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Somatic clonal evolution: A selection-centric perspective☆

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ABSTRACT

It is generally accepted that the initiation and progression of cancers is the result of somatic clonal evolution. Despite many peculiarities, evolution within populations of somatic cells should obey the same Darwinian principles as evolution within natural populations, i.e. variability of heritable phenotypes provides the substrate for context-specific selection forces leading to increased population frequencies of phenotypes, which are better adapted to their environment. Yet, within cancer biology, the more prevalent way to view evolution is as being entirely driven by the accumulation of "driver" mutations. Context-specific selection forces are either ignored, or viewed as constraints from which tumor cells liberate themselves during the course of malignant progression. In this review, we will argue that explicitly focusing on selection forces acting on the populations of neoplastic cells as the driving force of somatic clonal evolution might provide for a more accurate conceptual framework compared to the mutation-centric driver gene paradigm. Whereas little can be done to counteract the "bad luck" of stochastic occurrences of cancer-related mutations, changes in selective pressures and the phenotypic adaptations they induce can, in principle, be exploited to limit the incidence of cancers and to increase the efficiency of existing and future therapies. This article is part of a Special Issue entitled: Evolutionary principles - heterogeneity in cancer?, edited by Dr. Robert A. Gatenby.

1. Introduction

According to Ernst Mayr, biological causation can be separated into proximal causes that answer the "how" questions and ultimate causes that answer the "why" questions. The latter category is equated with evolutionary causation [1], epitomized in the famous saying of Theodosius Dobzhansky: "Nothing makes sense in biology except in the light of evolution" [2]. Indeed, Darwinian principles provide a unifying explanation for the astounding biological diversity and complexity. The main idea is elegantly simple: competition for limited resources within a population of individuals with heritably distinct phenotypes gives rise to increased population frequencies of individuals with phenotypes that are better adapted to a given environment. Thus, the process is shaped by the interplay between stochastic mutational processes and the deterministic context-specific natural selection.

A landmark paper by Peter Nowell in 1976 applied the concept of evolutionary causation to explain the initiation and progression of cancers. According to Nowell's argument, cancers occur and progress because of the underlying process of *somatic clonal evolution*. Genetic mutations within somatic cells generate heritable phenotypic variability, allowing for the outgrowth of sub-clones with higher fitness [3]. Whereas there is little disagreement about the Darwinian nature of cancer causation, the prevailing conceptual framework of somatic cancer evolution has been shaped by a mutation-centric argument articulated by Eric Fearon and Bert Vogelstein. They argued that the multistep cancer progression is the direct result of the mutational activation of oncogenes and inactivation of tumor suppressor genes, as these genomic changes "drive" tumor progression [4]. More generally, the idea of "driver" mutations is also applicable to clonally heritable changes in gene expression, without changes in sequence of the gene/protein, referred to as epimutations [5]. For the sake of simplicity, unless otherwise specified, we will use the term "mutations" to refer to both genetic mutations and epimutations.

Recent advances in DNA sequencing techniques have enabled the discovery of remarkable genetic heterogeneity within tumors, including differences in the mutational status of presumed drivers [6] suggesting a picture that is more complex than that of a series of clonal succession driven by acquisition of powerful driver mutations. Furthermore, research within the last two decades has also brought about the realization that alterations in tissue microenvironments play key roles in cancer initiation and progression. In spite of these developments, the mutation centric view of somatic evolution remains dominant, and the

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famous statement "The revolution in cancer research can be summed up in a single sentence: cancer, is, in essence, a genetic disease" [7] reflects a wide consensus within the cancer research community.

Whereas consideration of genes and altered gene activity provide an appropriate framework for the elucidation of proximal mechanisms of cancer causation, it might be inaccurate when applied to evolutionary causation. The evolution results from the interplay between mutational diversification and outgrowth of populations with phenotypes that are most fit within the dynamic and context-specific selection forces. Therefore, context-specific selection forces need to be taken into account to understand evolutionary changes. This distinction between proximal and evolutionary causes not only provides a more relevant framework for understanding origin and progression of cancers, but also offers new approaches for the prevention and treatment of the disease.

2. Somatic evolution in cancers: distinctive features

Somatic clonal cancer evolution follows the same Darwinian principles as evolutionary processes in natural populations [8], with most obvious parallels to evolution in asexual organisms such as bacteria [9]. Yet, it also has a number of unique features that need to be taken into consideration in order to adequately apply a Darwinian paradigm [10]. Therefore, we would like to precede the discussion of the evolutionary forces that shape somatic cancer evolution by an overview of its salient distinctions.

2.1. Partial retention of normal differentiation program

Somatic cancer evolution starts from originally normal somatic cells, which execute complex tissue-specific developmental programs. In spite of multiple mutational changes involved in oncogenic transformation and tumor progression, in most cases tumor cells partially retain the developmental programs characteristic of their tissue of origin. Phenotypic heterogeneity within many liquid and solid tumors partially parallels differentiation hierarchies observed in normal tissues [11,12]. Remarkably, this partially retained differentiation program can have stronger phenotypic impact than genetic and epigenetic changes associated with tumorigenesis. For example, expression profiles of CD44 +/ CD24- progenitor-like cancer cells isolated from primary breast tumors more closely resemble the expression profiles of their normal counterparts than those of their more differentiated CD44 −/CD24 + counterparts from the same tumor; the same is true for CD44 −/CD24 + cells [13]. The retention of the ability to execute a normal differentiation program can be even more dramatic. For example, breast cancer cells isolated from a metastatic tumor can contribute to the formation of a normal mammary gland when mixed with larger numbers of normal counterparts [14]. The retention of these differentiation programs is difficult to explain from a Darwinian perspective. Most likely, it represents a mal-adaptive atavism that has not been weeded out by selection due to the limited time horizon of somatic clonal evolution.

2.2. Limited time horizon

Evolution of species has been shaped by selection forces acting over the course of innumerable generations. Thus, their phenotypes should be attributable to evolutionary adaptations that increase organismal fitness. At the same time, genomes of multicellular species including humans have been shaped by selection forces that maximize reproductive success of the whole organism, necessitating evolution of multiple mechanisms to suppress somatic evolution that can lead to cancers [15,16]. Human cancers are not infectious and cannot be passed through the germline. Therefore all of the somatic evolutionary "experiments" start at some point within ontogeny and end with the death of the host. This limited time horizon leads to a question: how do we judge success of phenotypic adaptations of malignant clones? From a standpoint of maximizing reproductive success, tumors producing larger biomass should be deemed more successful, but many of the largest tumors are benign, like lipomas and keloids. From a clinical standpoint, invasive and metastatic cancers that cause the fastest demise of their hosts are deemed more "advanced". Regardless of how we judge evolutionary success, this consideration is applicable only over a very limited time frame, as ultimately all of the cases of somatic evolution in humans are evolutionary dead ends, ending with the death of the host.

A key consequence of the limited time horizon is that it might be imposing a limit on the extent of evolutionary adaptations that can be acquired by cancerous clones. On the other hand, this might not necessarily be the case, as an opposite assumption that populations of tumor cells quickly reach fitness maxima has led to accurate predictions validated by the analysis of primary patient samples [17].

2.3. Sources of heritable phenotypic variability

Darwinian evolution results from natural selection that acts on heritable phenotypic variability within populations. Since most cancers are considered to start from a single cell, the diversity of heritable phenotypes within the pre-malignant clone needs to be established for the evolution to occur. Therefore, the mechanisms generating heritable phenotypic diversity are of key importance. In natural populations, the major sources of heritable diversity are genetic mutations and sexual recombination (or parasexual recombination in asexual organisms such as bacteria). In principle, cell fusions between tumor cells or between tumor and normal cells can lead to parasexual recombination. However, cell fusions are not typically considered to be a significant factor in somatic evolution, although the relevance of cell fusions for cancer evolution is open for debate [18,19]. In contrast, the dominance of the mutation-centric paradigm in somatic evolution as well as DNA sequencing revolution have brought genetic mutations into the spotlight as the main source of phenotypic variability in tumors [20].

In addition to DNA point mutations and small-scale deletions/amplifications, cancer cells can tap into sources of diversity that are not easily accessible to species level evolution. First, genomes of the majority of spontaneous human cancers display changes in numbers of individual chromosomes (aneuploidy), large scale chromosomal amplifications/deletions and complex DNA rearrangements within and between chromosomes. Importantly, aneuploidy is strongly linked with increased probability of further chromosomal rearrangements – chromosomal instability (CIN) [21]. Multiple genomic rearrangements appear to be highly disadvantageous in unicellular organisms and in the germline of multicellular species. Even though aneuploidy and CIN are still disadvantageous in somatic cells [22], an excess of genetic information over what is required for cellular viability might buffer the detrimental impact of CIN, thus providing a powerful potential source of genetic diversification. Consistently, polyploidization that further elevates the excess of genetic information, has been linked with an increased CIN tolerance and elevated tumorigenic potential [23].

The impact of CIN is often viewed simply as an increased probability of amplification of oncogenes and deletion of tumor suppressor genes [24]. However, the effects of aneuploidy and genomic rearrangements are far more complex, as different patterns of aneuploidy lead to different gene expression imbalances that can be expected to translate into a large spectrum of potential phenotypes [25]. Some authors argue that karyotypic destabilization, rather than recurrent genetic mutations, is the main genetic determinant of cancer evolution [26,27], though this hypothesis is difficult to validate experimentally. Importantly, genomes of cancer cells frequently display highly complex genomic rearrangements indicative of a single catastrophic event [28]. Therefore, somatic cancer evolution might have access to saltatory changes that are generally thought to be unavailable for the evolution of species.

Another source of diversity unique to somatic evolution is epigenetic plasticity. The human genome has a very broad norm of reaction, as it is