Review of: "Somatic evolution of Cancer: A new synthesis"

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In their *Qeios* article entitled "Somatic evolution of Cancer: A new synthesis," Ulfat Baig, Rohini Kharate, and Milind Watve make two major claims regarding cancer development. First, they argue that the hallmarks (or phenotypes) of cancer do not necessarily arise as de novo cellular abilities, but instead represent dysregulation of pre-existing mechanisms related to wound healing and tissue regeneration, implying that known somatic evolutionary trajectories make constitutive the erstwhile discrete triggers of wound healing. This claim is well-founded and very worthy of continued investigation [1]. In what I view as a distinct argument, Baig, Kharate, and Watve argue that somatic evolution of cancer is not limited by mutations, but rather by selection. Their point is well taken that the study of oncogenesis has—to its great detriment—focused too many times entirely on mutation, rather than selection. However, they go too far in arguing that the somatic genetic evolutionary trajectory is somehow “selection-limited” rather than “mutation-limited”.

Their argument for the greater role of selection is that selection is dependent on many complex factors—but in their telling, primarily factors of the tissue microenvironment. However, the degree of dependence of selection on diverse factors, or limitation of selection by the state of the tissue microenvironment, does nothing to indicate the relative roles of mutation and selection in oncogenesis, as both mutation and selection must occur for the somatic genetic evolution of cancer. Baig, Kharate, and Watve are correct in pointing out the complex sieve of cellular state and microenvironmental context that control whether a mutation contributes to a cancerous lineage. This complexity, however, explains why we do *not* typically get cancer; it does nothing to diminish the importance of mutation when we do.

To understand why mutation remains important, *along* with selection, consider the analogy of selection to a complex, three-dimensional sieve, which directs most grains of sand (cells) away from the “cancer” urn above which it sits. As selective constraints are added—no matter how complex those constraints are—the sieve becomes increasingly unlikely for any given mutation to navigate, and fewer and fewer grains of sand (cells) will be introduced in just the right context so that they can pass through the sieve and lead to cancer. The consequence of such selective complexity is less cancer. However, if you add more sand to the top of the sieve, the consequence of adding mutation remains more cancer—in this analogy, a proportionally greater input will still yield a proportionally greater output. The complexity of selection does not mean that the underlying mutation rate is no longer important. Indeed, if there are fewer cell lineages that can become cancerous (due to the complexity of the selective sieve), then a greater mutation rate per cell is a mathematical necessity to explain the cancer that we do observe.

To specifically address every selective complexity introduced by Baig, Kharate, and Watve is beyond the scope of this review, but one prominent one will likely help to dispel some confusion. A straw man argument is often constructed that if

mutation “accumulation” were the whole story of cancer evolution, then the ages of individuals at which cancer arises would be different from what is actually observed. Such an argument is well-founded for the purpose of dismissing simple models of how cancer arises, but it is a straw man if used to argue that mutation rates themselves are unimportant compared to selective constraints [2]. Cellular states and microenvironmental selective contexts of cells are well known to change as we age, so one theory argues that changes of cellular state and micro-environmental context occur during our lifespan, enabling cancer [3]. Essentially, aging in this theory draws down our “defenses”, and makes it so that mutations that would otherwise be selected against are instead selected for. This conception is well-founded. However, it does not alter the importance of underlying mutations. To return to the analogy of the sieve, it argues that the sieve becomes less complex and simpler as we age. In that situation, it becomes increasingly likely for a given mutation to make it through the sieve and lead to cancer. No matter how the sieve changes over time, it remains the case that any increase in the mutation rate, *at any point in the lifetime*, monotonically increases the likelihood of cancer. In some less frequent selective contexts, mutations may occur earlier in life and lead to cancer at a young age. In other contexts, mutations may occur that do not lead to cancer at a young age but do lead to cancer at a later age. And in some cases, mutations occurring later in life in the aged context may lead to cancer. In any of these cases, increasing the mutation rate will increase the number of cellular lineages leading to cancer; in none of them does the mutation rate become less relevant due to the complexity of selective constraints.

In more general terms, the challenge to any relative comparison of the roles of mutation and selection in contributing to evolution is that they are fundamentally paired in the oncogenic result. For organic evolution to proceed, there must be genetic variation that is created by mutation, there must be inheritance of those variants, and those variants must lead to differential reproductive success [4]. Eliminating mutation and the generation of genetic variation in somatic tissues would stop oncogenic evolution; equivalently, so would eliminating selection via differential reproductive success. This point can be formalized by consideration of one of the most commonly used models of molecular evolution, the strong-selection weak-mutation (SSWM) model [5]. Starting with the result for a two-allele (consistent with weak mutation) haploid Wright-Fisher model, the expected number of fixed replacement-site differences over time is $2\mu \frac{2\gamma}{1-e^{-2\gamma}} t$, where μ is the mutation rate in an individual cell, γ is the population-scaled selection coefficient, and t is time [6]. Under strong selection (at high γ), this expected number asymptotes to $4\mu\gamma t$. Accordingly, the product of mutation rate and strength of selection dictates the speed of fixation of somatic mutations that lead—through many complexities of cellular and microenvironmental biology—to cancer. When the product of two factors determines a quantity of interest, it has little meaning to make a statement regarding which of the two “limit” that quantity. They both play essential roles.

Indeed, the only way in this context to address the relative importance of these two factors is through their empirical variance. If mutation rate were only about 10^{-8} per unit time for all sites and at all times and it were essentially unalterable, and only the scaled selection coefficient changed over time or was modifiable, then this extreme constancy of mutation would confer by our observations a near-zero relative impact on what we consider oncogenesis compared to a scaled selection coefficient that substantially varied by site, by time, by microenvironment, and by therapy. On the other hand, if “cancer drivers” all conveyed almost the same selective benefit for all driver genes at all sites and at all times (an

unfortunately still-prevalent concept of driver genes in cancer biology; [7]), then this extreme constancy of selection would confer by our observations a near-zero relative impact on what we consider oncogenesis compared to a mutation rate that varied substantially by site, by time, by microenvironment, and by therapy. Therefore, the question of the relative impact of mutation and selection on oncogenesis, if it is meaningful, is about their relative variances and variability, and is empirical.

In some contexts, the empirical question has already been quantitatively addressed. Single-nucleotide mutation rates can be fairly precisely assessed because of the frequent near-neutrality of synonymous mutations that do not change encoded amino acids [8]. The mutation rates for these synonymous-site changes vary by as much as four orders of magnitude across sites in the genome—and depending on the cancer type, selection on those sites varies by as much or more [9][10][11]. Indeed, even if we restrict our attention to "actionable" variance—variance in mutation rates that can in principle be addressed by prevention or intervention—it has been demonstrated that not only a substantial proportion of genomic mutation causation [12] can be attributed to preventable processes, but also a substantial proportion of cancer causation [13]. For some cancer types, such as melanoma and lung cancer, the preventable proportion is very high; for other cancer types, such as prostate, thyroid, and brain cancers, the preventable proportion is much lower [13]. Regardless of actionability, elucidating the oncogenic process depends fundamentally on better understanding how both mutation and selection vary in the context of diverse cellular, microenvironmental, organismal, and therapeutic states.

The fact that the strength of selection is complex and subject to many complex "ecological" or "social" phenomena, such as cell-cell cooperation and interaction, vasculature and angiogenesis, surveillance by the immune system and responsiveness to the broader microenvironment [14][15][16][17][18][19] does nothing to diminish the role of mutation in oncogenesis. It only emphasizes that there is a great deal of research to be done to better understand the vital role of selection in diverse contexts. Conducting that research will inevitably require simultaneous investigation of the role of mutation in similarly diverse contexts. Arguing that one or the other are limiting factors or are of discretely greater importance is likely only to obstruct the advancement of cancer biology. They are deeply and fundamentally linked by the biological process of evolution.

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