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Origin of Cancers: Gene-Centric Versus Cell-Centric

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The article by Gerlinger and colleagues (Mar. 8 issue) [1] is informative because it confirms what we already know. In the clinics, the genetic approach seems inadequate for us to solve the problem of tumor heterogeneity or reaching our goal of personalized care. However, we contend that the genetic approach is invaluable for our understanding of individual cancers and in our design of personalized care, provided that we have the right theory about the origin of cancers.

Currently, our prevailing theory about the origin of cancer is overwhelmingly gene-centric rather than cell-centric. But cancer is more than a genetic puzzle; it is also a cellular problem. When we talk about the genome, transcriptome, proteome, metabolome, etc., it is also imperative for us to know under what cellular context we are talking about the phenomen-ome!

For example, oncogenic alterations are also seen in nonmalignant cells. The BCR-ABL fusion transcript was also identified in normal mature blood cells [2]. Using probes to identify certain genetic mutations could not distinguish benign prostate hyperplasia from prostate cancer because the genetic mutations are present in both cell types [3]. Patients afflicted with rheumatoid arthritis possess abnormal synoviocytes, which contain p53 mutations [4].

It is evident that the genetic and epigenetic profiles of stem cells and cancer cells are similar, especially cancer stem cells, which may be involved in a cancer's myriad malignant phenotypes and its regenerative, metastatic, and heterogeneous potential [5]. Of importance, if a cancer-initiating cell has "stem-ness" features, then the source of aneuploidy could be traced to aberrant asymmetric division, and the origin of genetic instability, to abnormal stem-like cells. We propose that the dilemma posed by Gerlinger and colleagues could be resolved according to the "stem-cell" theory of cancers [5].

When we turn our attention to the cell, then cellular interactions and paracrine factors become crucial, and the microenvironment is paramount. In that setting, personalized care means targeting cells rather than genes. It implies targeting the microenvironment of defective cells as well as the defective cells themselves, which contain tens, hundreds, or perhaps even thousands of relevant and irrelevant mutated genes [5]. When we target the cancer cell at its very core—its cell of origin—we take care of its inherent pathology and diverse phenotypes without concern about the presence of redundant or incidental genetic defects.

It takes a correct theory to elucidate our many important observations of cancer, including tumor heterogeneity. A correct theory empowers us to ask the right questions and formulate the pertinent hypotheses. The correct theory ensures that we design the proper experiments and select the appropriate models. It enables us to make sound interpretation of laboratory results. More important, a correct theory will expedite our discovery of effective therapies, which will be the ultimate proof of its veracity. We propose that the incredible technology and data mining (e.g., DNA sequencing; genomic, transcriptomic, proteomic studies) performed by Gerlanger's group and other investigators will be even more invaluable under the auspices of a correct theory.

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