Breast Cancer : Macro and Micro environment

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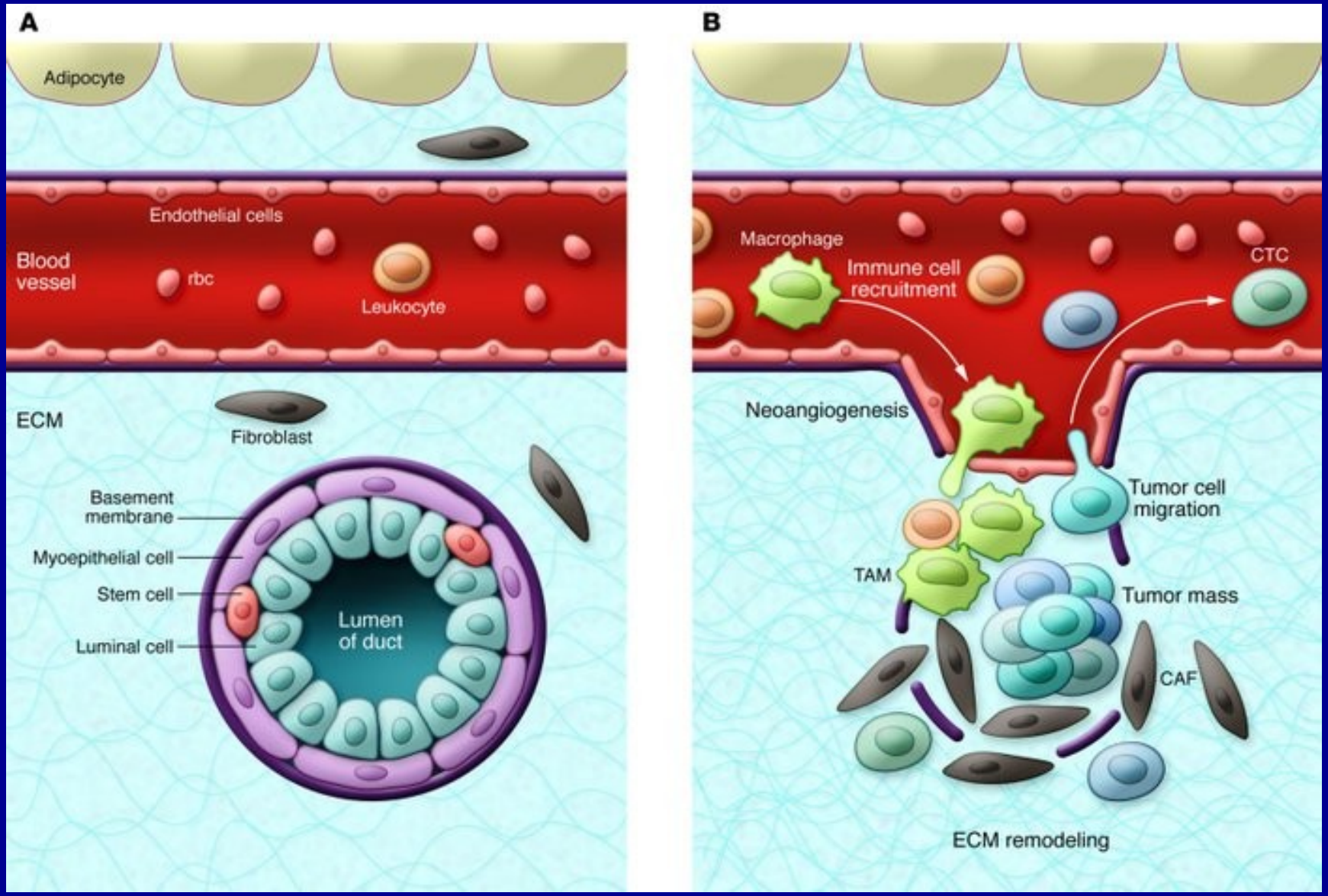
Selected elements contributing to breast tumor heterogeneity

Classifier	Classifications/variables
Histological	IDC NOS, ILC, medullary, neuroendocrine, tubular, apocrine, metaplastic, mucinous (A and B), inflammatory, comedo, adenoid cystic, micropapillary
Immunopathological	ER status, PR status, HER2 status
Transcriptional	Luminal A, luminal B, normal-like, basal/basal-like, HER2, claudin low, molecular apocrine
Genomic	17q12, basal complex, luminal simple, luminal complex, amplifier, mixed
Genomic heterogeneity	Monogenomic, polygenomic
miRNA-based	Multiple
Epigenetic	Multiple
Microenvironmental	Presence/activation status of local immune cells (T cells, B cells, dendritic cells, macrophages), fibroblast status, ECM composition, CAF status, angiogenesis, hypoxia
Macroenvironmental	Systemic hormone levels, BMI, overall immune status
Longitudinal	CTC features, metastatic features
Other	Intratumoral heterogeneity

(Bertos&Park, 2011)



(A) Normal breast architecture. (B) Breast tumor and surrounding stroma. TAM, tumor-associated macrophage. *(Bertos&Park, 2011)*

Genetic Factors

- Genetic alterations in the tumor-free and normal-appearing epithelial and mesenchymal tissues close to and away (at least 15-mm distance) from the breast cancer tissues.
- Skin fibroblasts displaying various oncofetal characteristics (invasion of embryonic organ culture, increase of saturation densities) in 90% of patients with familial breast cancer and in 50% of the clinically unaffected first-degree relatives of patients suffering from familial breast cancer.
- High incidence of male cells in normal breast tissues, but significantly less in most cancers

Table 3 Genetic alterations (LOH and MSI) in cancerous and non-cancerous breast tissues

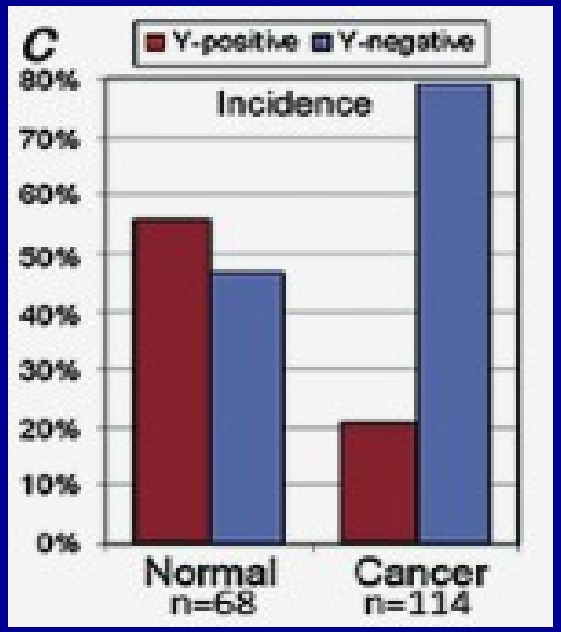
Case	*Invasive carcinoma*	*Ductal carcinoma in situ*	*Normal epithelium (at a distant from cancer)*	*Stroma close to invasive carcinoma*	*Normal stroma (at a distant from cancer)*	*Epidermis*	*Dermis*
1	●	—	—	—	●	—	●
2	●	—	●	●	●	●	●
3	●	●	●	●	—	●	●
4	—	—	—	♦	—	—	—
5	●	—	—	—	●	●	●
6	—	—	—	—	—	●	●
7	—	—	—	—	—	—	—
8	—	—	—	—	—	—	●
9	—	♦	—	—	●	●	● ♦
10	●	●	—	♦	● ♦	♦	—
11	—	●	—	—	—	—	●
12	● ♦	—	—	●	● ♦	♦	●

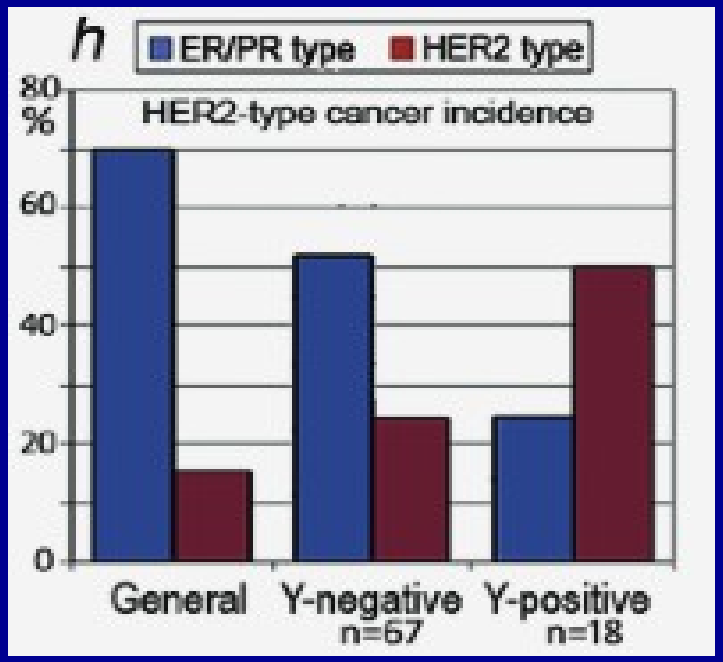
●, LOH (loss of heterozygosity); ♦, MSI (microsatellite instability); —, no change.
All changes are presented with at least one polymorphic DNA marker.

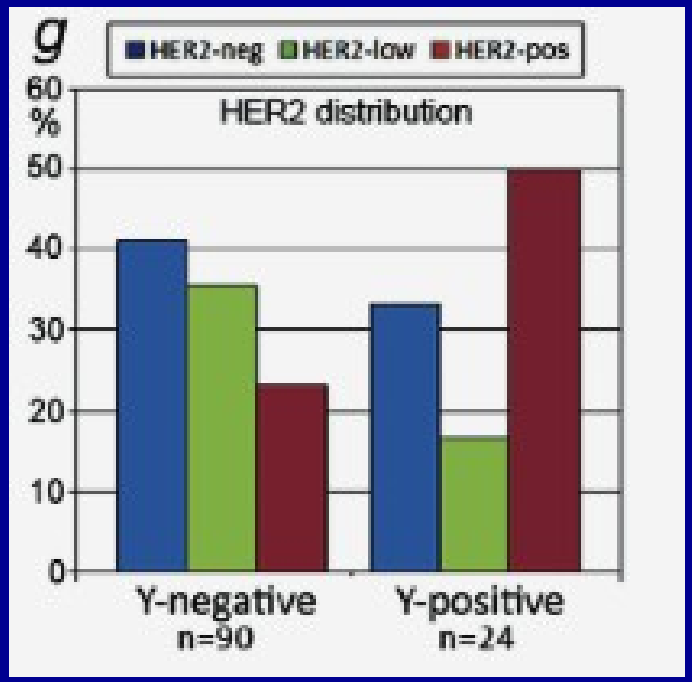
(Moinfar et al, 2008)

Genetic Factors

- High incidence of male cells in normal breast tissues, but significantly less in most cancers
- Hyperchimerism and HER2-type cancers, while Hypochimerism associates with ER/PR-positive (luminal-type) breast cancers







(Dhimolea et al, 2013)

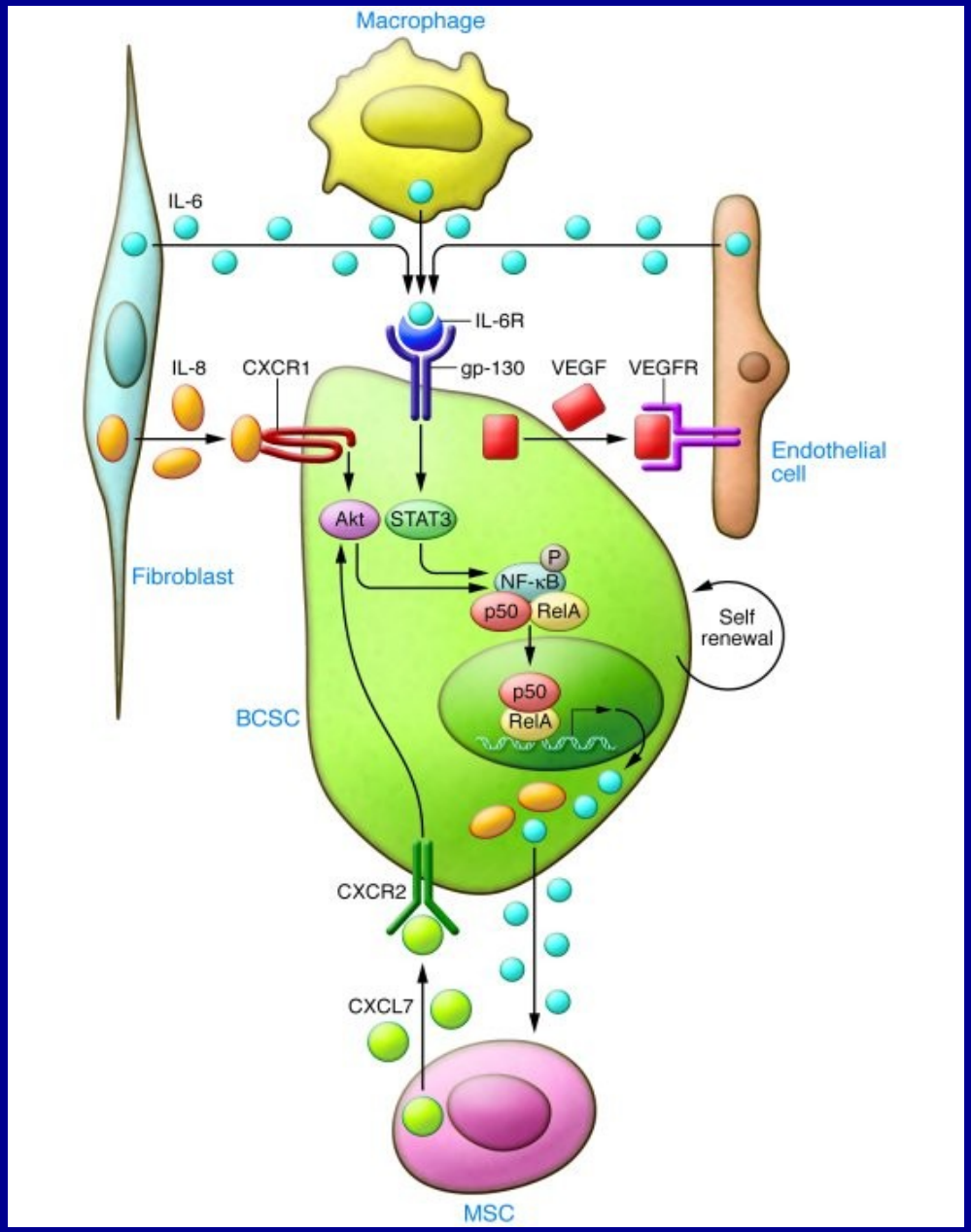
Epigenetic factors

- Breast tumor microenvironment constitutes diverse cell population which secretes various cytokines and growth factors resulted in dysregulation of stem cell regulatory pathways
- Proinflammatory cytokines in obesity
- Metformin

Breast tumor microenvironment constitutes diverse cell population which secretes various cytokines and growth factors

Cell types	Factors	Pathways activated
Mesenchymal cells	CCL5, IL-6, CXCL5, IL-8	PI3K/AKT, NF-κB
Fibroblasts/myofibroblasts	TGF-β, CXCL12, FGF, HGF, IGF, PDGF, Wnt, MMPs	NF-κB, PI3K/AKT, WNT/β-catenin
Endothelial cells	HGF, VEGF	PI3K/AKT, MAPK
Immune cells	IL-8, IL-6	PI3K/AKT, NF-κB, STAT3

(Kokarya et al, 2011)

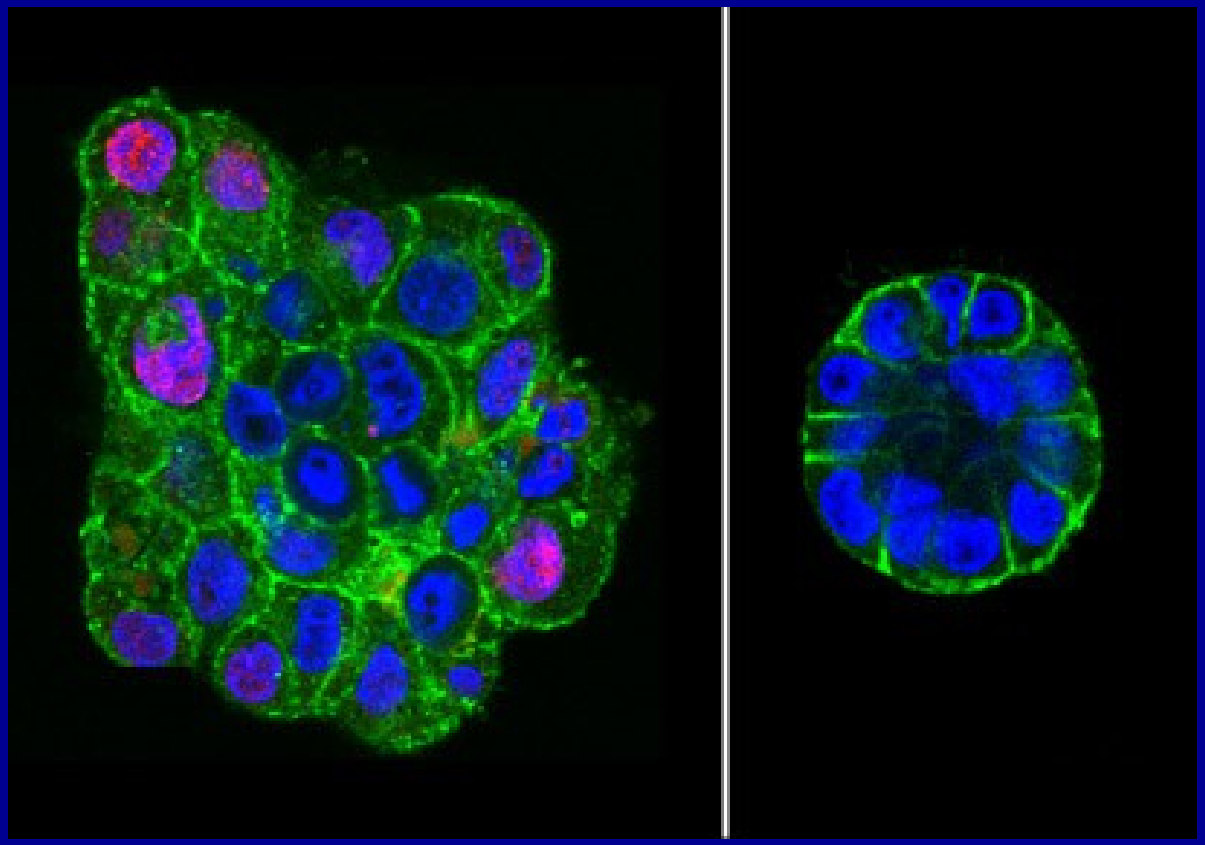


Tumor-associated fibroblasts (TAFs) and macrophages (TAMs) and MSCs have been shown to secrete IL-6, IL-8, and CXCL7, which in turn activate Stat3/NF-κB signaling, leading to self renewal of BCSCs. This generates a positive feedback loop between the tumor microenvironment and tumor cells.

(Kokarya et al, 2011)

Extracellular matrix

- The context in which a cell existed determined what a cell can do
- Tumor reversion by mechanical forces
- E-cadherin blocking agent



(Fletcher lab, 2012)

Chemicals in cosmetics

- Phthalates (nail polish, synthetic fragrance)
- Triclosan (soap, deodorant, toothpaste)
- 1,4-dioxane (shampoo, bath products)
- Parabens (antimicrobial, antifungal)
- Ethylene oxide (fragrance)
- 1,3 butadiene (propellant)
- Polycyclic Aromatic Hydrocarbons-PAHs (naphthalene)
- http://ntp.niehs.nih.gov/?objectid=03C9F0A4-B1C2-31DE-ABA8508AE9949C57

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