Tumor heterogeneity and tumor evolution

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Diversity is a hallmark of cancer

Differences between normal and neoplastic tissues

Normal tissue
- Noise: low
- Genotypes: homogeneous
- Environment: structured
- Network architecture: robust

Cellular phenotypes

Tumor
- Noise: high
- Genotypes: heterogeneous
- Environment: disorganized
- Network architecture: "noisy"

Low phenotypic heterogeneity

High phenotypic heterogeneity

Adapted from Marusyk, Almendro, Polyak. Nat Rev Can 2012
Why study intratumor heterogeneity?

Prognostic – predictive biomarker for patient stratification

Tool to trace back tumor evolution – relevance to prevention (both primary and secondary)

Develop better experimental models of human cancer

Required for the design of optimal & individualized therapy
Principles of evolution

Variability for hereditary *phenotypic* traits that impact fitness

Reproduction

Selection

Tumorigenesis is a somatic Darwinian evolution
Models of tumor evolution

- Linear Evolution
- Branching Evolution
- Neutral Evolution
- Punctuated Evolution
Changes in intratumor heterogeneity during different models of tumor evolution

Linear Evolution

Branching Evolution

Neutral Evolution

Punctuated Evolution

normal tissue

tumor initiation

advanced carcinoma

Davis & Navin. BBA Rev Cancer, 2017
Quantitative measures of diversity in tumors

Shannon index of diversity

\[ H' = -\sum_{i=1}^{S} (p_i \ln p_i) \]

Number of species
Individuals within species

Cancer cells with unique identifiable features: “species”

Diversity of the tumor microenvironment

Topologic distribution of “species”
Genetic, phenotypic, and topologic diversity in breast cancer during treatment

Almendro et al., Cell Reports 2014
Janiszewska et al., Nature Genetics, 2015
Functional relevance of intratumor subclonal heterogeneity

“The whole is greater than the sum of its parts.” Aristotle

Interactions among subclones

Subclonal frequency ≠ ability to drive tumor growth

Multiple “drivers” within the same tumor limit each other’s ability to expand

Polyclonal tumors are more likely to metastasize

Cancer is a systemic disease
Higher pre-treatment diversity is associated with therapeutic resistance

Topologic distribution of cells and changes in this during treatment predict clinical outcome

Tumor evolutionary models are needed to design optimal cancer therapies
Treatment strategies designed based on intratumor heterogeneity/evolution

Adaptive therapy – cycling On/OFF treatment (e.g., Abiraterone in metastatic castration-resistant prostate cancer) to prevent/slow expansion of resistant subclones

EGFR mutant NSCLC: Osimertinib targeting EGFR activating mutations and the T790M very common resistant subclone

BRAF mutant melanoma: BRAF-MEK inhibitor combination in to reduce expansion of resistant subclones