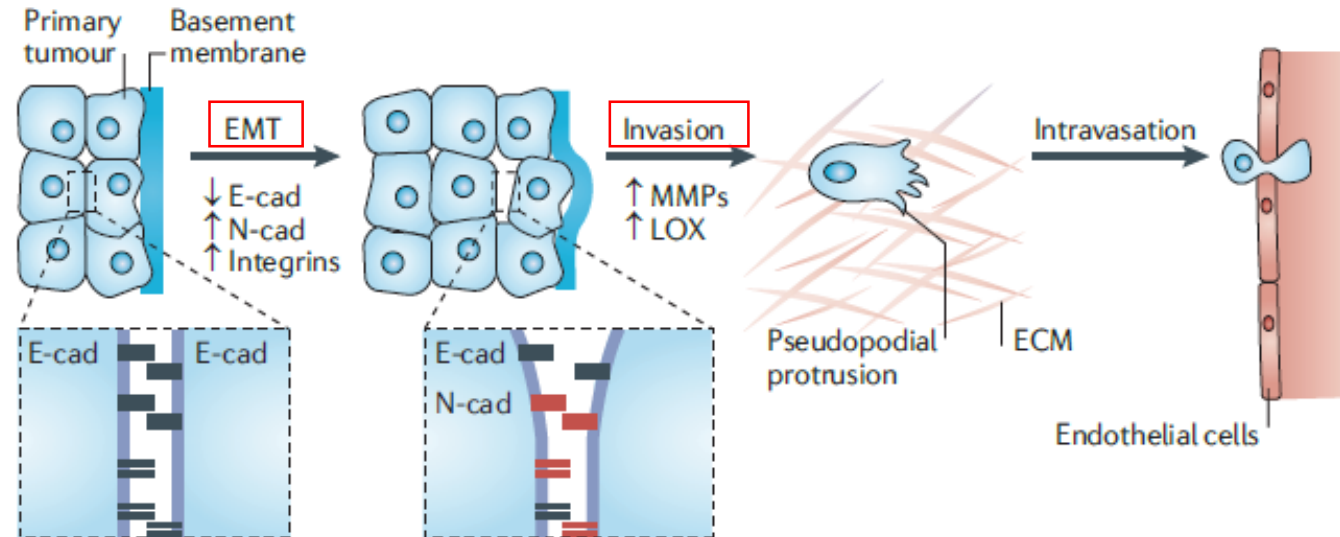
Invasion–metastasis cascade



Wirtz et al.(2011), Nature reviews. Cancer 11 (7), S. 512–522.

Physics of cancer cells

- The cell mechanics in invasion and intravasation

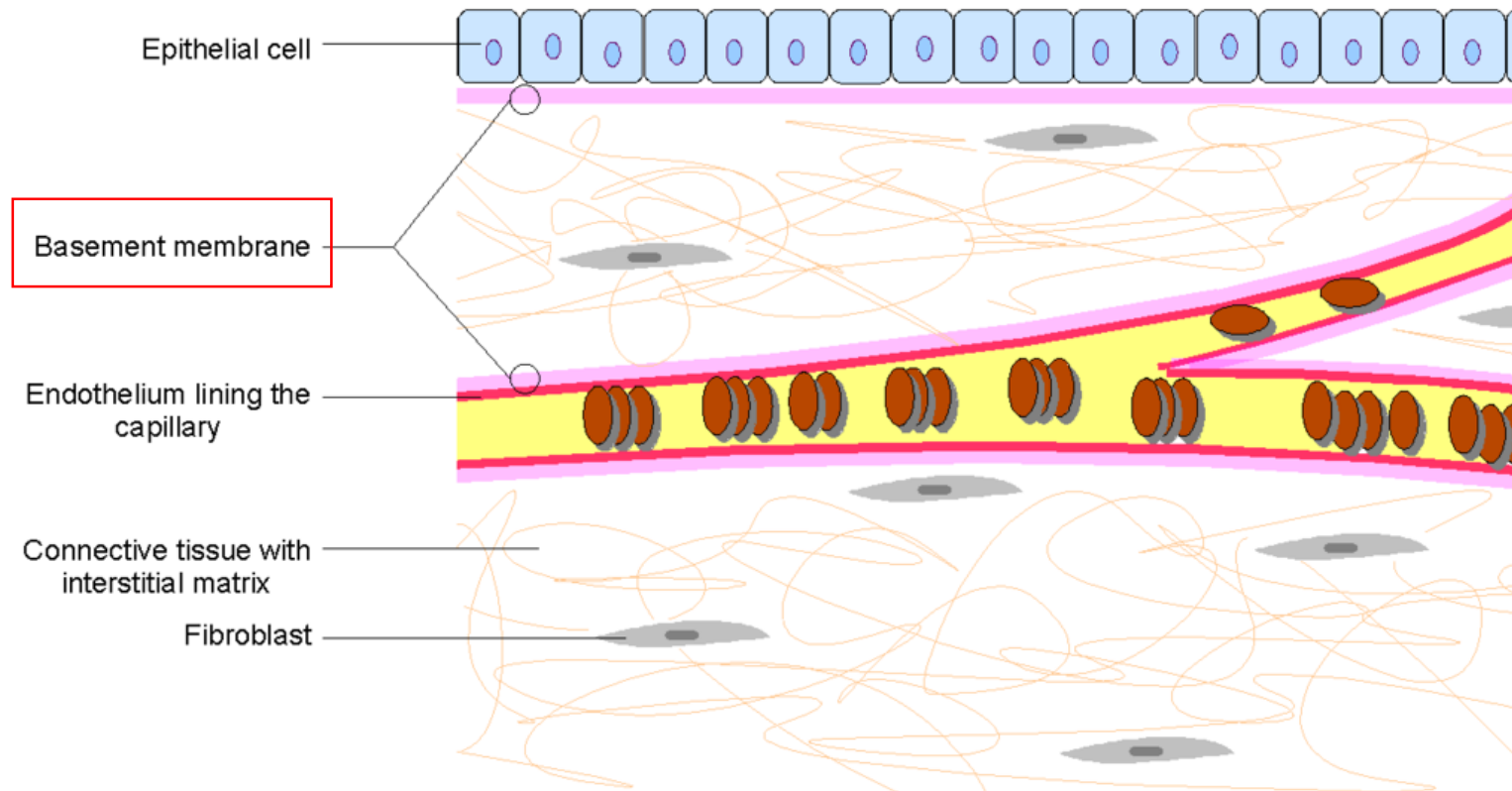


Wirtz et al.(2011), Nature reviews. Cancer
11 (7), S. 512–522.

Driving force: **epithelial-mesenchymal transition (EMT)**

Physics of cancer cells

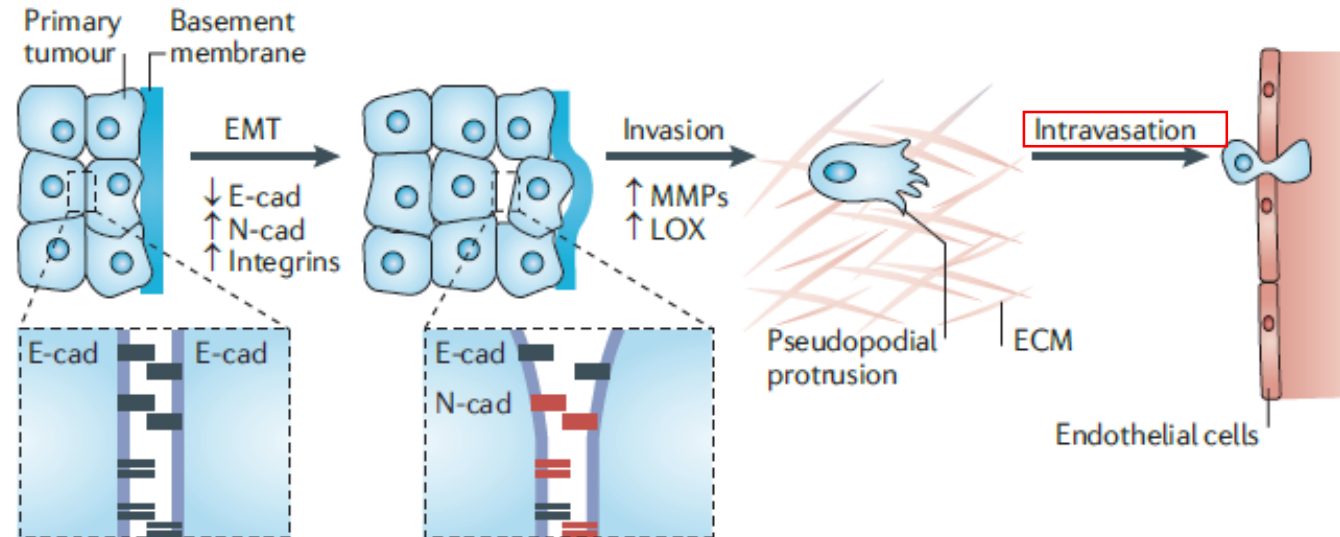
Illustration depicting extracellular matrix in relation to epithelium, endothelium and connective tissue



https://upload.wikimedia.org/wikipedia/commons/thumb/f/f5/Extracellular_Matrix.png/800px-Extracellular_Matrix.png

Physics of cancer cells

- The cell mechanics in invasion and intravasation

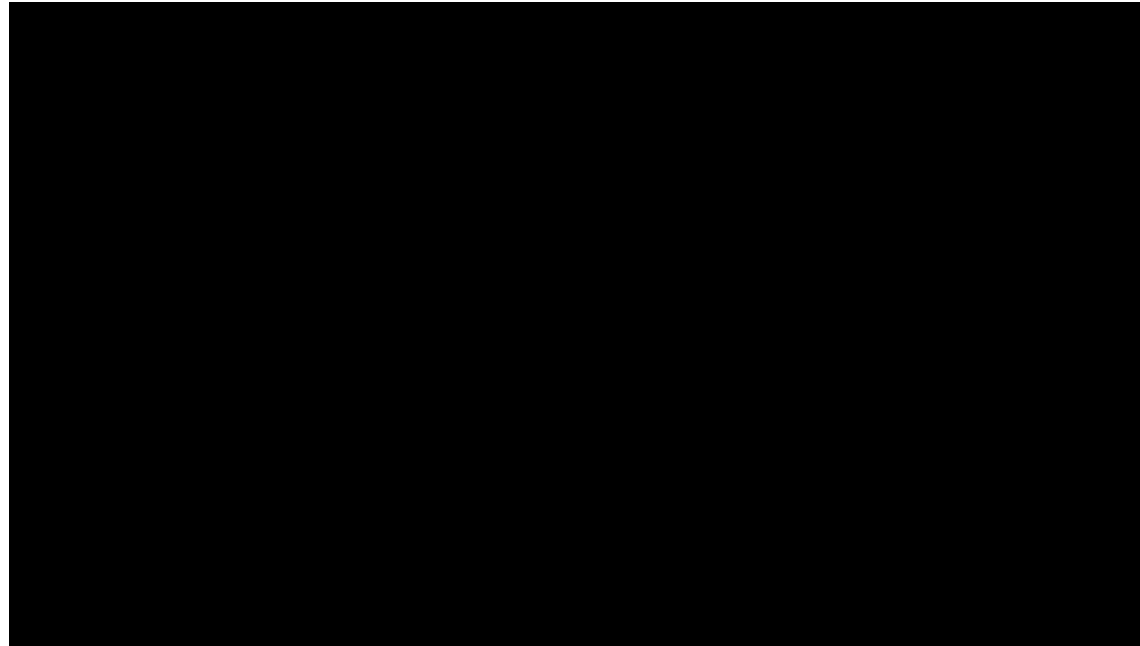


Wirtz et al.(2011), Nature reviews. Cancer
11 (7), S. 512–522.

Metastasis requires down-regulation of cell adhesion receptors necessary for tissue-specific, cell–cell attachment, as well as up-regulation of receptors that enhance cell motility



Microfluidic device to watch cells move through pore sizes

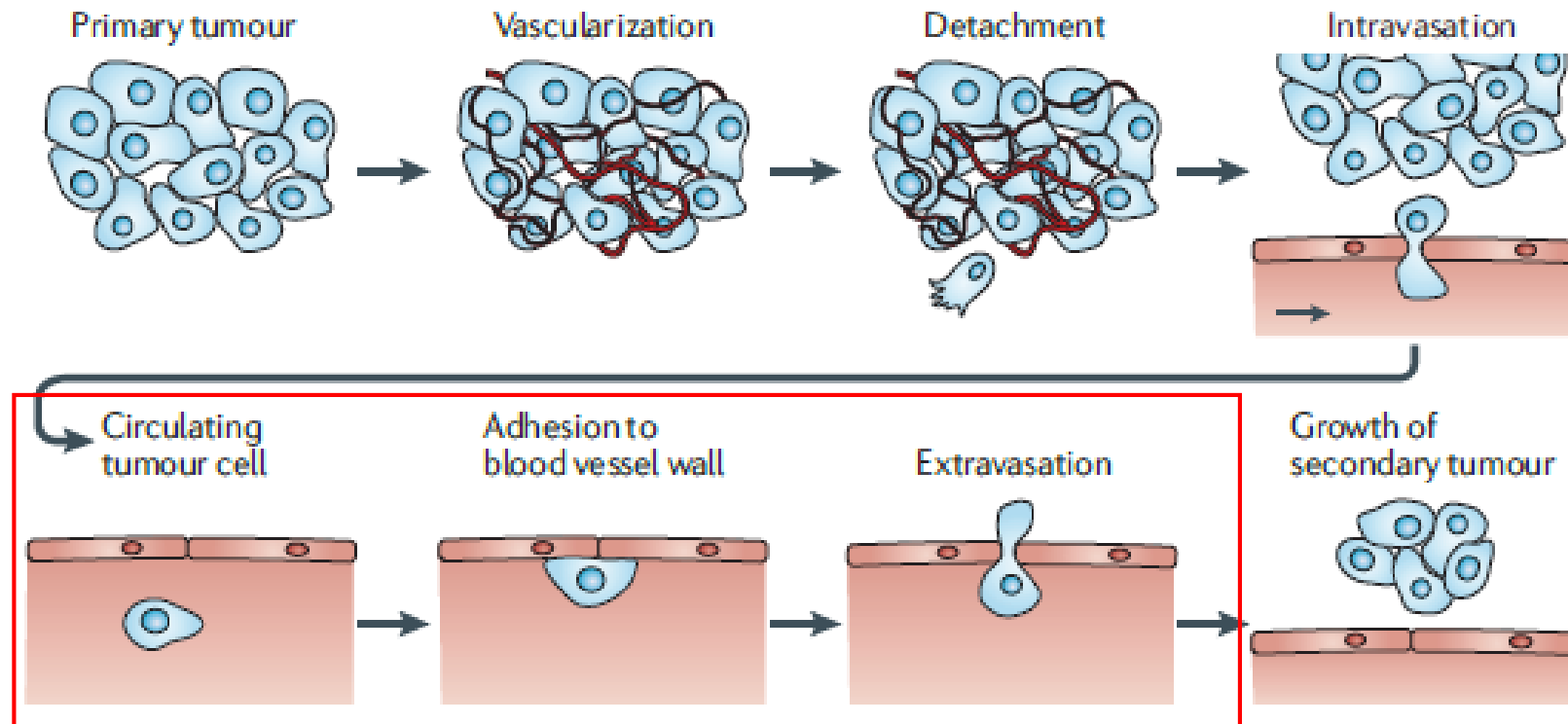


https://www.youtube.com/watch?time_continue=10&v=CawHfSR4Igl

<https://www.nih.gov/news-events/nih-research-matters/migration-creates-cancer-cell-vulnerabilities>

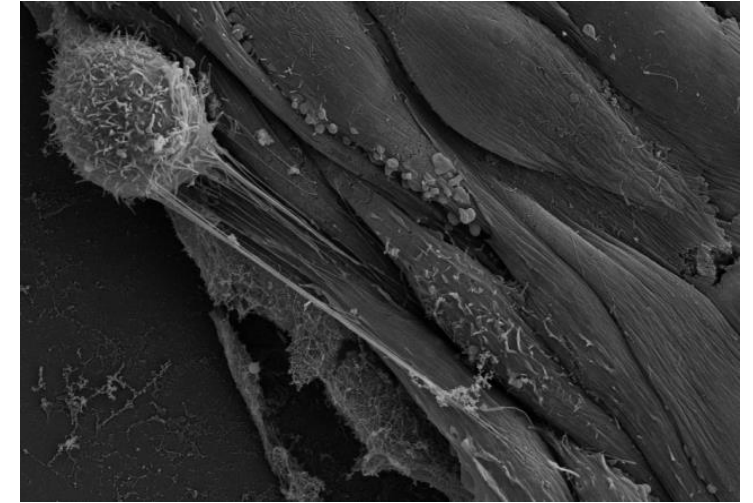
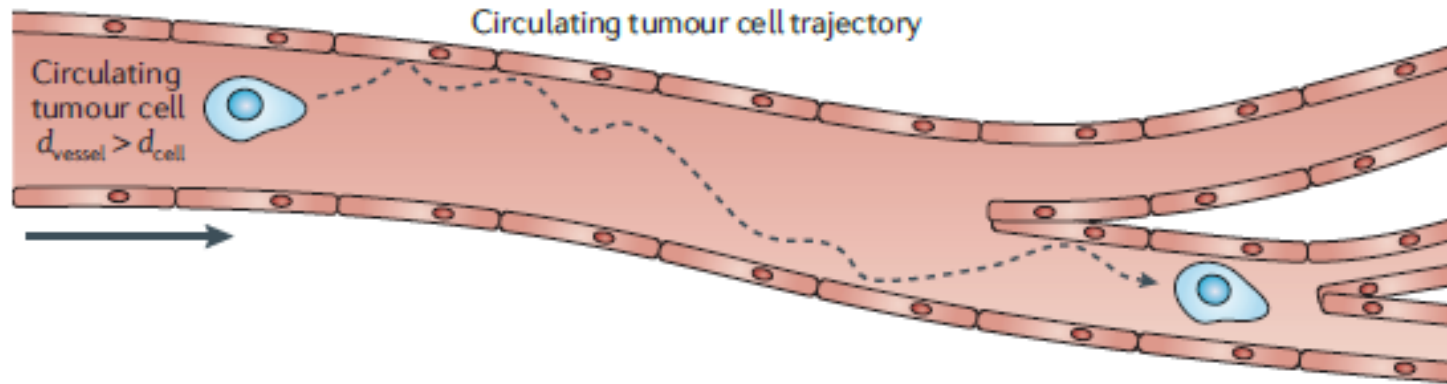
Physics of cancer cells

Invasion–metastasis cascade



Wirtz et al.(2011), Nature reviews. Cancer 11 (7), S. 512–522.

Physics of cancer cells – Circulating tumor cells



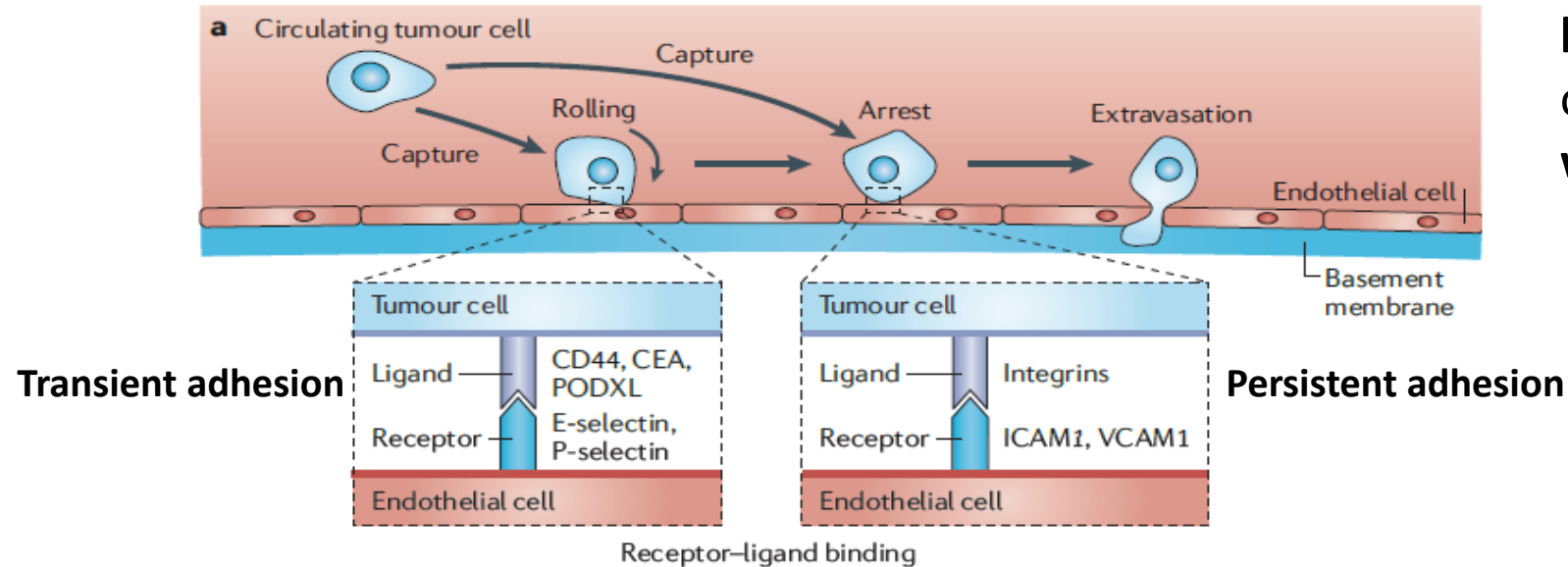
<http://news.mit.edu/2015/cancer-cells-escape-blood-vessels-1216>

Extravasation

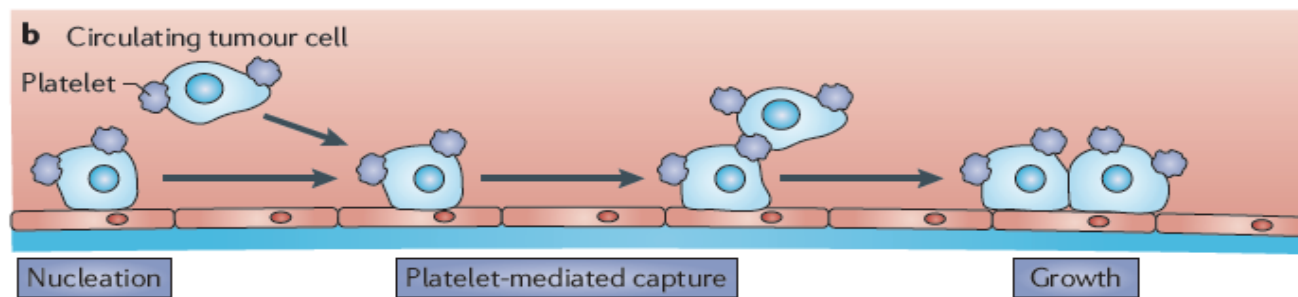
- Physical occlusion: $d_{\text{vessel}} < d_{\text{cell}}$ arrest can occur by mechanical trapping
- Adhesion: $d_{\text{cell}} < d_{\text{vessel}}$ depends on residence time and shear force

Wirtz et al.(2011), Nature reviews. Cancer
11 (7), S. 512–522.

Physics of cancer cells – Circulating tumor cells



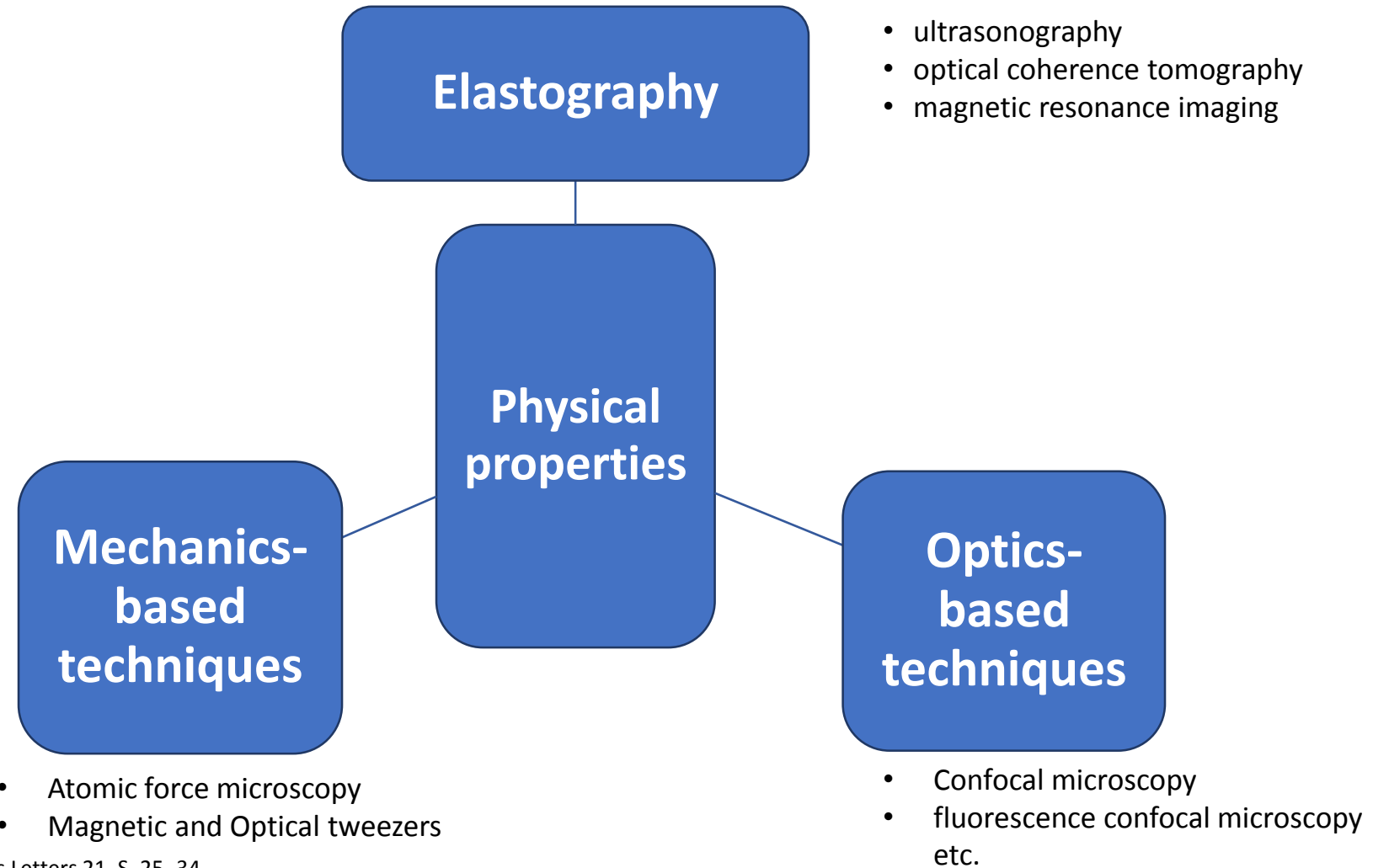
ligand–receptor interactions:
collision between a **cell** and a **vessel wall**



The **association of tumour cells with platelets** may enhance arrest through platelet-mediated capture

Wirtz et al.(2011), Nature reviews. Cancer 11 (7), S. 512–522.

Measuring physical properties in cancer



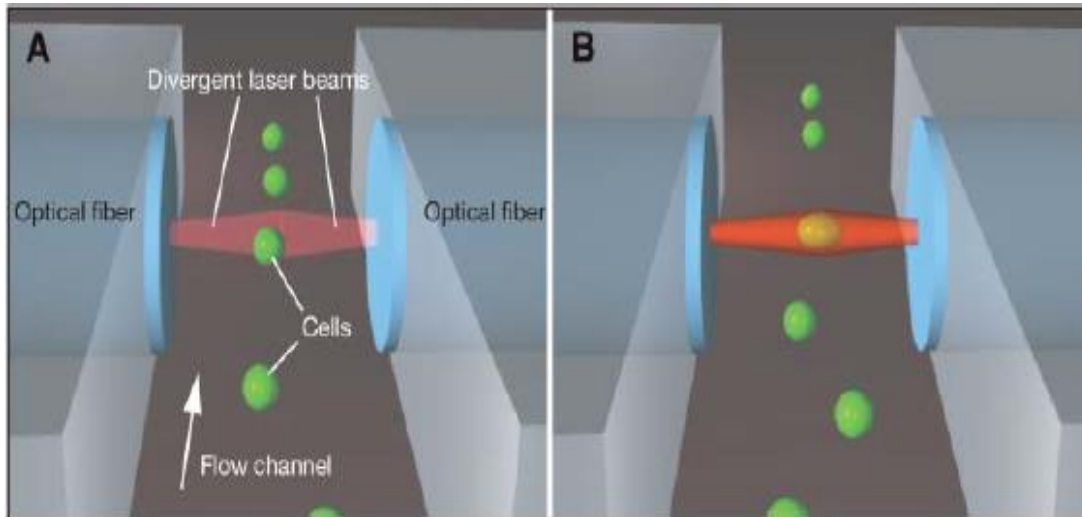
Malandrino et al. (2018), Extreme Mechanics Letters 21, S. 25–34.

Measuring physical properties in cancer

**General question:
Are tumor cells soft or stiff ?**

Optical Deformability as an Inherent Cell Marker for Testing Malignant Transformation and Metastatic Competence – Guck et al.

Microfluidic optical stretcher

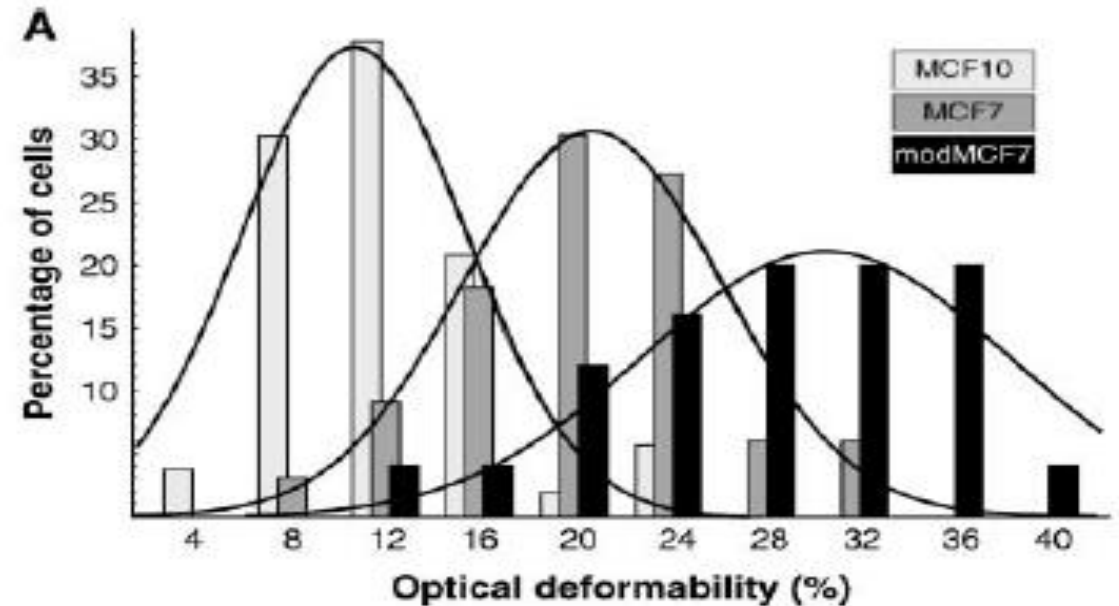
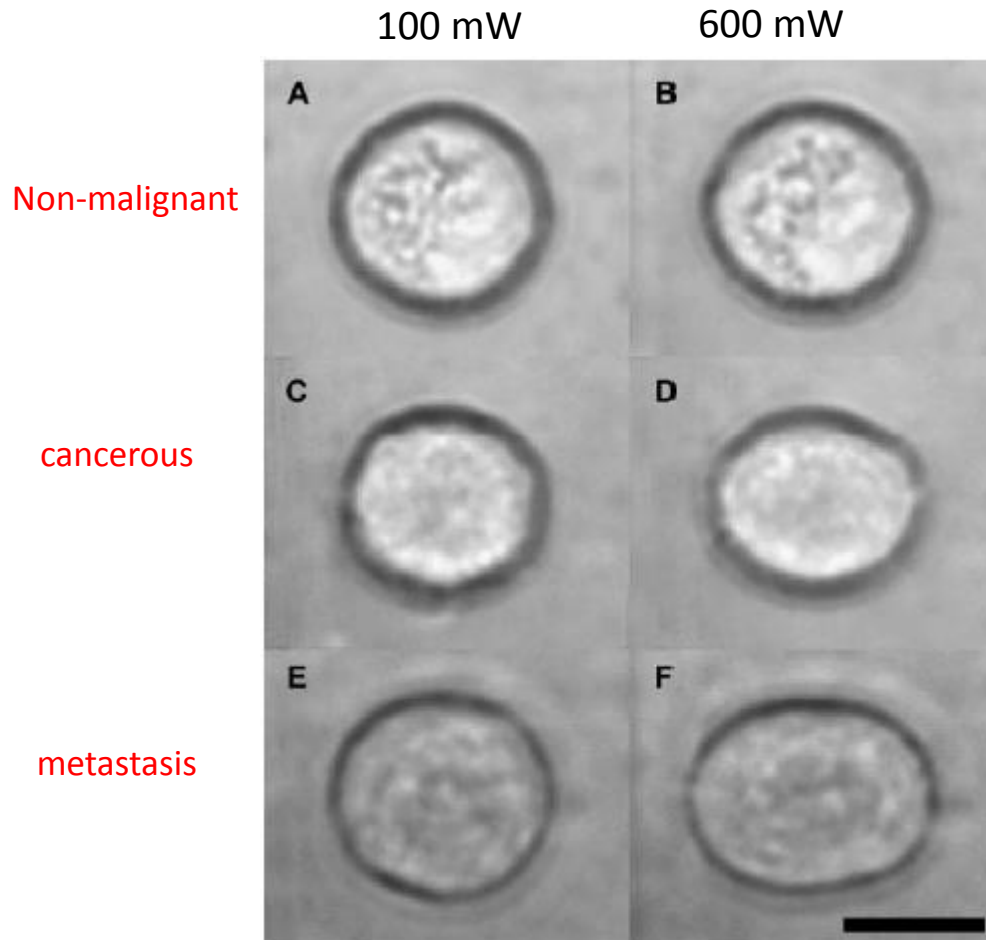


Degree of deformability
→ direct measure for the strength of the
cytoskeleton

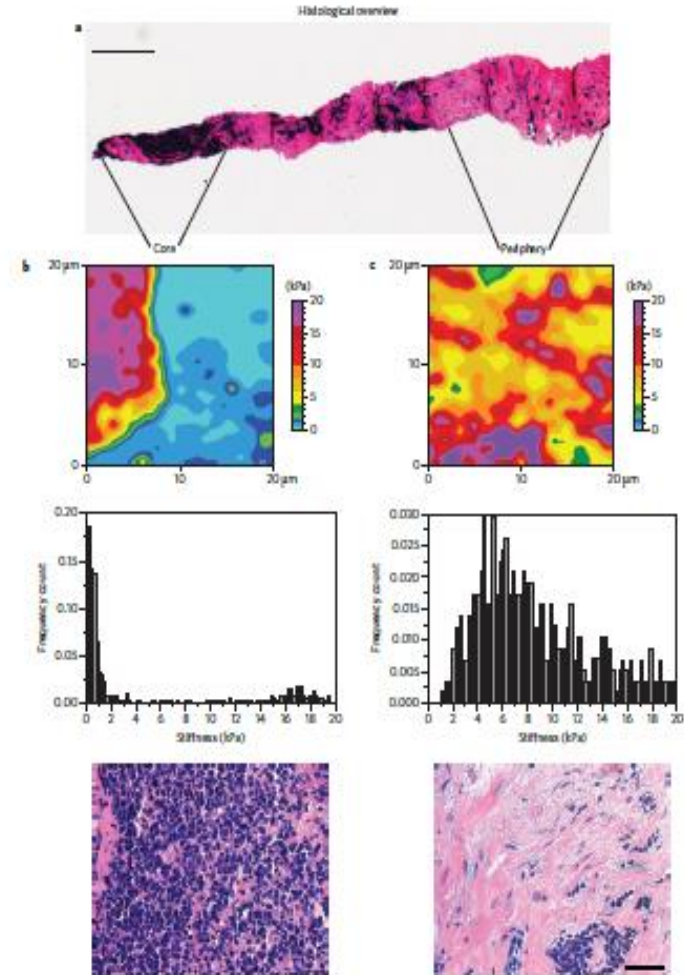
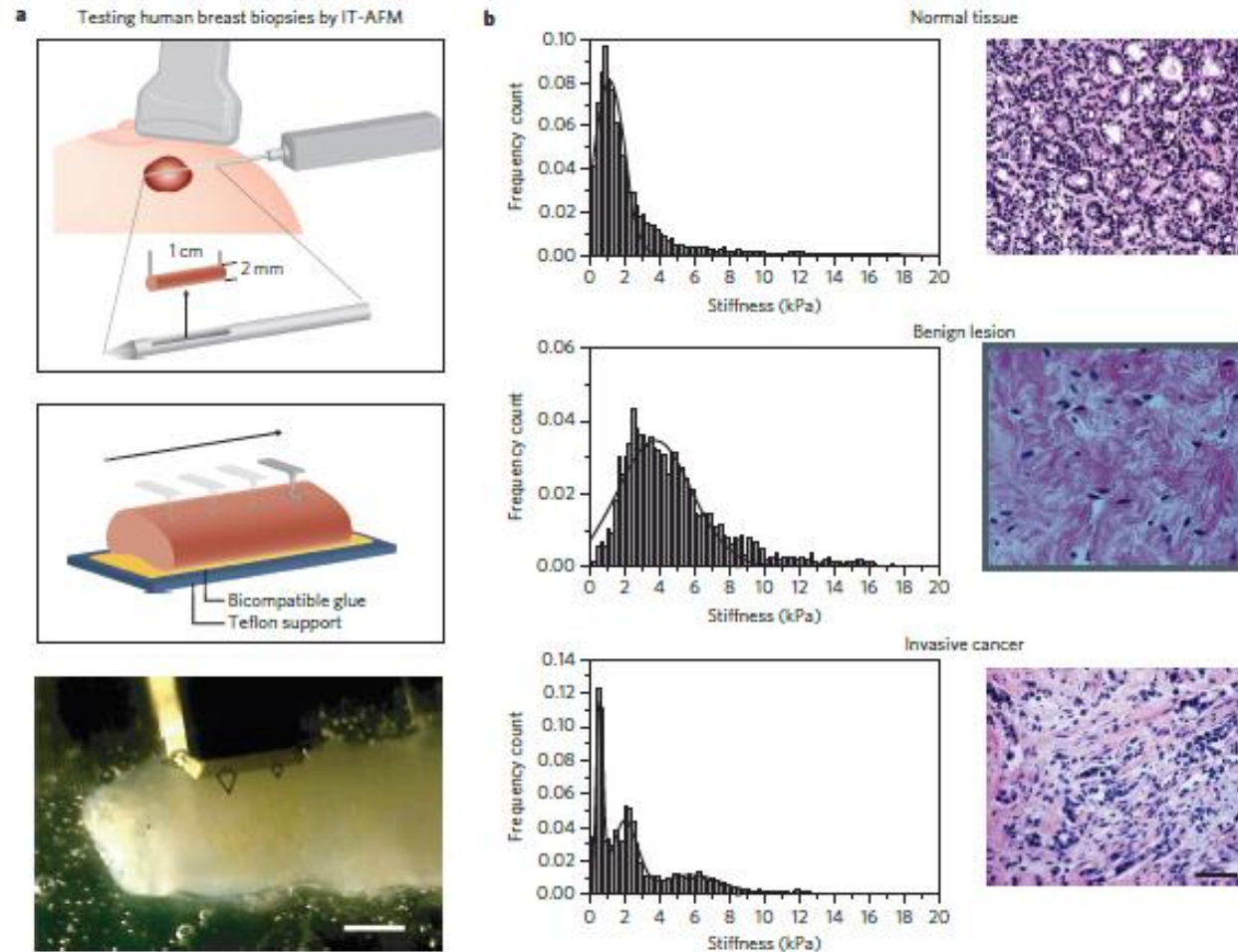


<http://rszelltechnik.com/technology/>

Optical Deformability as an Inherent Cell Marker for Testing Malignant Transformation and Metastatic Competence – Guck et al.



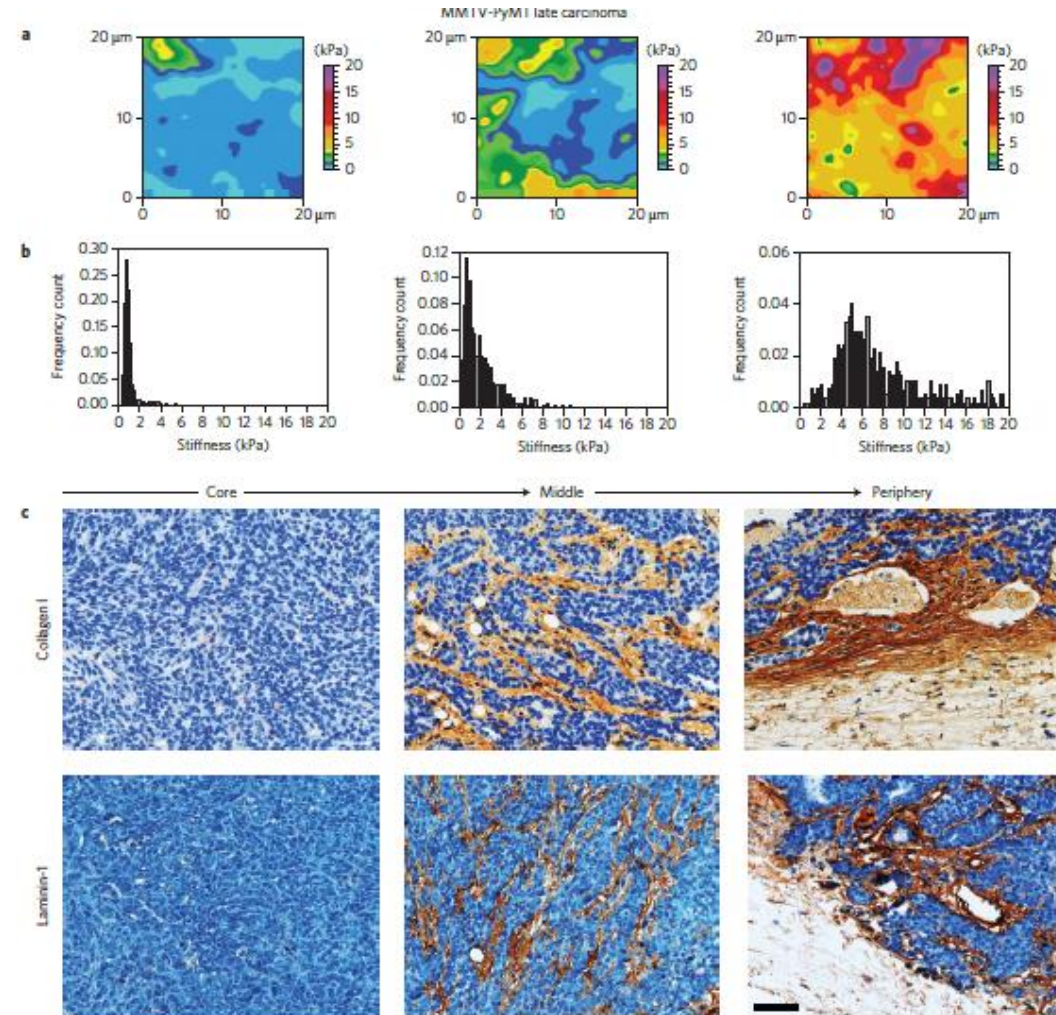
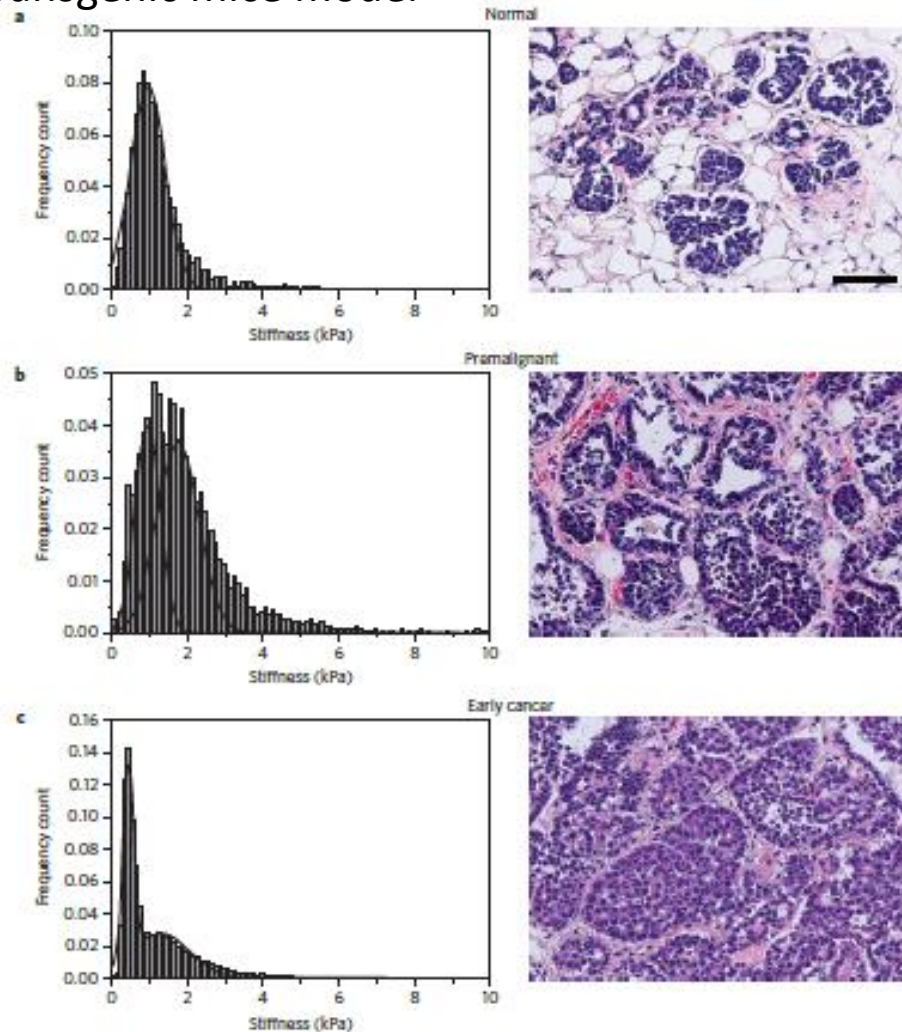
The nanomechanical signature of breast cancer – Schoenenberger et al.



The nanomechanical signature of breast cancer

– Schoenenberger et al.

Transgenic mice model



Physics of cancer cells

Are tumor cells soft or stiff?

Tumors are generally stiff, but can have soft cores consisting of cells that are softer than their normal counterparts

- Contradictory, but it is hypothesized that cancer cells need to generate **traction forces on stiff substrates to migrate**,
- but also need to be **soft** to extravasate or metastasize

Chin, LiKang et al. (2016), Current opinion in chemical engineering 11, S. 77–84..

Summary

- Cell-cell and cell-matrix interaction play major role in cell function and fate
- Cancer development is characterized by altered cell-cell and cell-matrix interaction
- Malignant cancer cell dissemination is a result of the invasion-metastasis cascade



Summary

Better understanding of the mechanisms of deformability of cancer cells and the role of physical interaction and mechanical forces provide new and important insights into the progression of cancer

→ Provide new therapeutic approaches and developments

Thank you for your attention! 😊

Literature

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Literature

The biology of cancer
Robert A. Weinberg

