

Imaging mass cytometry and multiplatform genomics define the phenogenomic landscape of breast cancer

Source: Ali, H.R., Jackson, H.W., Zanutelli, V.R.T. *et al.* Imaging mass cytometry and multiplatform genomics define the phenogenomic landscape of breast cancer. *Nat Cancer* 1, 163–175 (2020). <https://doi.org/10.1038/s43018-020-0026-6>

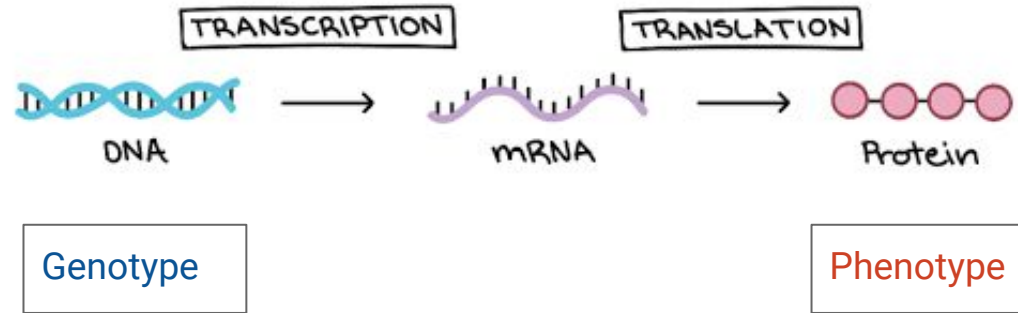
Wayne and Vanessa

Research Problem

- **Problem:** Genomic alterations shape cell phenotypes and the structure of tumor systems in poorly defined ways
- **Research:** To investigate these relationships, the researchers used imaging mass cyometry to quantify the expression of 37 proteins with subcellular spatial resolution in 483 tumors from the METABRIC cohort

Background

Background: Central dogma



Normal cell

Proto-oncogenes

Tumor-suppressor gene

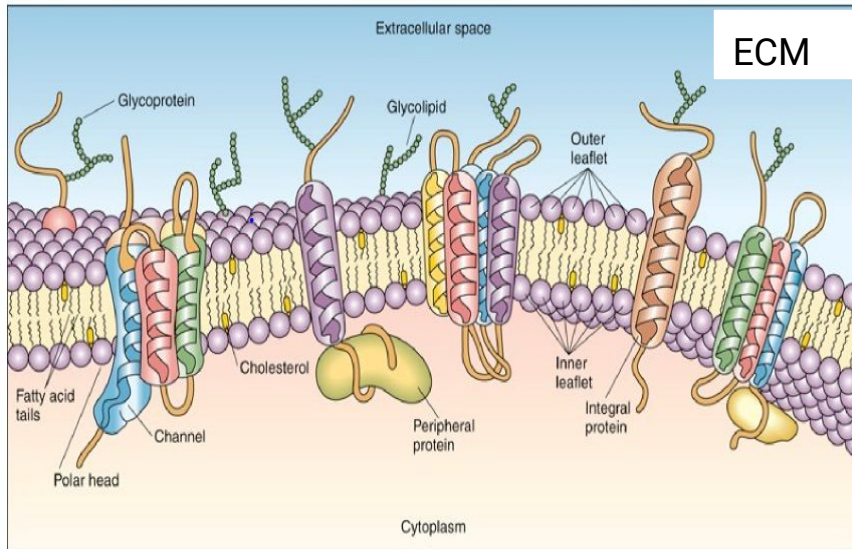
Mutation

Cancer cell

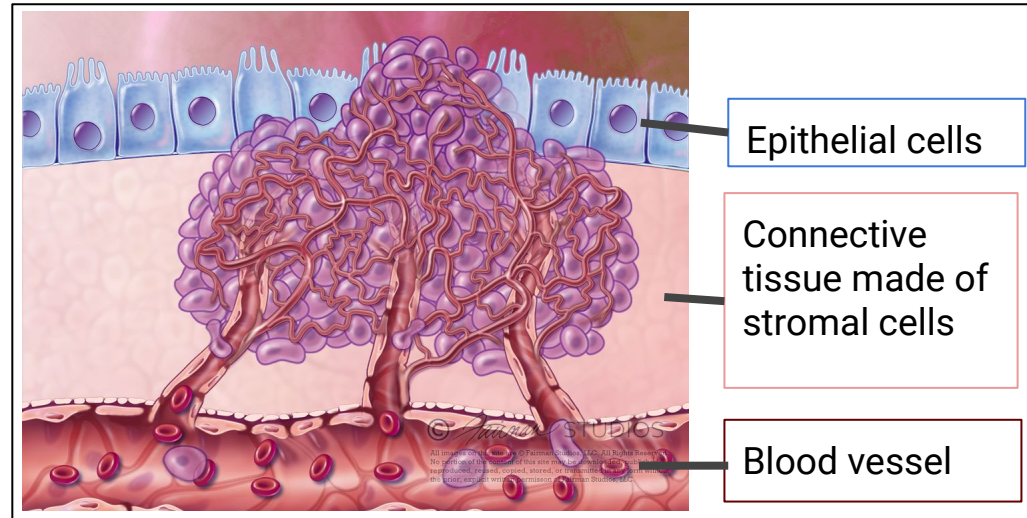
Oncogenes

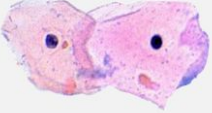

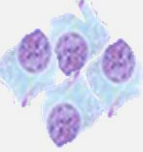
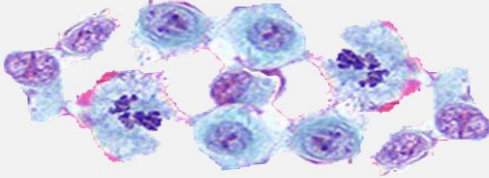

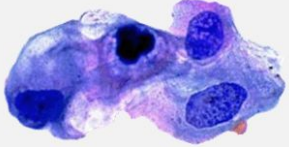
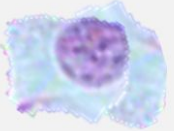
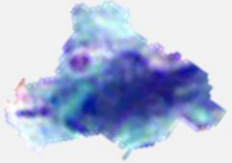
Mutated tumor-suppressor genes

-increased proliferation, decreased apoptosis,
increased mutation rate



Singer and Nicolson, 1972 (Science, 1972 Feb 18;175(23):720-31)



Normal	Cancer	
		Large, variably shaped nuclei
		Many dividing cells; Disorganized arrangement
		Variation in size and shape
		Loss of normal features

Key terms

IMC: imaging mass cytometry, an expansion of **mass cytometry**, but rather than analyzing single cells in suspension, it uses laser ablation to generate plumes of particles that are carried to the **mass cytometer** by a stream of inert gas

assay: testing procedure for estimating the concentration of a pharmaceutically active substance in a formulated product or bulk material

prognosis: the likely course of a disease

heterogeneity: diversity

Data source

Data Source: METABRIC study

- study population and genomic assays
- patients were diagnosed with primary invasive carcinoma (type of breast cancer) and treated in Cambridge, UK, between 1985 and 2005
- uses biospecimens with linked pseudo-anonymized clinical data

Results

D

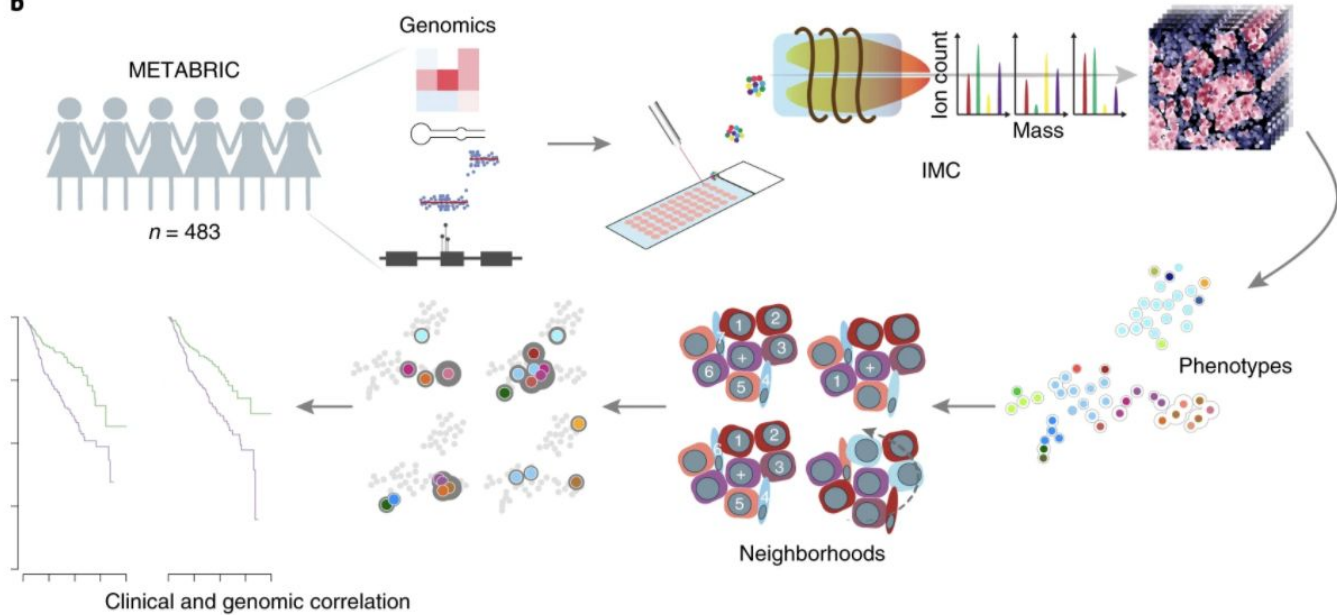


Fig. 1b, Ali et al., Imaging mass cytometry and multiplatform genomics define the phenogenomic landscape of breast cancer

- Spatially resolved phenotyping of breast tumor ecosystems by IMC
- Data-driven derivation of cell phenotypes
- Multidimensional images from IMC were processed, single cells were segmented and cellular neighborhoods were quantified

b

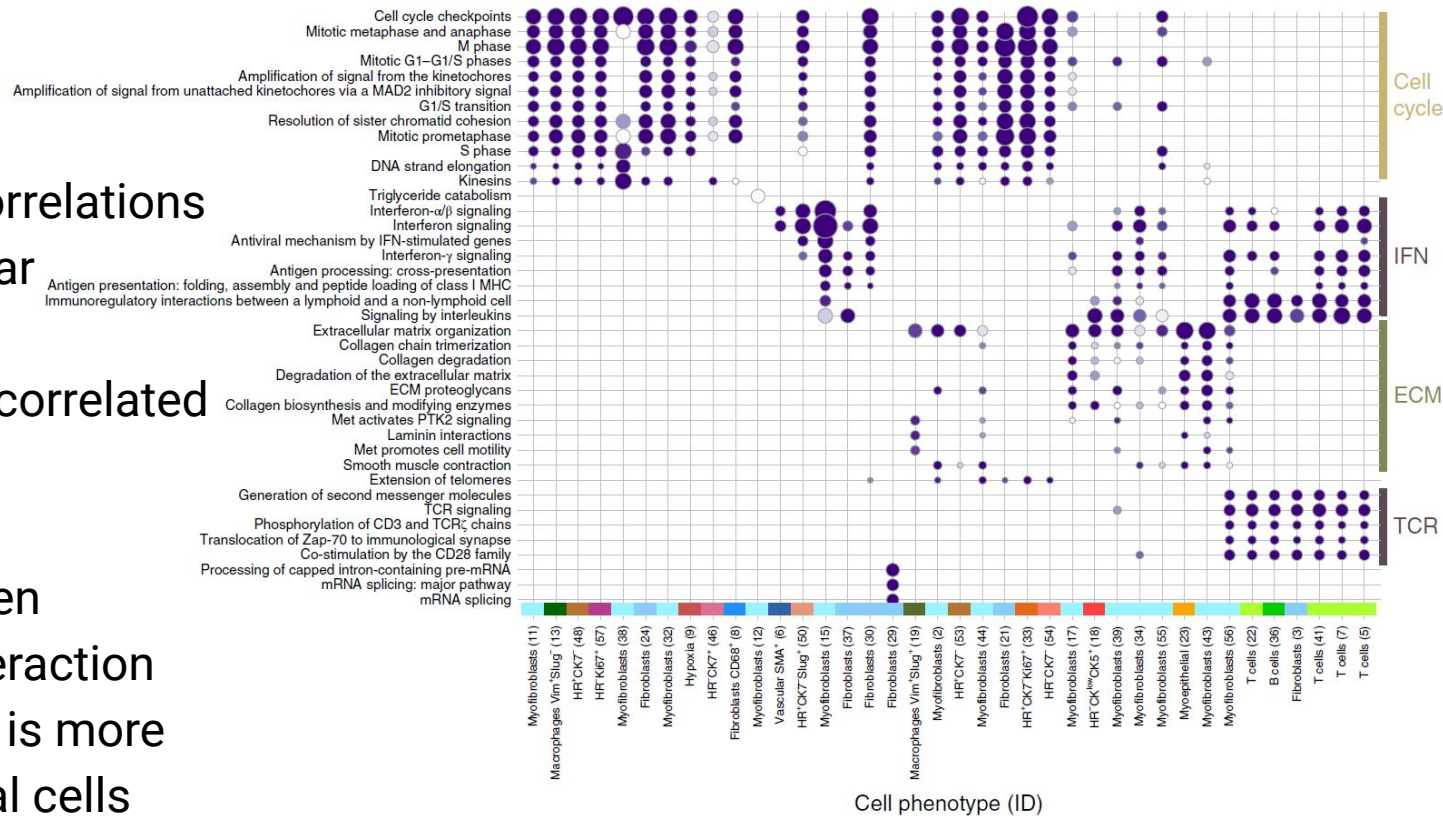
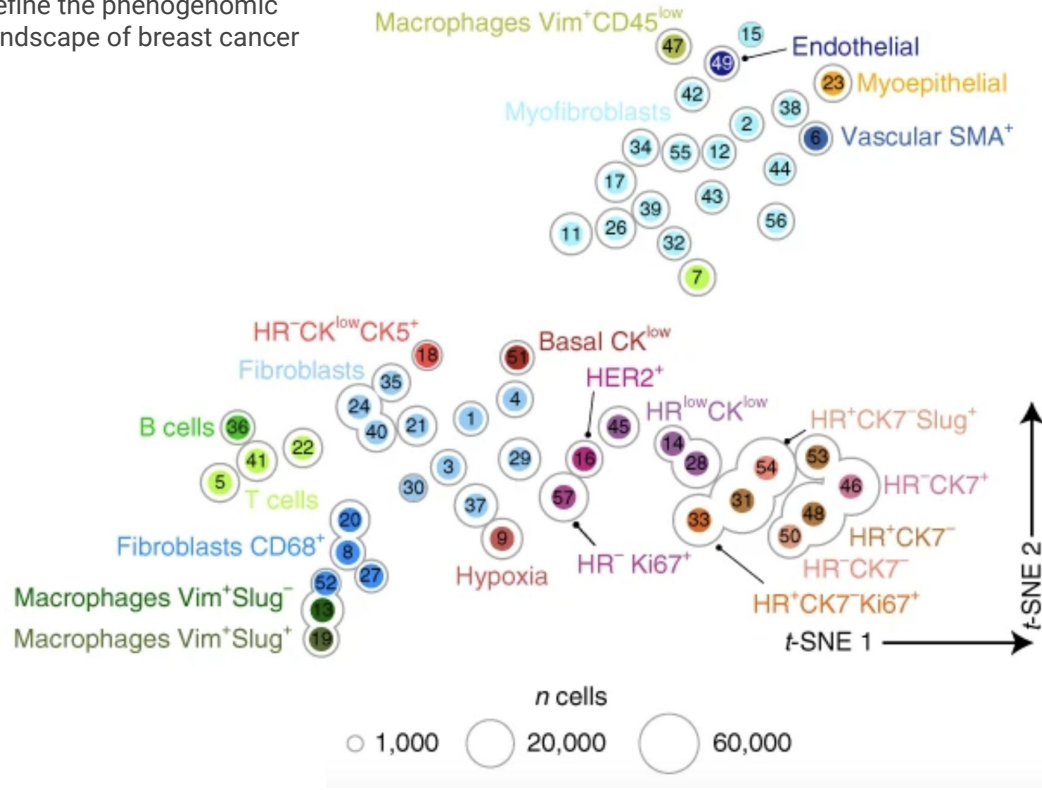


Fig. 3b, Ali et al., Imaging mass cyometry and multiplatform genomics define the phenogenomic landscape of breast cancer

Fig. 4, Ali et al., Imaging mass cytometry and multiplatform genomics define the phenogenomic landscape of breast cancer



- Phenotype enrichment in genomic breast cancer subtypes
- Genomic subtypes of breast cancer are characterized by diverse tumor ecosystems
- Schematic map indicates position by cell phenotype

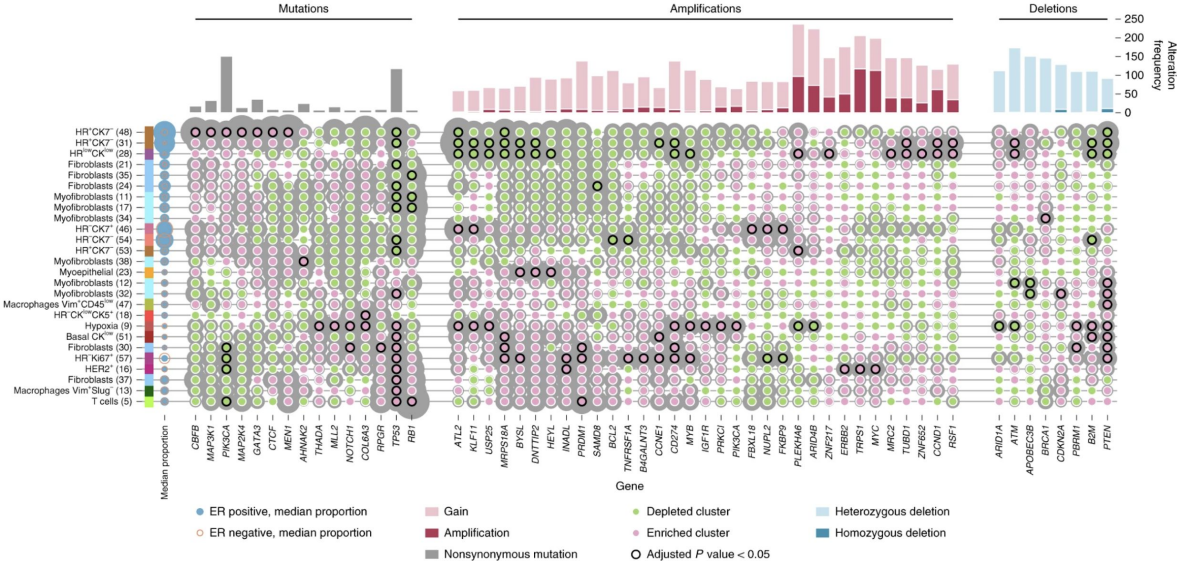
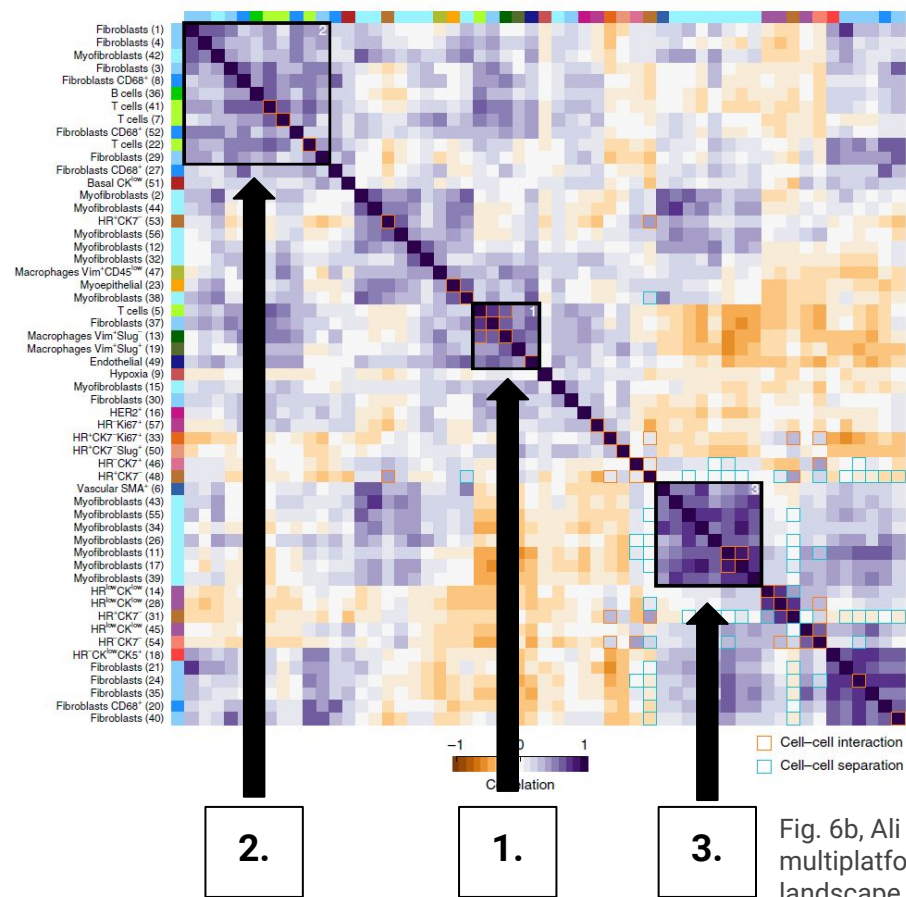


Fig. 5, Ali et al., Imaging mass cytometry and multiplatform genomics define the phenogenomic landscape of breast cancer

- Somatic genomic alterations influence cell phenotypes
- Phenotypic features of tumor ecosystems are driven by a specific repertoire of large underlying genomic events that span genomic subtypes
- Somatic genomic aberrations exert influence over the cellular composition of both tumor cells and cells of the tumor microenvironment



- The prognostic impact of cell phenotypes depends on their genomic context.
- A spectrum of microenvironments
 1. immune cells + epithelial cells
 2. lymphocytes + stromal cell
 3. myofibroblast without immune cells

Fig. 6b, Ali et al., Imaging mass cytometry and multiplatform genomics define the phenogenomic landscape of breast cancer

Discussion

- Quantitative molecular mapping of cancer tissues, particularly longitudinal tracking of cell composition, may enable improved clinical decision-making
- A subset of luminal breast tumors of favorable prognosis are characterized by fibroblast activation
- The researchers have identified cellular phenotypic correlates of somatic genomic alterations and demonstrated their variable influence on tumor ecosystems
- Findings suggest that somatic genomic alterations collectively manifest as characteristic tumor ecosystems
- Characterization of these ecosystems will further understanding of tumor evolution and will potentially enable identification of features that can be used to stratify patients and that can serve as targets for development of novel therapies

Thank you