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Research Article

Intra-Tumor Phenotypic Heterogeneity in Solid Tumors: An Epigenetic View of Tumor Ecology

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Editorial

Cancer treatment often combines systemic cytotoxic chemotherapy with radiation and/or surgery. Overall, this paradigm has had limited success due to the fact that not all patients respond equally and relapses are common. An explanation for this lack of effectiveness may lie in the assumption that a tumor, being clonally derived, is composed of a homogeneous population of cells; therefore, all the cells within the tumor are expected to respond uniformly to specific chemotherapeutic agents. However, advanced stage human cancers frequently display substantial intra-tumor heterogeneity in many phenotypic features, including cellular morphology, gene expression, metabolism, motility, proliferation, immunogenicity, and metastatic potential. These factors likely impact therapeutic resistance and disease recurrence, while at the same time confound the development of novel, target-specific therapies.

At the molecular level both genetic and epigenetic differences contribute to the development of intra-tumoral phenotypic heterogeneity. The clonal evolution model first proposed by Nowell [1], posits that heterogeneity is primarily genetic and develops stochastically as the result of random acquisition of mutations and Darwinian selection of clones with a fitness advantage. In this model, maximum fitness is never achieved and new populations with increased fitness will continue to arise. An alternative view is that phenotypic heterogeneity is primarily epigenetic in nature and arises as a result of the local variations in the topography of the tumor microenvironment that select for different phenotypic properties. The nature of malignant growth in solid tumors creates a distinct and highly unstable microenvironment. Continued unrestrained proliferation and resistance to cell death by nascent tumor cells and the presence of leaky and poorly functioning vessels results in extreme variations in nutrient availability, tissue oxygenation, stromal composition, and pH that is not only inhospitable to normal cells but dynamic and heterogeneous as well.

In advanced stage tumors (especially resistant or recurrent tumors) manifesting all the hallmark activities obligate for tumor growth and progression the genetic alterations necessary for the tumorigenic process are likely fixed. Thus while genotyping is an effective means of constructing clonal ontogenies/phylogenies and determining the spatial distribution of genetically heterogeneous tumor sub-populations, it is difficult to infer genotype/phenotype relationships. It is our belief that intra-tumor phenotypic heterogeneity is epigenetic and a manifestation of "fine tuning" of the tumorigenic process whereby, biologically incompatible or mutually exclusive malignant properties are partitioned into distinct cellular compartments to maximize growth or survival, but not both. The divergence in phenotypes is an adaptive response to extrinsic stress stimuli stemming from the microenvironment that reprograms the epigenome. The functional outcome is dependent upon the nature of the stress (frequency/duration/magnitude) and the epigenetic state of the target cell. In contrast to clonal evolution in this model a fitness maxima can be achieved and the development of intra-tumor heterogeneity is a deterministic process that should be generally predictable with sufficient understanding of tumor topography and the Darwinian dynamics of the ecosystem.

Using the malignant hallmarks described by Hanahan and Weinberg [2] as a conceptual frame work we have generated a model illustrating intra-tumor phenotypic heterogeneity in

which Darwinian selection would divide the tumor into two populations reflecting different epigenetic states. The first population maximized for growth and proliferation that displays sustained proliferative signaling, evasion of growth suppressors, replicative immortality, deregulated cellular energetics, and genome instability. The second population would be optimized for survival and exhibit increased resistance to cell death, angiogenic capacity, inflammatory activity, as well as, pro-invasive, metastatic, and immune-modulatory properties. These two sub-populations along with vascular tissue and non-malignant tumor-associated stroma and immune cells create localized "niches" that, collectively, make up the tumor ecosystem and support the growth of malignant cells and promote tumor progression.

In terms of therapy this view suggests that normalization or disruption of the tumor microenvironment in a manner that 1) decreases heterogeneity of response to treatment, 2) selects for tumor cells with increased chemo-sensitivity, 3) increases tumor immunogenicity, or 4) drives malignant cells to adopt a more benign phenotype may be the key to enhancing the effectiveness of anti-neoplastic drugs that are currently in use as frontline therapies. Of course, understanding exactly how to do this is the challenge and will require a more thorough examination of the tumor ecosystem and the epigenetic nature of intra-tumor heterogeneity within it.

References

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2. Hanahan D, Weinberg RA (2011) Hallmarks of cancer: the next generation. Cell 144: 646-674.