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CCBIO on Tumor Microenvironment

Cancer is a leading cause of death worldwide and a major health challenge; over half of current adults under the age of 65 years will be diagnosed with cancer at some point in their lifetime. Encouragingly, our understanding of the molecular basis of cancer has evolved remarkably during the past two decades. The Cancer Genome Atlas (TCGA) program, following on the coattails of the Human Genome Project, has sequenced thousands of cancer cell genomes. TCGA has identified a broad range of recurrent gene mutations and genomic rearrangements that contribute to tumorigenesis. In concert with this, the pharmaceutical industry, following the success of imatinib (a small molecule targeting the BCR-ABL protein) for chronic myeloid leukemia (CML), and erlotinib (an EGF receptor inhibitor) for non-small cell lung cancer (NSCLC), has developed scores of molecularly targeted therapeutics, including many against specific protein mutations. In spite of this remarkable progress, most cancer patients still do not experience durable clinical responses, due to acquired drug resistance and subsequent relapse; and the War on Cancer continues.

The confounding reality for cancer treatment is the heterogeneity of tumors. This is a reflection not only of the intrinsic genetic instability of tumors but also of the extrinsic selective forces acting on an evolving tumor cell. The breakdown of normal tissue structure during malignant progression exposes tumor cells to numerous biophysical challenges, nutritional deprivation and a hostile non-native microenvironment comprising different matrix proteins and a variety of stromal cells. Philosophers refer to a confrontation that causes us to become aware of our own weaknesses as a "boundary situation". A key outcome of the boundary situation is a realization of the necessity to communicate. Indeed, tumor cells that encounter a reactive stroma engage in reciprocal interactions that trigger adaptive, cellular plasticity related to stem cell differentiation and transdifferentiation, characteristic of adult tissue homeostasis and repair. This endows tumor cells with a remarkable phenotypic and functional flexibility, as evidenced by tumor vascular mimicry, epithelial-to-mesenchymal transition, and acquired drug resistance. This ability to assume different phenotypic states ("shape-shifting") allows adaptation to different niches within a dynamic tumor microenvironment. This new "hallmark" of cancer, tumor cell plasticity, is central to cancer progression and treatment failure. Indeed, tumor cell plasticity represents a unifying theme, reconciling different models of carcinogenesis (i.e. stochastic vs hierarchical) and is an important target for future cancer therapeutic development.

With the knowledge that an entire human being is derived from a single genome, we shouldn't be surprised that multigenomic tumors are phenotypically diverse. Hence, deeper mechanistic insight into how the interaction between extrinsic microenvironmental and intrinsic genomic factors activates phenotypic plasticity programs in tumor cells is required to understand the tumor heterogeneity that undermines current treatments and to develop new therapeutic concepts to treat cancer. The investigators at CCBIO endeavor to better understand the molecular basis of tumor-stroma interactions that can inform improved treatment decisions and new therapeutic concepts. ••