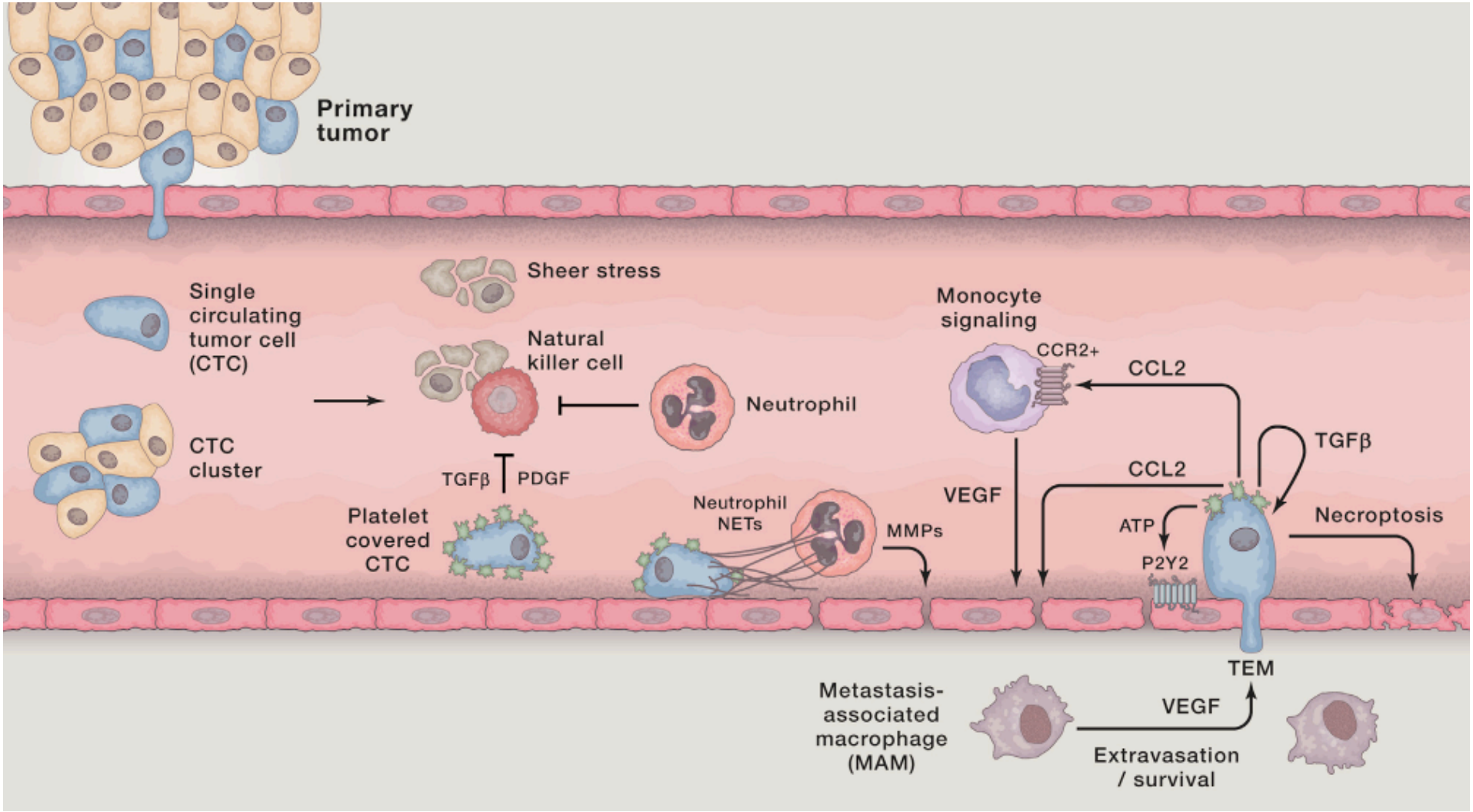
Corso di Biologia Cellulare del Cancro AA 2019-2020

Disseminazione, dormienza e colonizzazione metastatica

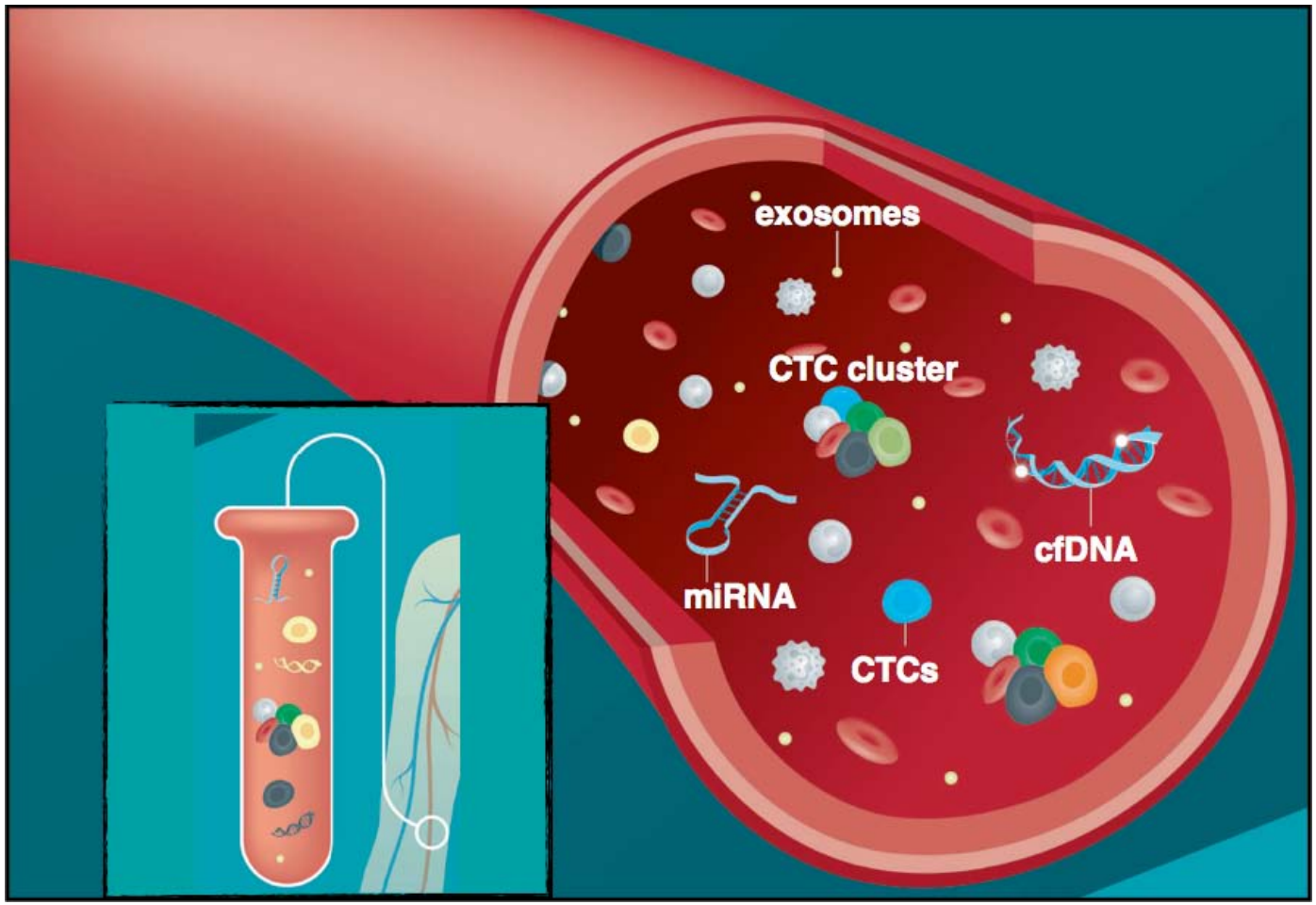
Rilascio di CTCs dal tumore primario



L'interazione con le piastrine sostituisce l'assenza dello stroma nel circolo

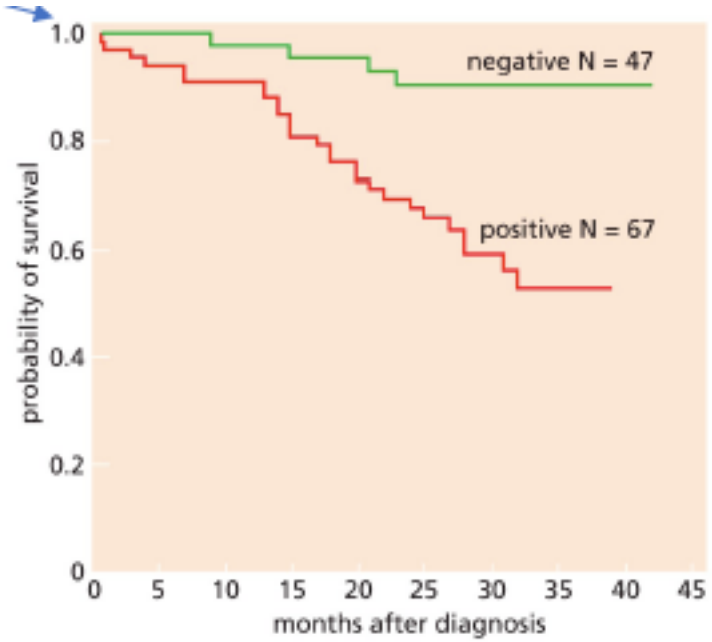
Lambert et al Cell 2017

Analisi di CTC mediante BIOPSIA LIQUIDA



Le CTC non sono necessariamente metastatiche

Number of **Disseminated tumor cells (DTC) in the marrow seems to be a better prognostic marker than the concentration** of **CTC (Circulating Tumor cells) in the blood**



Cytokeratin –positive cells in the marrow (Micrometastatis) of a BC patients Have a bad prognosis (50% of them dying In 3 years from diagnosis)

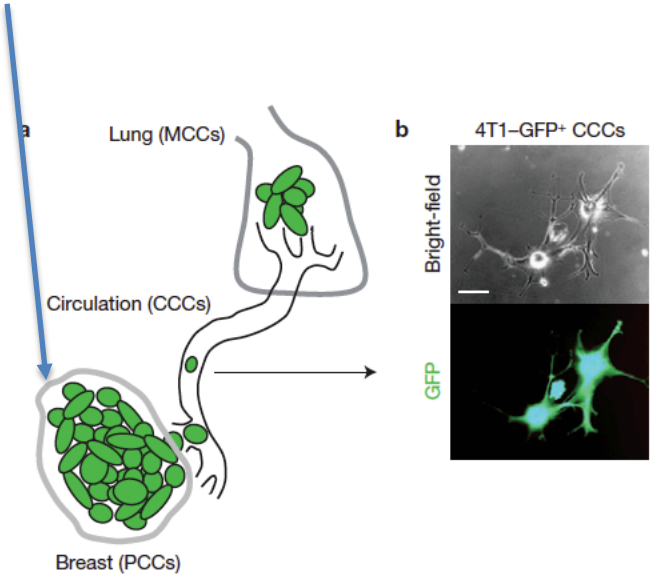
Metabolic reprogramming in disseminated cells

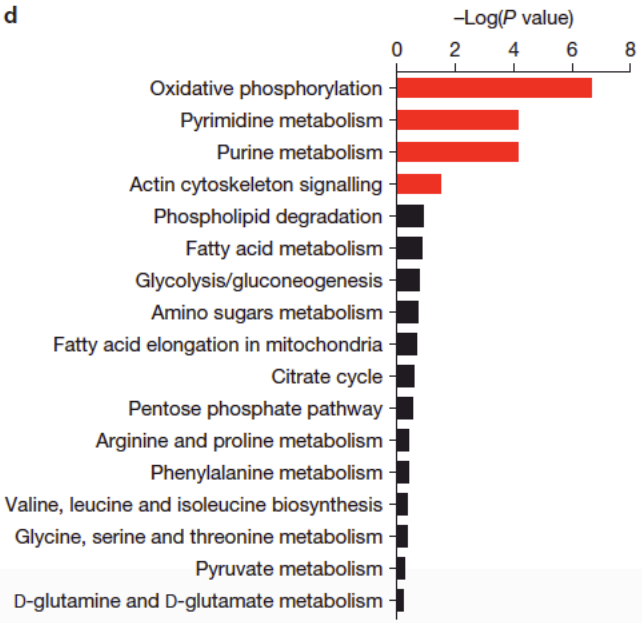
OxPhos

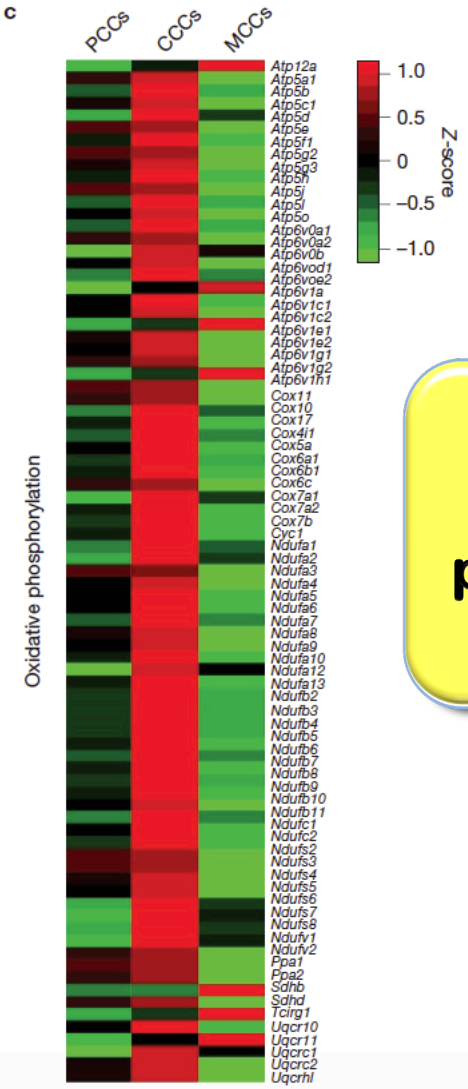
nature cell biology

4T1-GFP tumor cells

PGC-1α mediates mitochondrial biogenesis and oxidative phosphorylation in cancer cells to promote metastasis

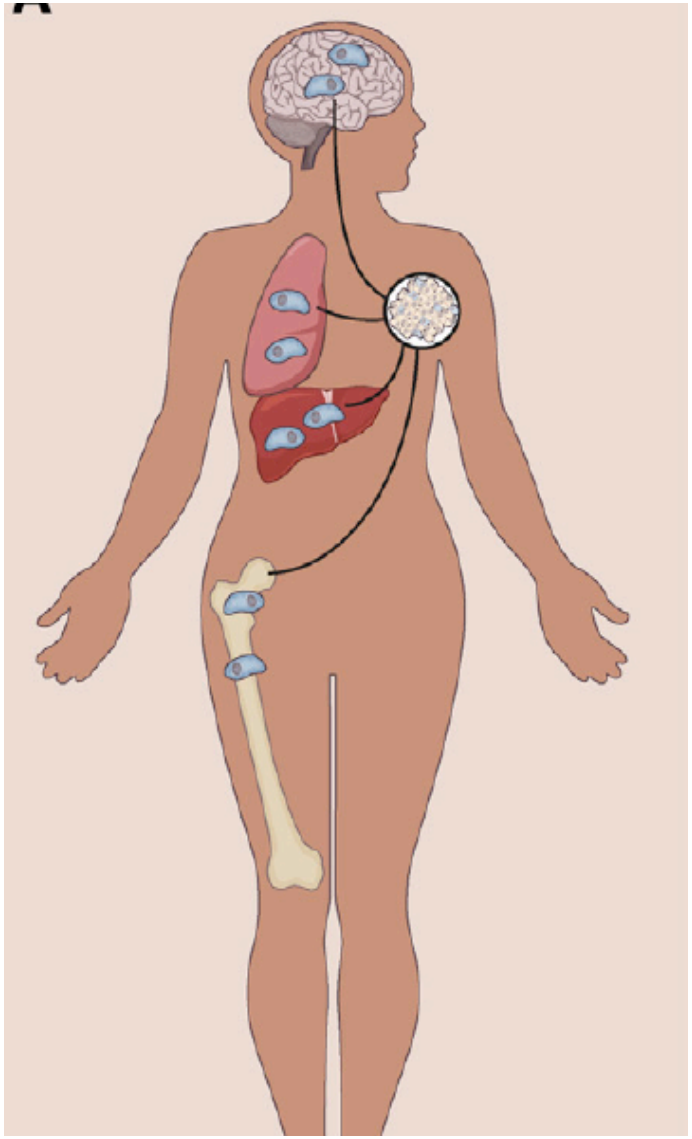


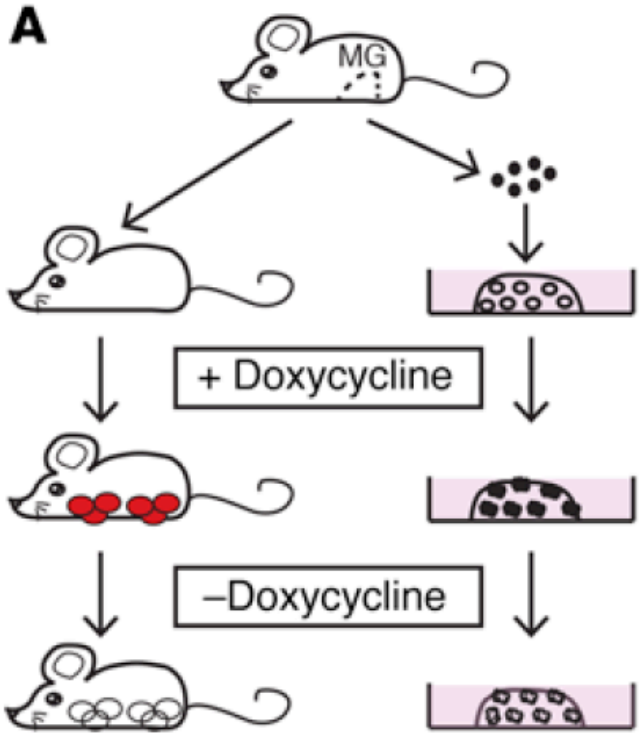




Le CTCs hanno un metabolismo volto a produrre ATP anzichè biomassa

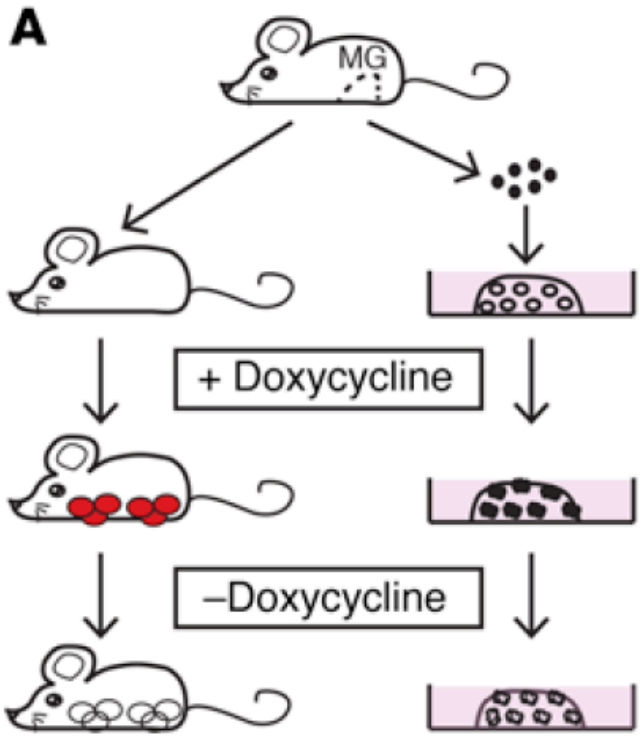
Disseminated tumor cells DTCs (minimal residual disease)

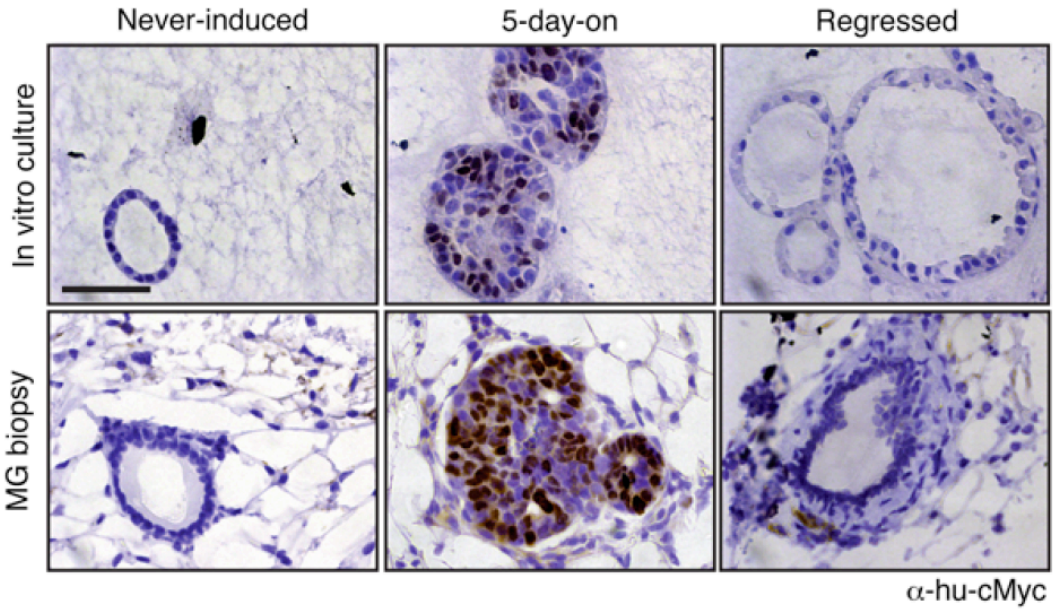




Metabolic shifts in residual breast cancer drive tumor recurrence

Kristina M. Havas,[1,2] Vladislava Milchevskaya,[3] Ksenija Radic,[3] Ashna Alladin,[3] Eleni Kafkia,[3] Marta Garcia,[3] Jens Stolte,[1] Bernd Klaus,[3] Nicole Rotmensz,[4] Toby J. Gibson,[3] Barbara Burwinkel,[5] Andreas Schneeweiss,[6] Giancarlo Pruneri,[7] Kiran R. Patil,[3] Rocio Sotillo,[1,8,9] and Martin Jechlinger[1,3]





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Tumor recurrence is the leading cause of breast cancer–related death. Recurrences are largely driven by cancer cells that survive therapeutic intervention. This poorly understood population is referred to as minimal residual disease. Here, using mouse models that faithfully recapitulate human disease together with organoid cultures, we have demonstrated that residual cells acquire a transcriptionally distinct state from normal epithelium and primary tumors. Gene expression changes and functional characterization revealed altered lipid metabolism and elevated ROS as hallmarks of the cells that survive tumor regression. These residual cells exhibited increased oxidative DNA damage, potentiating the acquisition of somatic mutations during hormonal-induced expansion of the mammary cell population. Inhibition of either cellular fatty acid synthesis or fatty acid transport into mitochondria reduced cellular ROS levels and DNA damage, linking these features to lipid metabolism. Direct perturbation of these hallmarks in vivo, either by scavenging ROS or by halting the cyclic mammary cell population expansion, attenuated tumor recurrence. Finally, these observations were mirrored in transcriptomic and histological signatures of residual cancer cells from neoadjuvant-treated breast cancer patients. These results highlight the potential of lipid metabolism and ROS as therapeutic targets for reducing tumor recurrence in breast cancer patients.

Ruolo dei lipidi nella progressione tumorale

Tumour progression and drug resistance

Migration

- Biophysical properties of structural lipids alter membrane fluidity
- Prostaglandin E_2 (PGE_2) production by transforming growth factor-β induces epithelial-to-mesenchymal transition
- Small GTPases are prenylated via the mevalonate pathway

Angiogenesis

- PGE_2 secretion by cancer cells induces blood vessel outgrowth
- Free FAs induce vascular endothelial growth factor (VEGF) expression by binding to and activating peroxisome proliferator-activated receptor-γ (PPARγ)

Immunosuppression

- PGE_2 induces reprogramming of macrophages to the M2 subtype
- Release of PGE_2 blocks the type 1 interferon-dependent innate immune response
- Secretion of linoleic acid causes loss of T helper cells
- Metabolic competition between cancer cells and immune cells restricts immune cell function

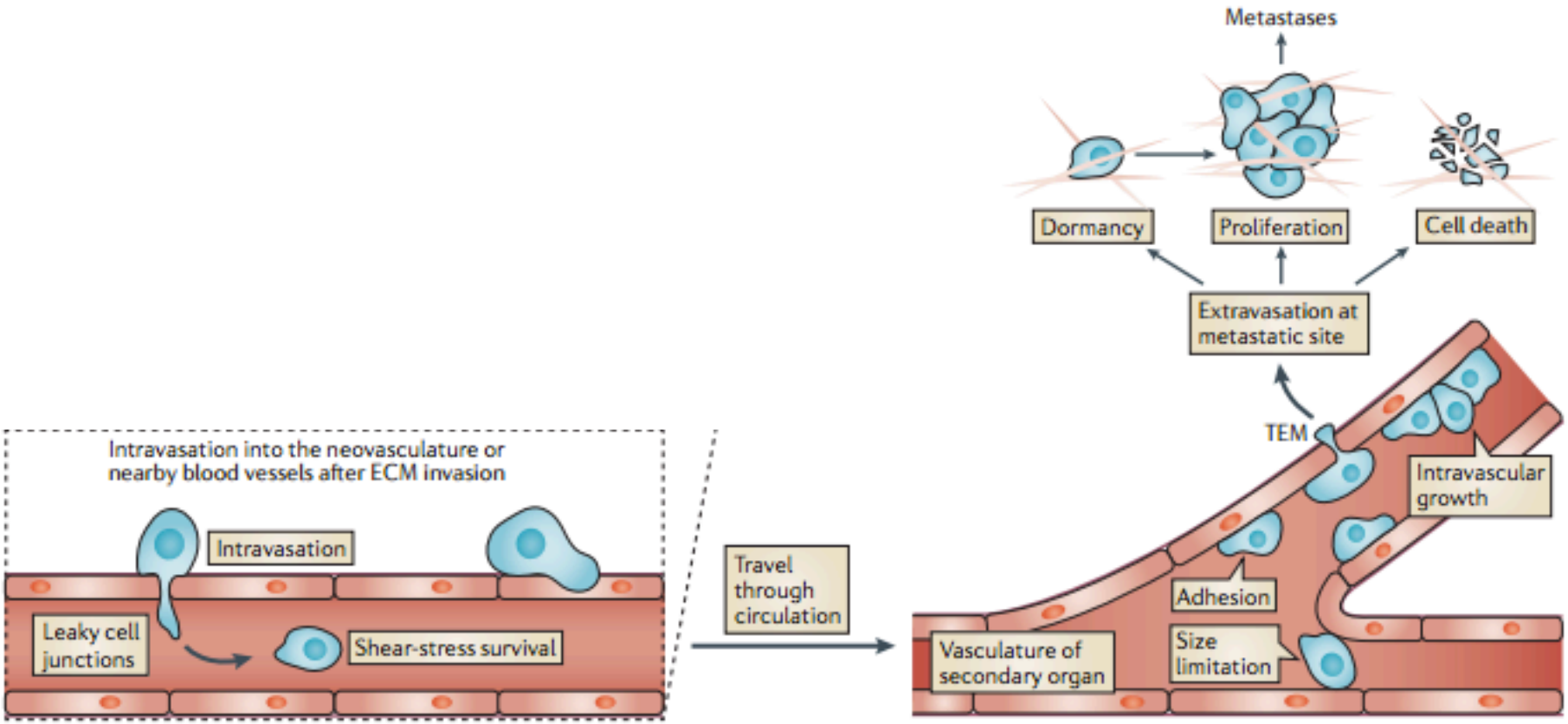
Metabolic symbiosis

- Cancer cells induce lipolysis in adipocytes to obtain substrates for energy generation
- Lipids may participate in the exchange of metabolites between different cell populations

Drug resistance

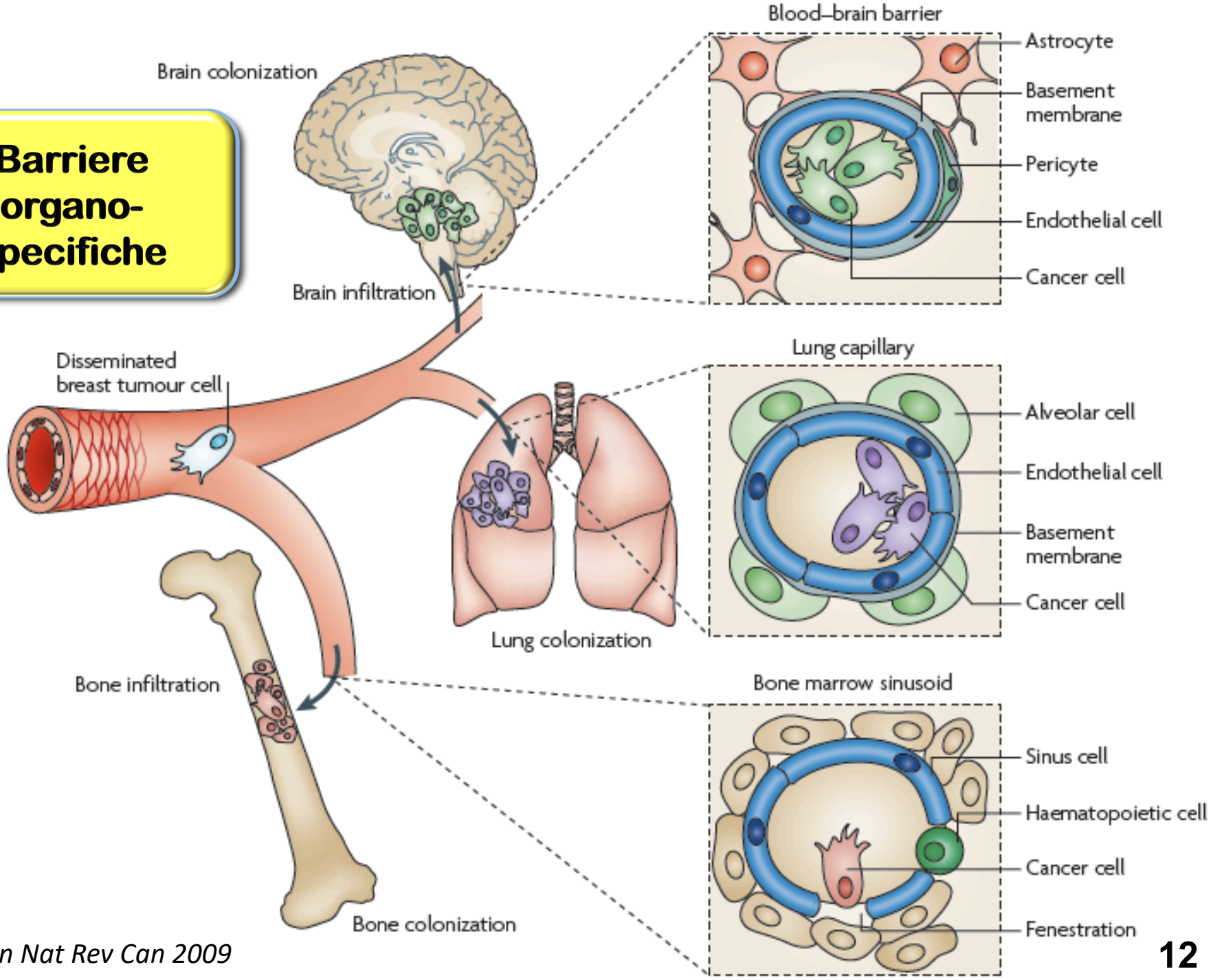
- Lipid composition of the mitochondrial membrane determines chemosensitivity of cancer cells
- Degree of saturation of membrane lipids increases oxidative stress tolerance

Extravasazione e formazione di micrometastasi



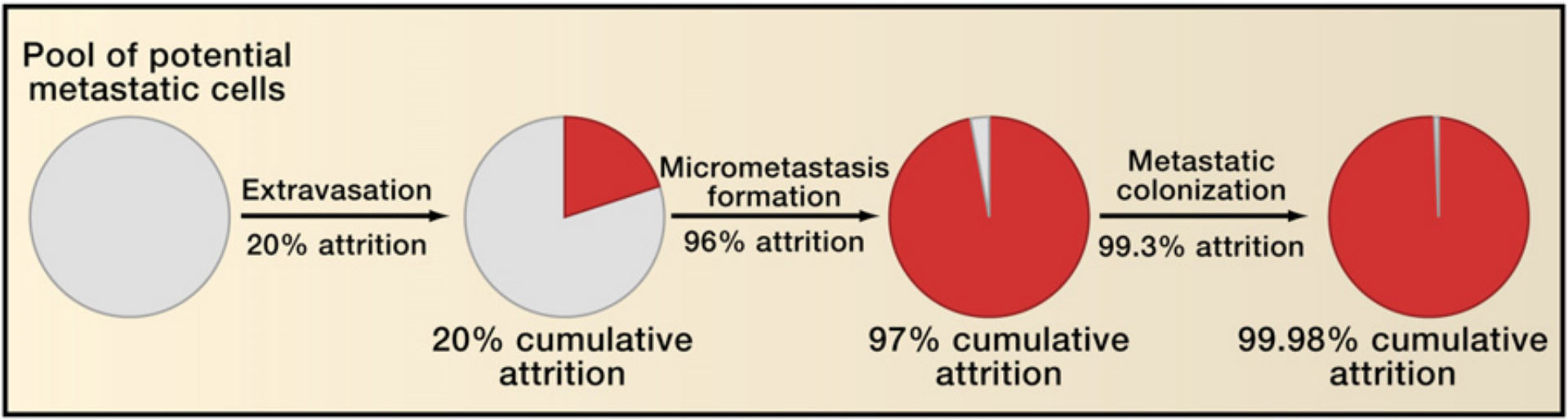
Reymond et al. Nat Rev Cancer 2013

Barriere organo-specifiche



Nguyen Nat Rev Can 2009

Il processo di COLONIZZAZIONE è poco efficiente (rate-limiting step della cascata metastatica)



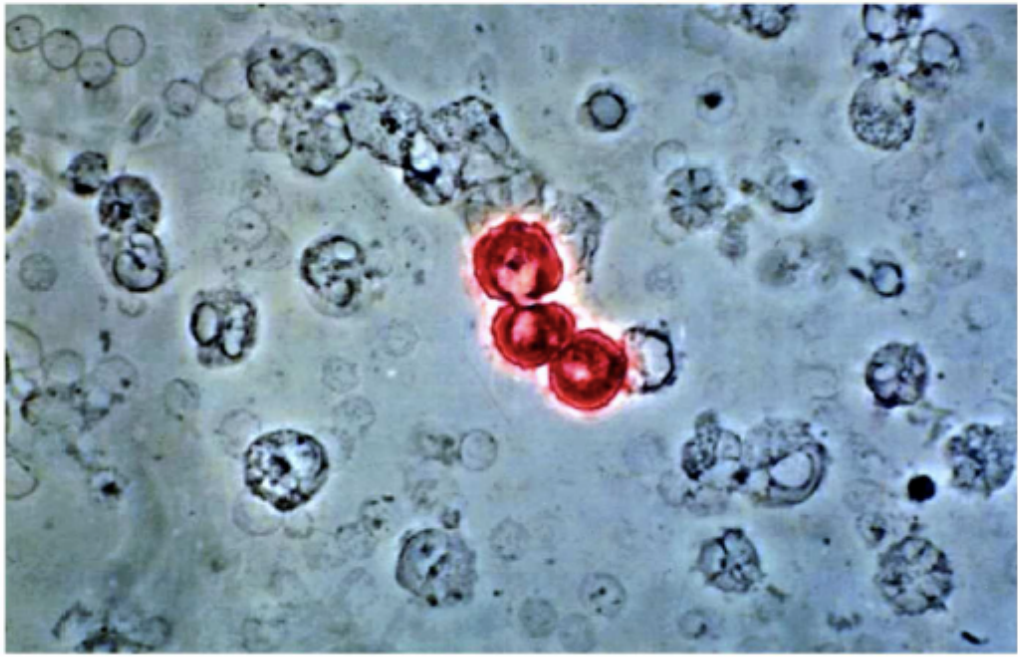
Valastyan & WeinbergCell 2011

Formazione di micrometastasi

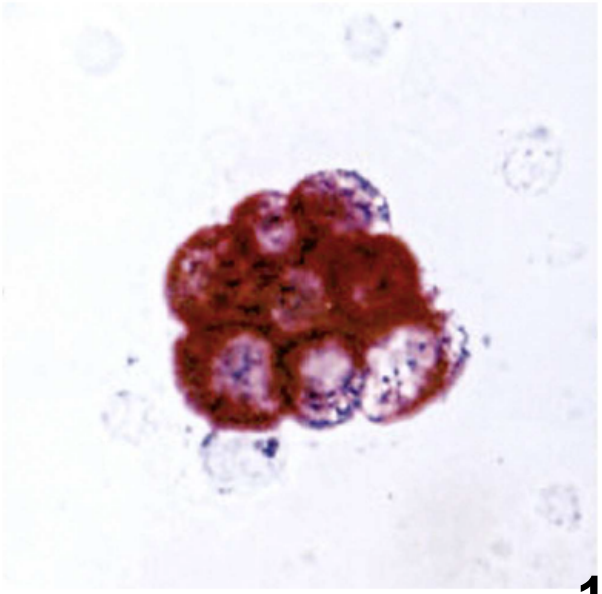
La maggiorparte delle CTC (circulating tumor cells) che extravasano sono eliminate dal parechima (apoptosi o killing dal sistema immunitario) oppure entrano in uno stato di dormienza a lungo termine (settimane, mesi, anni): DTC (disseminated tumor cells)

Micro-metastasis in bone marrow: colon cancer

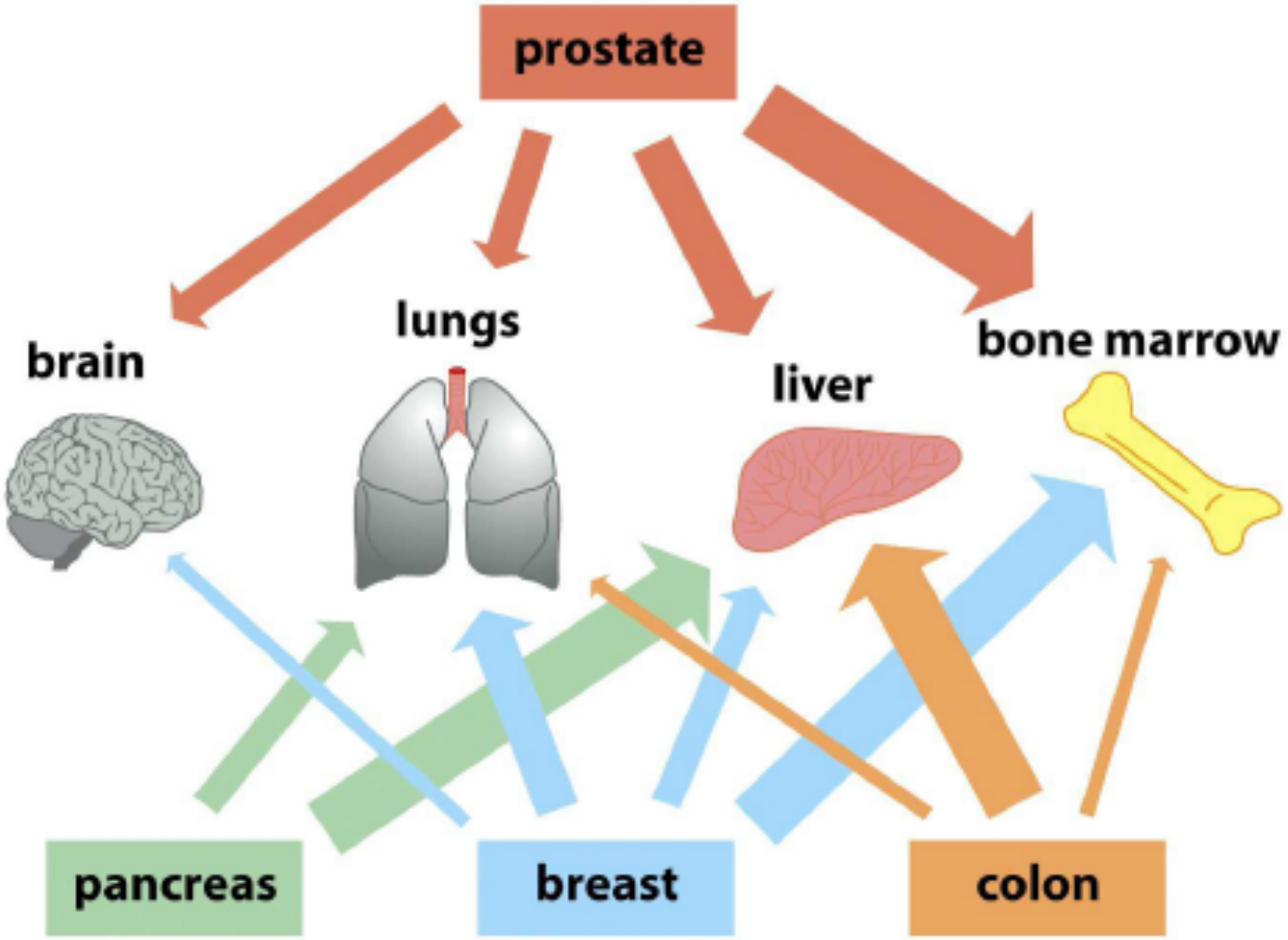
(anti-cytokeratin antibody stain)



Micro-metastasis in bone marrow: breast cancer

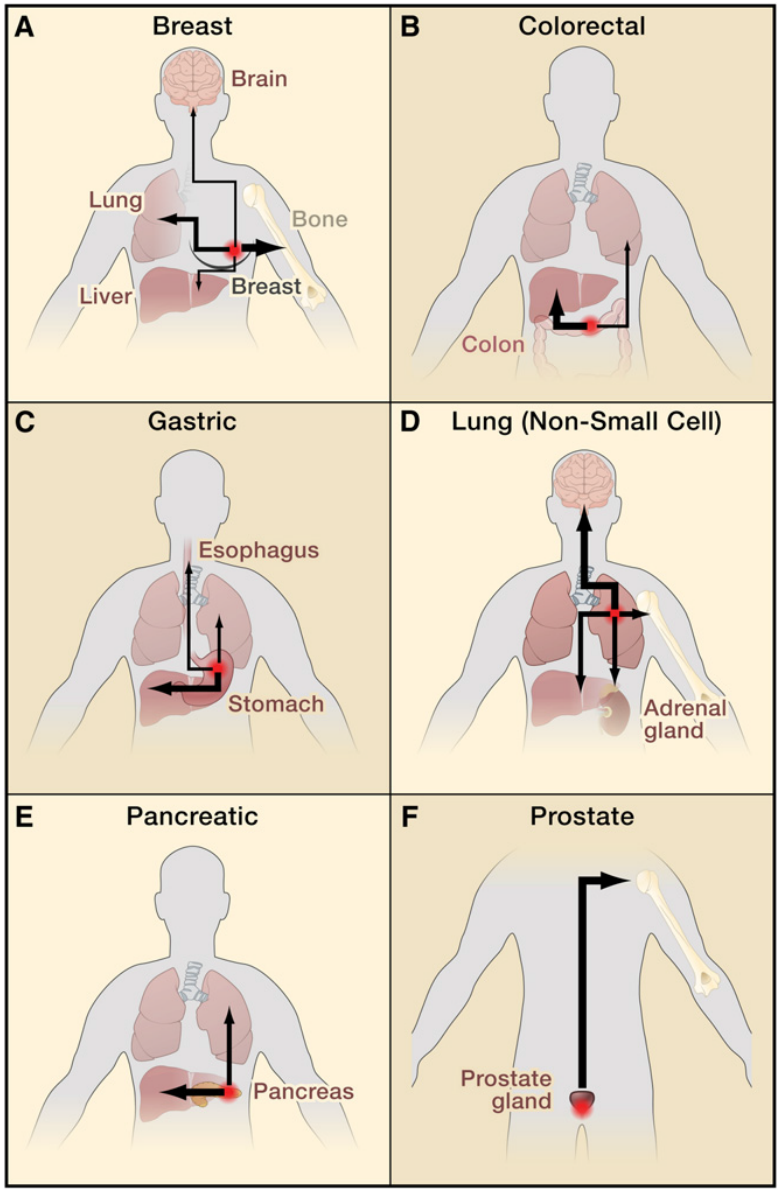


Tropismo metastatico: processo passivo o attivo?



I carcinomi di un particolare tessuto epiteliale formano metastasi diagnosticabili solo in alcuni organi tra tutti quelli teoricamente raggiungibili

Tropismo metastatico: processo passivo o attivo?



Organ tropism of metastatic cells

Metastasis results from disseminated cancer cells that initiate new tumors at distant organ sites. The metastatic cascade involves multiple steps, including invasion, entry into the circulation from the primary tumor, systemic dissemination, arrest and extravasation in secondary organs, settlement into latency, reactivation, outgrowth, and potential seeding of tertiary metastasis. **The pattern of affected organs is remarkably variable depending on the cancer type**. Some cancer types predominantly spread to one organ (e.g. prostate cancer to bone, pancreatic cancer and uveal melanoma to liver), or show **sequential** organ specific colonization (e.g. colorectal cancer, CRC, frequently metastasizes first to the liver, later to lungs and brain). Other cancer types, such **as breast cancer, lung cancer, or melanoma, are able to colonize many different organ sites, either sequentially or synchronously**.

What determines the organ tropism of metastases? Each organ varies in its **physical accessibility**, vascular and nutrient **supply, and stromal composition**, thus placing different demands on infiltrating cancer cells. The organ-specific **circulation pattern** and the anatomy of vessels certainly influence metastatic spread. However, this does not fully explain the organ-specific pattern of metastasis clinically observed in most cancers.

Discrepancy between anatomy and metastasis in different organs has long been observed and forms the basis for the '**seed and soil' hypothesis**, according to which, cancer cell seeds have intrinsic compatibilities with certain, welcoming organ microenvironment soils.

The seed and soil hypothesis

"What is it that decides what organs shall suffer a case of disseminated cancer?"

"When a plant goes to seed, its **seeds** are carried in all directions….,but they can only live and grow if they fall on congenial **soil**."
-Stephen Paget 1889-

EVOLUZIONE METASTATICA

Metastasis is above all a **Darwinian selection** process in which cancer cells with distinct **metastatic traits** that enable them to **overcome metastatic bottlenecks**, are being selected from a genetically and epigenetically heterogeneous tumor cell population.

General mediators of metastasis, such as those supporting invasion, ability to amplify survival pathways, or immune evasion increase the probability of cancer cells to adapt and, consequently, survive through multiple specific challenges in multiple organs.
In contrast, **certain genes and pathways enable passage through critical organ-specific barriers**, such as crossing the blood-brain barrier, or mediate beneficial interactions with organ-specific cell types, such as the osteoclasts in the bone marrow.

Anna C. Obenauf and Joan Massagué
Trends Cancer. 2015

Caratteristiche delle DTCs competenti per la colonizzazione

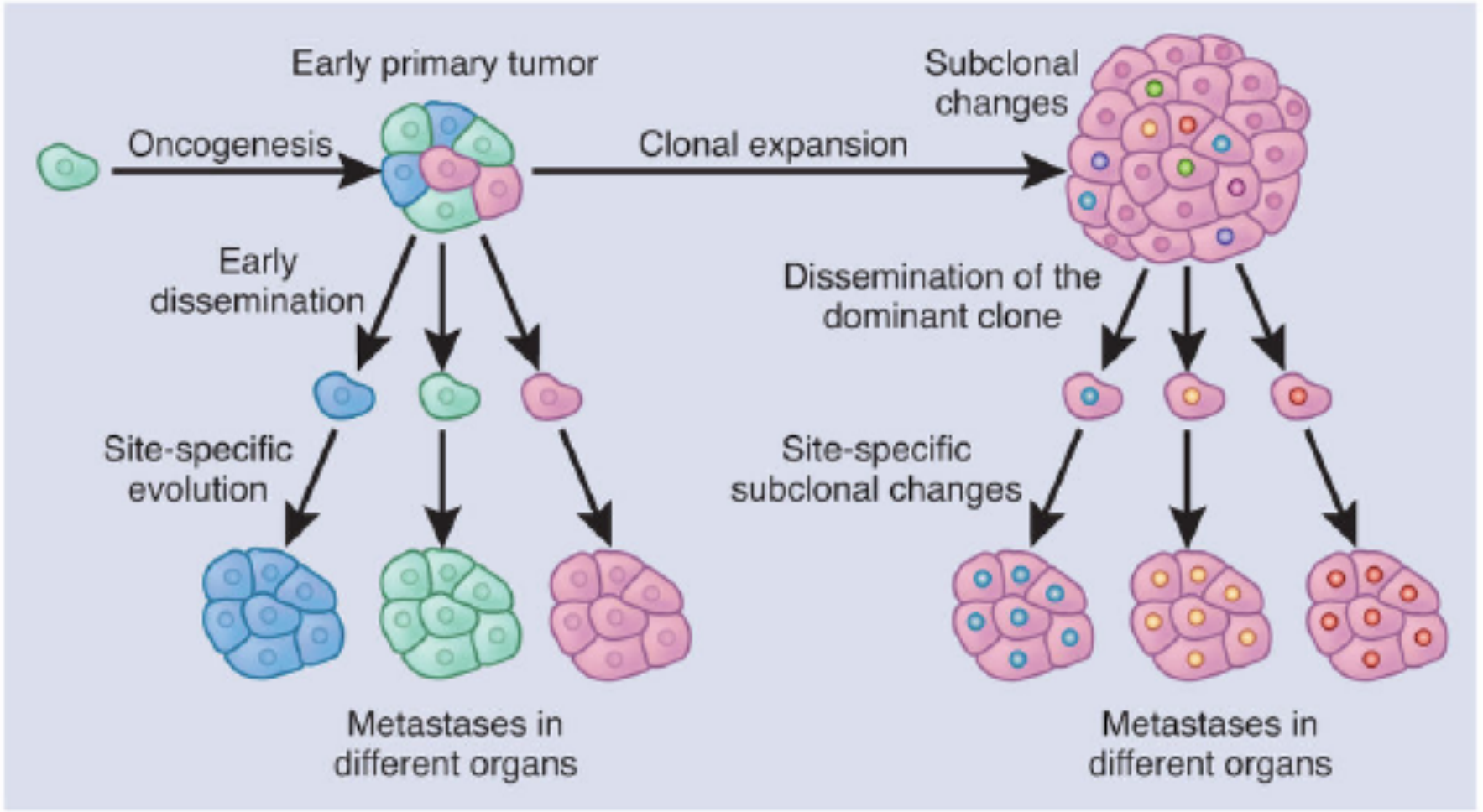
- They must possess **tumor-initiating ability** (CSC feature)

- They must build **adaptive programs enabling them to survive and grow in the microenvironment** present in the parenchyma of distant tissues.

- in certain cases, the organ-specific tropism of metastatic cells is **influenced by the design of the circulatory system**. Es Colorectal carcinoma (CRC) metastasis to the liver is strongly favored simply because the portal vein draining the gut empties directly into the liver and thus the cells are trapped there.

- a **diverse array of organ-specific metastatic programs** that mediate colonization of the bone, lung, liver, and brain have been reported

2 modelli di progressione metastatica: PARALLELO E LINEARE



PROGRESSIONE PARALLELA **PROGRESSIONE LINEARE**

- **Parallel progression model**

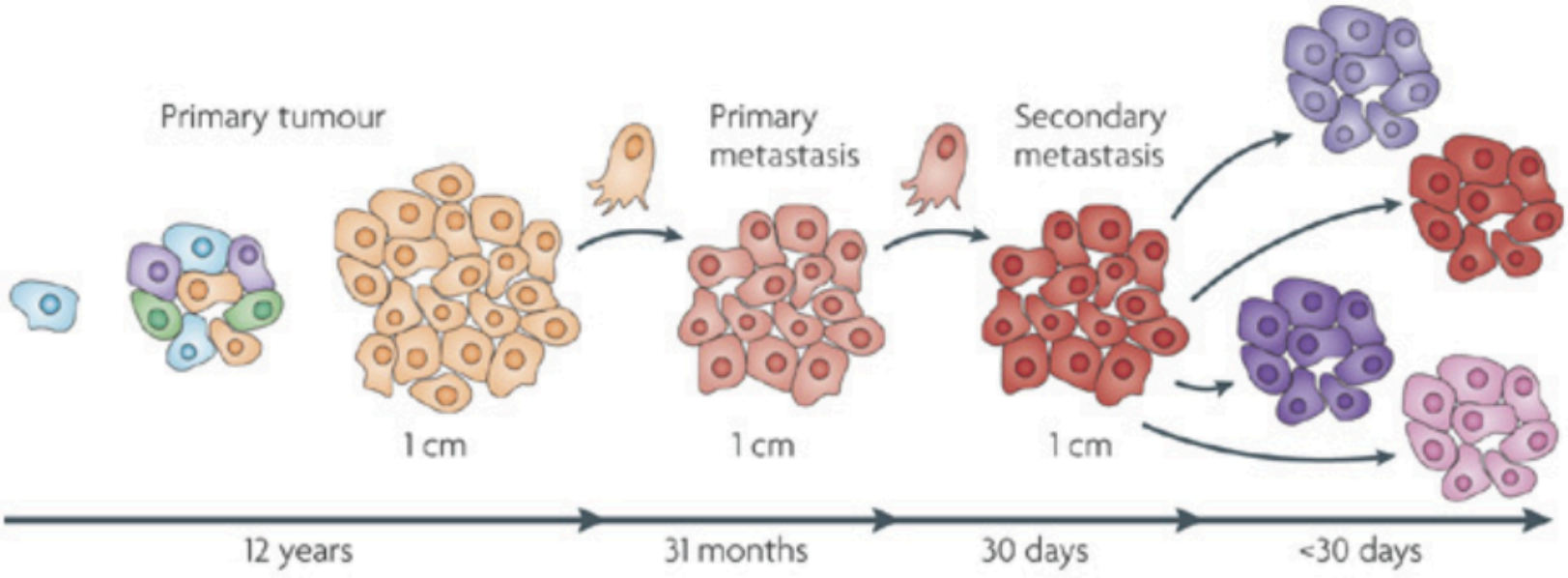
  dissemination starts early, and different tumor cell clones are seeded in **parallel** to different organs. These DTCs remain dormant or develop into overt metastasis after **considerable genetic evolution** that occurs independently

- **Linear progression model**

  tumor cells undergo **clonal selection**, during which the advantageous clones expand and dominate over the others, with additional subclonal and mutational changes occurring within the clonal populations, hence resulting in different degrees of tumor heterogeneity. When disseminated, these heterogeneous cells seed and colonize different organs. Additional site-specific subclonal changes could occur that endow these DTCs with additional metastatic properties that are needed for the formation of overt metastases.

Progressione lineare

Le cellule tumorali disseminano DOPO aver acquisito la COMPETENZA METASTATICA nel tumore primario



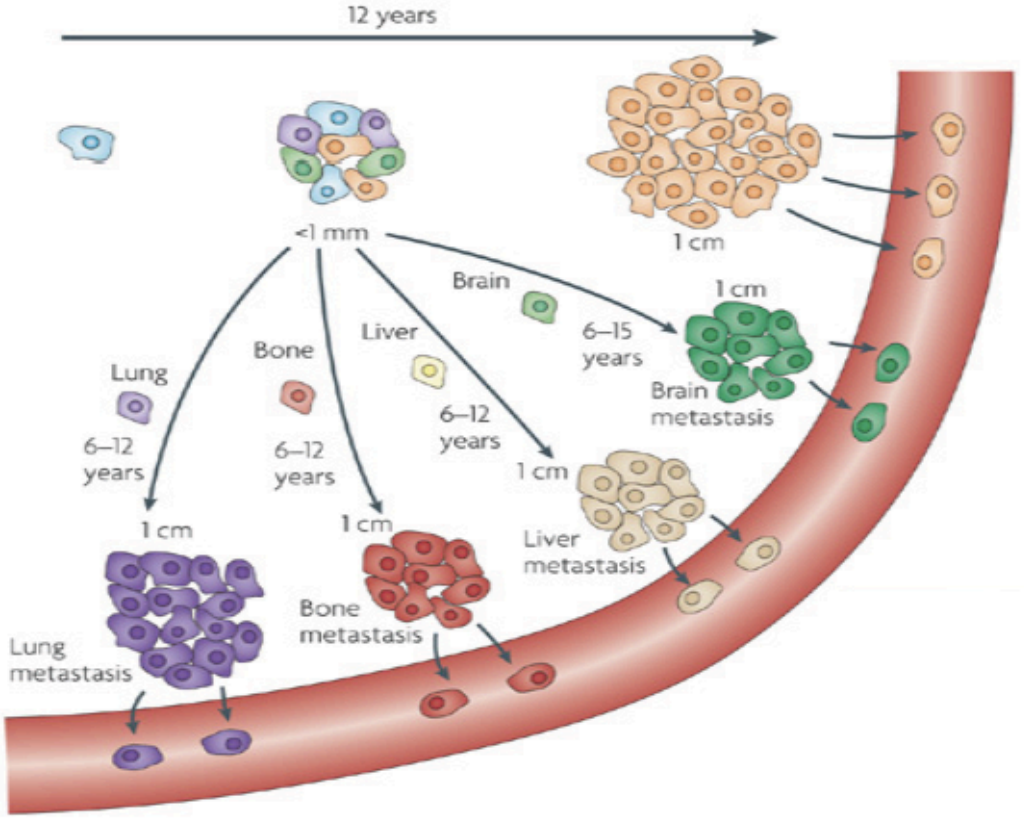
Progressione parallela

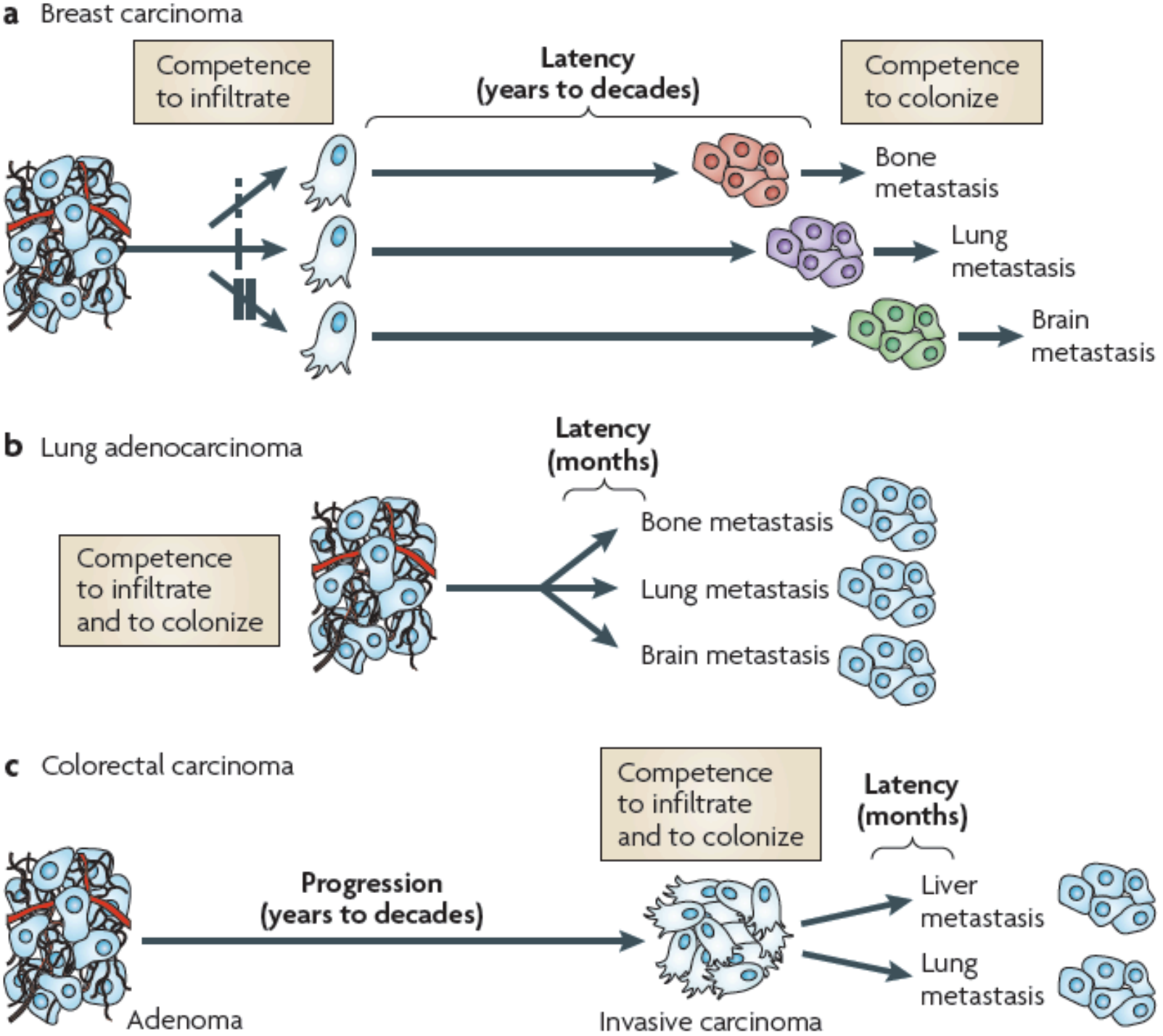
Le cellule tumorali disseminano PRIMA di aver acquisito la COMPETENZA METASTATICA
La acquisiscono durante o dopo la disseminazione

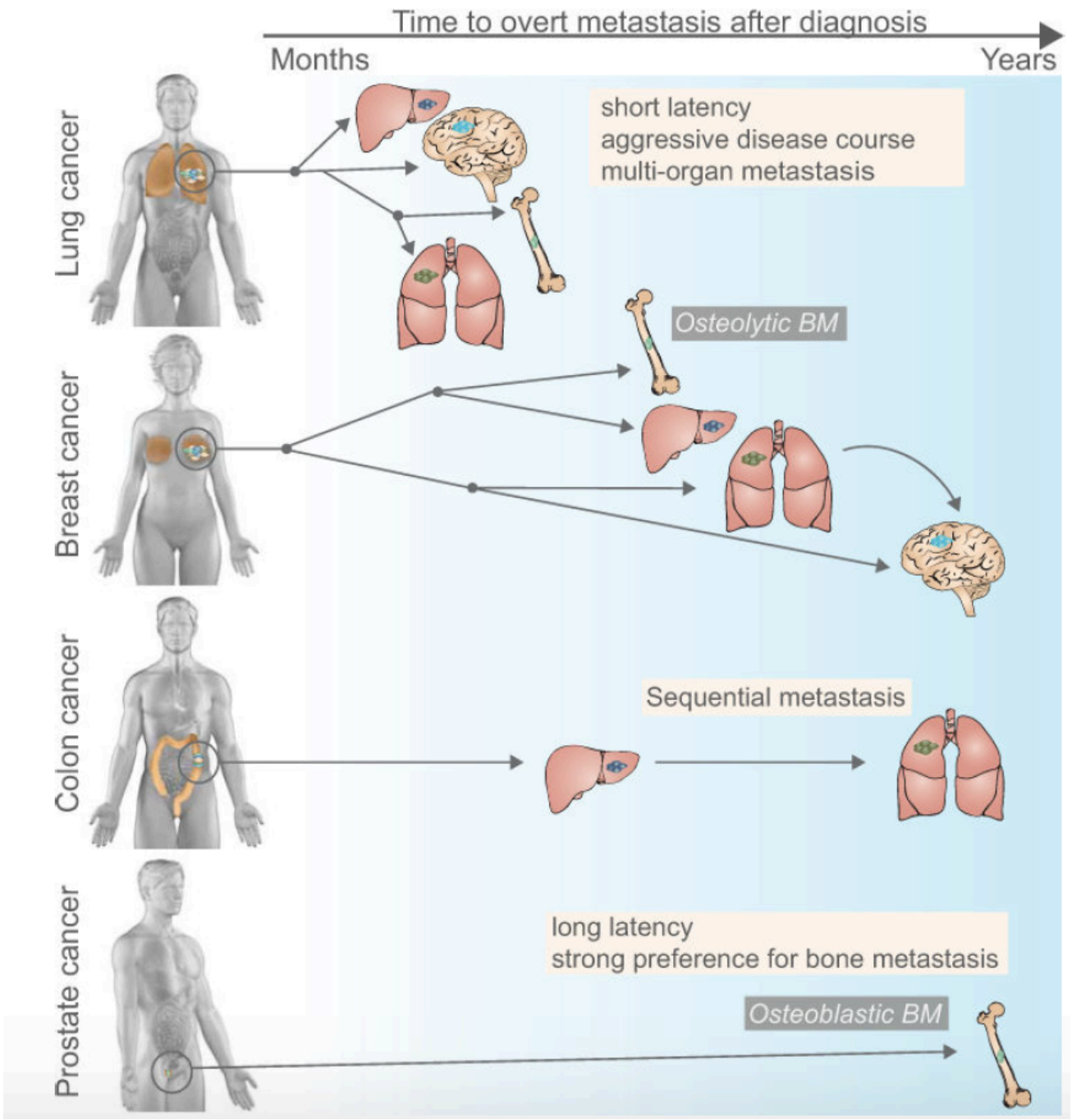
a) Accumulation of mutations indipendently and parallel to the primary cancer

b) During dissemination acquire the capability to growth in different microenvironment

c) The maturation of the metastatic phenotype can occur at different times




a Breast carcinoma
Competence to infiltrate
Latency (years to decades)
Competence to colonize
Bone metastasis
Lung metastasis
Brain metastasis
b Lung adenocarcinoma
Latency (months)
Competence to infiltrate and to colonize
Bone metastasis
Lung metastasis
Brain metastasis
c Colorectal carcinoma
Competence to infiltrate and to colonize
Latency (months)
Progression (years to decades)
Liver metastasis
Lung metastasis
Adenoma
Invasive carcinoma


Time to overt metastasis after diagnosis
Months
Years
Lung cancer
short latency
aggressive disease course
multi-organ metastasis
Osteolytic BM
Breast cancer
Colon cancer
Sequential metastasis
Prostate cancer
long latency
strong preference for bone metastasis
Osteoblastic BM

The course of metastasis can vary according to the tumour type.

a | In oestrogen receptor-positive breast tumours,
Cancer cells can be competent to disperse and infiltrate distant organs at early stages but they frequently enter a prolonged period of latency. During this period, disseminated cancer cells can remain dormant or enter a proliferative state that is counterbalanced by cell death. **Through unknown mechanisms, a subset of these latent tumour cells (or their microenvironment) can accumulate the full set of functions that are required for overt colonization. In this model, disseminated breast cancer cells complete their evolution into metastatic entities under selection in a particular host microenvironment, producing organ-specific metastases.**
b | Lung adenocarcinoma cells also target the brain, bone and contralateral lung but do so without a long intervening lag between infiltration and colonization. This course of metastasis implies the existence of mechanisms that render lung adenocarcinoma cells competent for infiltration and colonization of multiple organs.
c | Colorectal adenomas can take decades to develop into locally invasive carcinomas but, once this stage is reached, dissemination and colonization of the liver and, less frequently, of the lungs rapidly ensue.

Therefore, the different courses of metastasis in these types of cancer **imply different mechanisms for the acquisition of infiltration, survival and colonization functions**.

Nguyen Nat Rev Can 2009