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Origin of Cancer: Founder Clones

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The article by Walter et al. [1] provides some invaluable insights on the origin and nature of secondary acute myeloid leukemia. Because they used human tumor samples rather than animal models or cell lines, their results have immediate relevance. Importantly, studies like theirs may finally answer some fundamental questions about the origin of cancer.

The idea of a clonal origin of cancer is not new. But, to demonstrate this idea in relevant human cases is significant. Although they implied it, the authors did not address the phenotype of the founding clone. They cautiously mentioned that the founding clone must have retained the capacity for self-renewal. Whether the founding clone possesses "stemness" features and therefore, represents a cancer stem cell is unknown. Further, it remains unclear, whether the founding clone originates from disparate cells in a stem-cell hierarchy that give rise to different diseases with distinct clinical outcomes (e.g. UPN461282 and UPN266395 have survival times of 67 and 11 months from diagnosis, respectively). The stem-cell theory of cancers [2] could account for the apparent paradox that malignancies with worse clinical outcome have fewer mutations (6.7% versus 37.8%); their inherent stemness obviates the need to acquire more mutations to become malignant, because many stemness properties are also potential malignant characteristics.

With the Walter et al. [1] article, we have in our hands for the first time, clinical cases rather than experimental models that may reveal a stem-cell origin versus de-differentiation of cancers. The database they provided enables testing to see, whether a founding clone with stemness properties becomes aberrant by accumulating mutations, or a founding clone with somatic phenotypes becomes malignant by acquiring stemness properties. Even if both scenarios were possible, we would suspect that the two separate founding clones give rise to distinct diseases with different clinical courses.

Undoubtedly, the strength of this study lies in its focus on the genotype of the serial tumors. It would have been even more informative, if it had identified the phenotype of the founding clones. Ironically, the results of this study may signal a shift from our gene-centric view of cancer to a cell-centric view. Although genetic mutations are critical, the cellular context within which they occur is also paramount in our understanding of cancer. Otherwise, why are the vast majority of mutations in the current study considered to be random background mutations? [1]. Why would apparently similar tumors contain different mutations [3] and the same mutations be found in different tumors? [4]. I believe that a common link between the founding clones and the mutations they contain is the cell of origin.

Results of the study by Walter et al. [1] have important clinical implications, as far as personalized care is concerned. The authors correctly stated that treatments targeting the founding clone are likely to be more efficacious than those that do not target it. But, should we target the mutated genes within a cell or the aberrant cell itself? That is the ultimate question. Alas, when we target specific genetic mutations, we tend to ignore the proper cellular context. After all, there are tens, if not hundreds of genetic mutations within a complex web of redundant pathways, which remind us of the very cellular entity we have so far neglected. Consequently, when we target one mutation (e.g. PIK3Ca), the cell adapts and compensates by enhancing another aberrancy (e.g. c-Myc overexpression) [5]. In contrast, when we target an aberrant founder clone with its whole package of genetic mutations rather than the individual mutations themselves, we are simultaneously treating a whole system of molecular, intracellular, intercellular, and microenvironmental networks and pathways. I propose that personalized care will be more effective, if it targets a particular cellular entity rather than a specific genetic mutation within it.

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