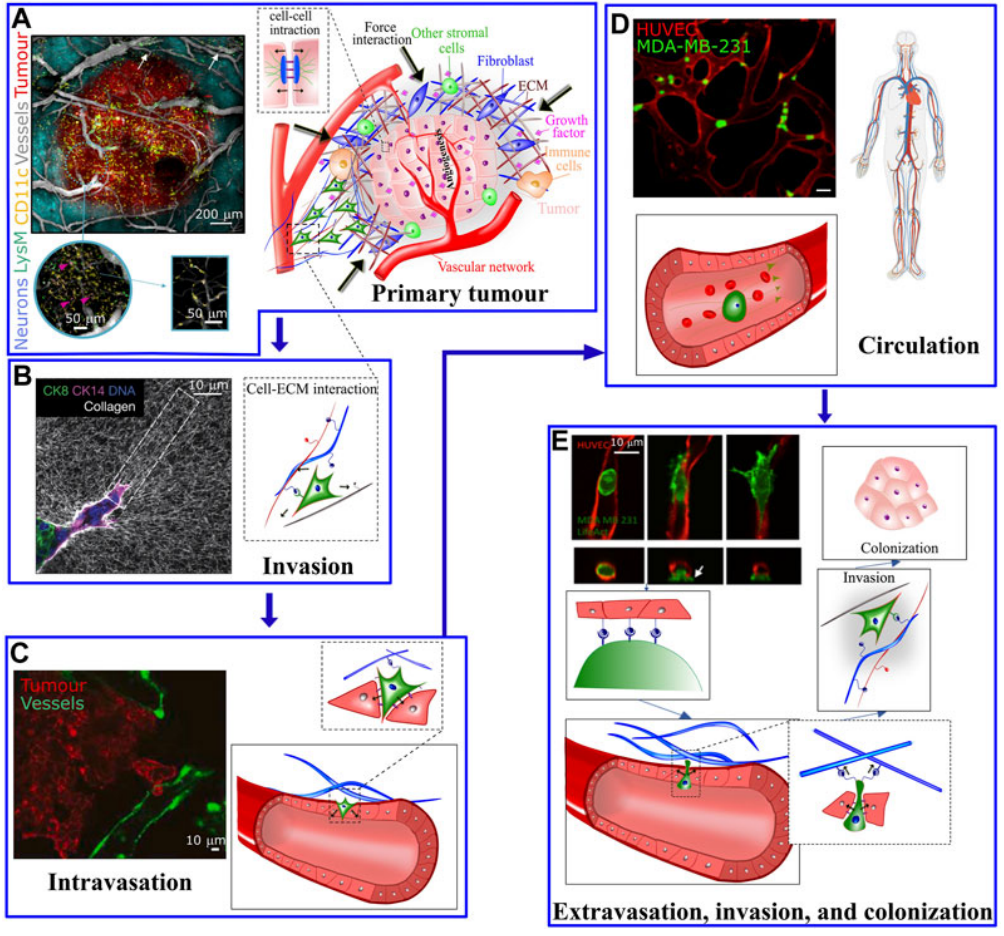
Cancer mechanobiology

Tumor microenvironment

- primary tumor cells gain aggressive and migratory phenotypes --> invading the local tissue --> transmigrating through the endothelial barrier --> survival of cancer cells in blood circulation --> exit from the vessels at distal tissues --> invade and colonize in the secondary sites



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Mechanical forces in tumor

- In the setting of cancer transformation, when epithelial cells are cultured on a compliant substrate, normal cells show a decrease in the rate of DNA synthesis and an increase in the rate of apoptosis while transformed cancer cells maintain their growth and apoptotic characteristics
- Furthermore, transformed cells exert higher traction forces compared to non-transformed cells.
- Consequently, the increase in ECM stiffness and the extent of compression can lead to activation and increased expression of Rho GTPase --> that facilitate the process of epithelial-mesenchymal transformation (EMT)
- it has been found that cancer cells are consistently softer than their non-cancerous counterparts and that the softening correlates positively with metastatic potential

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Mechanical forces in invasion

- Biochemical and biophysical characteristics of the ECM influences cell migration
  - Chemotaxis
  - Durotaxis
  - Haptotaxis
  - contact guidance
- heterogeneity of stiffness in tumor microenvironment, triggered by matrix remodeling can mechanically guide the tumor cells directional migration
- External stimuli including the presence of interstitial flow, ECM stiffness, 2D or 3D dimensionality, and availability of binding sites for cell surface receptors may influence the nature and deformability of the cell membrane and cytoskeleton.
- For instance, features that appear to be important for 2D motility—focal adhesion, stress fibres, broad lamellipodia—are largely absent for models of 3D invasion, particularly in invasive cancer cells.

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Tumor angiogenesis

- The generation of a new tumor-specific vasculature facilitates the escape of tumor cells into the circulation.
- the growth of an avascular tumor is limited to a critical size (<1 mm) because of the inability of diffusion mechanisms to supply oxygen and soluble factors into the tumor core.
- This phenomenon results in the development of a necrotic/hypoxic region at the tumor core, which is surrounded by a highly proliferative outer rim.
- Vascularization of the tumor and surrounding areas is initiated and maintained through the recruitment and activation of endothelial cells
- The newly developed vessels perturb the normal architecture of blood and lymphatic networks leading to high levels of the interstitial fluid pressure and the lack of gas and nutrients
- Due to such a chemically and mechanically disordered tumor environment, direct drug delivery to solid tumors is often inefficient

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EMT: Epithelial to mesenchymal transition

- EMT is a critical process in metastasis and involves loss of epithelial characteristics
  - downregulation of cell-cell adhesion strength
  - acquisition of a mesenchymal phenotype via activation of migratory processes
- EMT process disrupts cellular force balances and polarity leading to morphological changes and detachment of tumor cells from the tumor epithelium
- the modulation of cellular shape and forces in combination with mechanisms favouring migration including proteolytic (matrix metalloproteinase), adhesive, protrusive (-podia) and contractile processes, promote invasion of cancer cells

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Intravasation and extravasation

- On average, pore sizes are on the scale of nanometers (<1 micron) while tumor cell size ranges 5–30 microns in diameter
- One of the rate limiting steps of migration is the deformation of the tumor cell nucleus, which is approximately 5–10 times stiffer than the cytoplasm
- Tumor cells are known to secrete matrix metalloproteinase (MMPs) to enable collagen proteolysis indicating an active role of degradation.
- While matrix degradation could decrease the burden for the cell to undergo severe deformation, recent work has also shown the ability of tumor cells to exhibit substantial morphological changes in the absence of matrix loss
- Microvessels are lined with a single layer of endothelial cells connected to each other through junctional proteins such as VE-cadherin
- The open gaps between endothelial cells are typically less than a few microns, suggesting that the transmigration of tumor cells may involve deformation of both tumor and endothelial cells.

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Circulating tumor cells (CTCs)

- The average shear stresses a CTC experiences is estimated to be around 1–4 dyn/cm2 (0.1-0.4Pa) in the venous circulation, and 4–30 dyn/cm2 in arterial circulation.
- Thus, it is highly possible that shear stress levels experienced by CTCs are significant enough to induce mechanotransductive cellular responses.
- CTCs migration in groups exhibit higher survival rates due to protection from deleterious shear stresses
- Tumor cell extravasation is thought to first require the firm adhesion and arrest of tumor cells on the endothelium
  - physical occlusion in capillaries
  - active adhesion between endothelial-tumor cell ligands/receptors

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