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The somatic molecular evolution of cancer: Mutation, selection, and epistasis

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ABSTRACT

Cancer progression has been attributed to somatic changes in single-nucleotide variants, copy-number aberrations, loss of heterozygosity, chromosomal instability, epistatic interactions, and the tumor microenvironment. It is not entirely clear which of these changes are essential and which are ancillary to cancer. The dynamic nature of cancer evolution in a patient can be illuminated using several concepts and tools from classical evolutionary biology. Neutral mutation rates in cancer cells are calculable from genomic data such as synonymous mutations, and selective pressures are calculable from rates of fixation occurring beyond the expectation by neutral mutation and drift. However, these cancer effect sizes of mutations are complicated by epistatic interactions that can determine the likely sequence of gene mutations. In turn, longitudinal phylogenetic analyses of somatic cancer progression offer an opportunity to identify key moments in cancer evolution, relating the timing of driver mutations to corresponding landmarks in the clinical timeline. These analyses reveal temporal aspects of genetic and phenotypic change during tumorigenesis and across clinical timescales. Using a related framework, clonal deconvolution, physical locations of clones, and their phylogenetic relations can be used to infer tumor migration histories. Additionally, genetic interactions with the tumor microenvironment can be analyzed with longstanding approaches applied to organismal genotype-by-environment interactions. Fitness landscapes for cancer evolution relating to genotype, phenotype, and environment could enable more accurate, personalized therapeutic strategies. An understanding of the trajectories underlying the evolution of neoplasms, primary, and metastatic tumors promises fundamental advances toward accurate and personalized predictions of therapeutic response.

1. Introduction

Over the last decade, cancer discovery has been dominated by a search for molecular variants underlying a somatic evolutionary process from normal tissue to cancerous growth. This molecular evolutionary process has the potential to be illuminated by the application of classical molecular evolutionary theory. In describing the many facets of molecular evolutionary theory in cancer, several themes emerge that delineate the contribution of each facet to the study of cancer—genetic factors, phenotypic factors and other influences, fitness, cancer development and progression, and the clinical applications of such knowledge. Here we explore these themes and their relation to five topic areas (Table 1): how classical molecular evolutionary studies can inform cancer discovery, how the hallmarks of cancer and cancer fitness landscapes “add up,” how we can build molecular evolutionary models of cancer's special characters, and how to bring together diverse areas including molecular evolutionary theory and keep communicating (Somarelli et al., 2020b).

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Table 1
Themes across topics in the somatic molecular evolution of cancer.

Topic	Theme				
	Stepwise genetic factors	Complex factors	Fitness	Cancer development and progression	Clinical applications
Molecular evolutionary models of cancer's special characters	Cancer exhibits genetic characters rarely observed in other contexts, including loss of heterozygosity and copy-number aberrations.	Larger-scale events like cell fusions and massive genomic rearrangements are also observed.	Mutations to these characters are frequently detrimental to fitness but sometimes offer the cell a competitive advantage.	These special characters can have substantial effects on cancer phenotype, driving cancer evolution.	Multi-region multi-omics and non- or minimally invasive sampling techniques should be applied to study these characters and can illuminate treatment.
Hallmarks of cancer and cancer fitness landscapes	Mutation rate of a gene is only one of the factors affecting how frequently that mutation is observed in patients; prevalence in tumors is dependent on context and selection.	The contributions of the hallmarks of cancer can be clarified by integration into cancer fitness landscapes.	Cancer therapy can be viewed as imposing a fitness landscape wherein selection quantifies importance of mutations.	Cancer is likely highly dependent on mutations with high selection intensity/ cancer effect size because they offer new capabilities for tumor growth.	Cancer effect sizes can guide basic research, clinical trial design, and pharmaceutical development, maximizing the efficacy of research and drug design.
Epistasis among cancer drivers	The presence of some somatic mutations can substantially alter the selective advantage of epistatically-partnered mutations.	Antagonistic and synergistic epistasis often result in mutual exclusivity and co-occurrence—but these patterns can also arise from commonalities of mutagenic signatures among tumors.	Due to the high frequency and substantial impacts of epistatic interactions, fitness in cancer is best described with reference to the occurrence of epistatic partners in the tumor sample.	Cancer features several instances of epistasis such as when there are mutations affecting proteins operating in a linear pathway (*KEAP1/ NRF2)*, indicating dependencies on sets of mutations.	Epistatically partnered mutations can be targeted especially effectively if they exhibit synthetic lethality or synergistic clinical effects, lowering the potential for evolution of resistance.
Longitudinal studies and metastatic migration histories	Genetic variation observed through multi-regional sampling can be leveraged to illuminate the evolutionary histories of cancers.	The evolutionary histories can be analyzed with consideration of factors such as treatment type and duration and physical location of the tumor.	Therapies have dramatic effects on cancer fitness landscapes. Evolutionary perspectives on therapeutic response have led to treatment models such as adaptive therapy.	The capacity of cancers to adapt to their environment, resist therapies, and migrate is linked to their extensive mutational variation, so this variation can be used to better understand and respond to cancer.	Longitudinal studies of somatic genetics will be useful to identify key events in cancer progression and therapy response. Metastatic migration histories offer insight into how cancers spread and escape therapy.
Genotype-by-environment interactions	In cancer, a large variety of genotypes converges on a smaller set of pathological phenotypes that enable the tumor to survive in its environment.	The set of phenotypes most beneficial to the tumor can be influenced by its microenvironment. Therapy-associated microenvironmental changes can result in copy-number variation, mutation, and chromosome rearrangement.	Differences in environment produce differences in adaptive landscapes. Accordingly, fitness contributions of mutations can be highly dynamic.	The mutational profile of tumors is influenced by its microenvironment, but tumors also alter their microenvironment in ways that provision sufficient nutrients for growth and avoid the immune system.	Immune-checkpoint inhibition takes advantage of microenvironmental interactions, allowing the immune microenvironment to create an unfavorable landscape for cancer.

1.1. Molecular evolutionary models of cancer's special characters

Evolutionary biology has a long history of working with sequence evolution and examining how individual single-nucleotide mutations change over time. Because cancers possess many special characters, we need to consider them within a framework of evolutionary theory so that we can understand their effects on the evolution of cancer and tumors. This requires building models outside of what evolutionary biology has already produced that are capable of accommodating cancer's characters. The creation of these models requires loss of heterozygosity and copy number variation, which are stable, and epigenetics, which could be considered plastic and heritable in the short-term, to be considered in the context of evolutionary stability and range (Somarelli et al., 2020b). Massive genomic rearrangements must also be accommodated including chromothripsis—a chromosome shattering and rearrangement event amongst one or a few chromosomes (Cortés-Ciriano et al., 2020; Rode et al., 2016; Stephens et al., 2011), chromoanasynthesis—a related rearrangement event resulting in multiple DNA copy number aberrations and underpinned by a replication-based mechanism (Pellestor and Gatinois, 2018; Vasmatzis et al., 2018), and chromoplexy—a multi-chromosome event resulting in several translocations and deletions (Pellestor and Gatinois, 2020; Shen, 2013). Cell fusions and giant cancer cells as well as their characteristic polyploidy are other examples of massive genomic rearrangements linked to cancer initiation and metastasis (Niu et al., 2016; Shabo et al., 2020). Integration of these genomic rearrangement events into a molecular evolutionary framework has already begun with one possible system involving a two-phased evolution: punctuated macro-evolution—characterized by large changes in the karyotype—followed by microevolution (Heng and Heng, 2020; Ye et al., 2020). Thus far, these fundamental molecular insights have only begun to be supported by clinical data regarding the effects of large-scale genomic alterations (Favero et al., 2015; Stephens et al., 2011; Vasmatzis et al., 2018). Translation of these findings regarding large-scale genomic alterations into clinical interventions is an important next step that could be guided by molecular evolutionary models.

The evolutionary study of cancer can also benefit tremendously from multi-omics studies examining multiple regions throughout patient care (Hsieh and Cheng, 2016; Martinez et al., 2013; Somarelli et al., 2020b; Watkins et al., 2020). For example, study of a cohort of patients with non-small-cell lung cancer (NSCLC; Jamal-Hanjani et al., 2017) has revealed that the majority of subclonal driver mutations could be misinterpreted as clonal without multi-region whole-exome sequencing. Additionally, it provided evidence that chromosomal instability increases the frequency of parallel somatic evolution and may be a crucial component of prognostic prediction. Related studies also continue to explore the associations between chromosomal instability, loss of heterozygosity, somatic copy number aberrations, and whole-genome doubling—recurrent

events in many cancers (Watkins et al., 2020). Although their relationships have been challenging to define on a genomic scale in precise terms, there is evidence in NSCLC that loss of heterozygosity, presence of deleterious mutations, and copy number aberrations provide a selective pressure for whole-genome doubling that compensates for the accumulating effects of deleterious alterations (Jamal-Hanjani et al., 2017; López et al., 2020).

While longitudinal samples would likely improve our understanding of tumor evolution, the ability to collect these samples has traditionally been hampered by several barriers. Serial biopsies that provide multi-region and temporal sampling are invasive, create a series of risks and cost obstacles to the patient, and are often inaccessible (Dagogo-Jack and Shaw, 2018; Xiao et al., 2020). Novel technological breakthroughs have overcome some of these barriers, enabling the use of smaller sample sizes and improving the ability to capture pure samples with high consistency, maximizing the information gained from a sample (Grafen et al., 2017; Kirana et al., 2019). The selective nature of laser-capture microdissection, for example, makes it useful for studying intratumoral heterogeneity (von Eggeling and Hoffmann, 2020). Similarly, fine-needle aspirations—a less invasive procedure—can collect small volumes of tumor sample for genome sequencing (Steward et al., 2019). Samples can also be collected via liquid biopsies, from which circulating tumor DNA (ctDNA) or circulating tumor cells (CTCs) may be obtained. Deep sequencing has been performed on ctDNA for early cancer detection, sensitive genotyping, and evaluation of tumor heterogeneity (Chabon et al., 2016; Ma et al., 2020; Park et al., 2018; Sundaresan et al., 2016). Sequencing and molecular profiling of CTCs and ctDNA has been used to assess tumor heterogeneity (Dagogo-Jack and Shaw, 2018; Gupta et al., 2020) as a prognostic tool (Keller and Pantel, 2019; Sparano et al., 2018) and in the development of predictive biomarkers (Armstrong et al., 2019). While results based on CTCs are often challenging to apply broadly to all patients due to their rarity, specific capture technologies used, and a lack of knowledge of their biology (Keller and Pantel, 2019; Rossi and Zamarchi, 2019), these technologies represent promising new tools to analyze tumor evolution over time.

1.2. Hallmarks of cancer and cancer fitness landscapes

The classical hallmarks of cancer and cancer fitness landscapes have not been integrated coherently. Viewed from the lens of ecological fitness, cancer hallmarks represent the phenotypes necessary for cancers to maintain survival and reproduction (proliferation; Somarelli, 2021)—but what are the relative roles and interactions in their contribution to cancer? The fitness landscapes of hallmark phenotypes are known to change with age and insult (Watson et al., 2020) and with tissue context and cell identity (Laughlin and Messier, 2015; Lee et al., 2011; Somarelli et al., 2020b; Wenbo and Wang, 2017). Landscapes also change across the evolutionary process: epistasis dictates selection on hallmark phenotypes, affecting the order of mutations and the manifestations of cancer in each patient (Somarelli et al., 2020b). A major question for evolutionary biologists is to understand how these hallmarks relate to the fitness landscapes that underlie the trajectories of the evolution of cancer.

We can understand the landscape of an individual patient evolving with cancer therapy in a similar way as a fitness landscape. Previous cancer genomics studies have been largely focused on finding one or a few genes that are solely responsible for cancer's characteristics. A central issue in these studies is the concept that mutation frequency among the sampled tumor set is the most important indicator of the potential for carcinogenesis. However, there are vastly different numbers of single-nucleotide mutations among different cancer types as well as among different tumors within a cancer type (Lawrence et al., 2013). Mutation rate correlates with DNA replication time and average expression level: mutation rate is lower with high gene expression due to transcription-enabled repair, and it is higher with later replication times (Lawrence et al., 2013). These covariates can be used to estimate the underlying mutation rates of individual genes, which is essential to the calculation of the *P* value for whether a gene is overburdened with mutations in a genome. Two important quantities are usually reported to justify a claim that a driver gene is important: a gene-specific *P* value of whether the tumor is significantly overburdened with mutations, and the overall prevalence of mutations in that gene (Lawrence et al., 2014). If a statistically significantly higher frequency of a specific mutation was observed in a tumor type than expected by mutation rate, then a likely conclusion in such a study would be that the mutation is related to cancer development. Generally, there was a correlation between prevalence and *P* value, but there were multiple exceptions such as *HRAS* and *EPHA2* in head and neck cancers and *U2AF1* in acute myeloid leukemia (Lawrence et al., 2014). However, neither the *P* value nor the prevalence can act as a measure of the effect of a mutation (Cannataro et al., 2018; Kelley and Preacher, 2012; Sullivan and Feinn, 2012). In order to obtain the cancer effect size, the prevalence must be deconvolved into the baseline mutation rate and the degree of selection for the mutation in the cancer lineage.

Given the mutation rate and prevalence of a mutation in any given site in any given gene, Cannataro et al. calculated the selection intensity, the relative cancer effect of the mutation, by deconvolving the mutation rate and prevalence (2018). Expected substitution rates for each gene were calculated by normalizing the average per-site synonymous mutation rate by the average weight of the trinucleotide mutational signature burden for the tissue (Cannataro et al., 2018). Comparing the expected and observed substitution rates, the table of observed rates was a greatly reduced representation of the table of expected rates, providing evidence for natural selection for those observed mutations in causing cancer. Mutations observed at high frequency when sequencing is performed may well be selectively advantageous to cancer cell lineages, but the range of genes with high expected mutation rates indicated several possibilities that do not end up contributing to cancer (Cannataro et al., 2018).

Having the calculated cancer effect of mutations is essential because it can take mutation rate and prevalence one step further to show specifically which mutations contribute to the evolution of cancer, which cannot be done with either measure alone. For example, the Cannataro et al. (2018) study applied selection intensities of multiple KRAS G12 mutations (G12A, D, C, V) in lung adenocarcinoma (LUAD) to a previous finding that the G12 cysteine (G12C) mutation was highly prevalent in LUAD while it was minor in pancreas and colorectal adenocarcinomas (Porta et al., 2009). Although it may be inferred from the prevalence that G12C was especially effective at causing LUAD, the selection intensities showed that G12C had almost the least effect on the cancer relative to the other G12 mutations. The analysis instead supports the idea that G12C mutations in LUAD are more prevalent as a direct consequence of the specific kinds of nucleotide mutations induced by smoking (Cannataro et al., 2018).

The cancer effect size can be calculated for single-nucleotide mutations for any sufficiently large set or subset of tumors. Treatments can be devised based on inhibiting mutated genes with high selection intensity such as BRAF V600E in skin cutaneous melanoma, but the capacity for the evolution of resistance against the treatment isn't indicated by the effect size tool (Cannataro et al., 2018). The full distribution of scaled selection coefficients for single-nucleotide variants (SNVs) can also be calculated across

many different cancer types (Cannataro and Townsend, 2018). Given the availability of these selection coefficients, future analyses should consider the calculated cancer effect of SNVs they are examining. Future work on the tool would benefit by incorporating not just single nucleotide mutations but also multi-nucleotide variants (Kaplanis et al., 2019; Srinivasan et al., 2021), copy number variation (Beroukhim et al., 2010; Pladsen et al., 2020), chromosomal alterations such as chromoanagenesis and polyploidy (Pellestor and Gatinois, 2020; Shabo et al., 2020), and epigenetic alterations (Chatterjee et al., 2018).

When candidate cancer drivers are determined via sequence-based comparison of effect size (Cannataro and Townsend, 2018), further biological investigation may be conducted via molecular investigation *in vitro* (Cannataro et al., 2019), as well as in genetically engineered mouse models (GEMMs; Webster et al., 2020), patient-derived organoids (PDOs; Wensink et al., 2021), patient-derived xenografts (PDXs; Evrard et al., 2020), and companion animals (Somarelli et al., 2020a). Much has been said regarding the relative merits of these experimental models: they demonstrate varying abilities to mimic the somatic molecular evolutionary process of *in vivo* human tumors. While typical culture of human cell lines can operate in a human germline genetic context that is very close to the evolution of cancer in humans, cell lines are limited by their homogeneity and lack of microenvironmental interactions. Cell lines—the cheapest and most readily available models—offer a means for quickly testing the effects of mutations and treatments. However, their homogeneity in culture belies the complex environmental interactions of cells and microenvironment within the body (Hynds et al., 2021); they also evolve markedly over time in laboratories (Ben-David et al., 2018). Highly influenced by their ex situ microenvironment, they do not recapitulate intra-tumoral heterogeneity. Some but not all of these weaknesses can be addressed by culturing PDOs in which tumor cells are embedded into a 3D culture (Huang et al., 2020; Neal et al., 2018; Yang et al., 2018). Others can be addressed by culturing patient-derived xenografts (PDXs); implanting human tumor tissue into immune-modified mice maintains some aspects of the immune microenvironment in the short term, histopathological structure, and gene expression associated with their original source, and provides a particularly effective mimesis of human tumors when chemotherapeutics are tested (Cho, 2020; Evans et al., 2017; Reyal et al., 2012; Zhao et al., 2012). Alternatively, GEMMs and (even more so) companion animals provide a whole-organism microenvironment that is highly analogous to the human somatic evolution of cancer—at the cost of a substantially divergent starting germline genotype, and organismal and immune-system phenotype. The capacity for these models to incorporate such considerations significantly affects how we must interpret their results.

The selective effects of mutations represent a mapping of genotype to the uber-phenotype of fitness; further analysis could break fitness down into known phenotypes (hallmarks) of cancer. All of the hallmarks of cancer as mentioned by Hanahan and Weinberg (2011) are incorporated in cancer effect, but genome instability and mutation is a particularly key factor because the other hallmarks are phenotypes of cancer while genome instability may also be due to genetic or environmental changes and is thus important in understanding the initial development of cancer. Studies of genotype-phenotype relationships in RNA complexes have shown that more frequent phenotypes can reach fixation in a population even if other, but less frequent, phenotypes potentially exist (Schaper and Louis, 2014). This model may help explain differences in the observed rates of therapy resistance mechanisms. For example, prostate cancer patients receiving hormone therapy rarely exhibit the F877L point mutation in the androgen receptor, even though these mutations convert the drug into a partial agonist (Joseph et al., 2013; Korpal et al., 2013). Conversely, hormone therapy commonly leads to enrichment of alternative splicing isoforms of the androgen receptor in which the drug binding site is lost (Armstrong et al., 2019). It is likely that the more frequently-observed splicing-mediated resistance driver, which lacks the drug-binding domain, is less fit than the agonistic mutation in the presence of the drug. However, the agonistic mutation, which requires a precise mutation to arise in a single nucleotide within the whole genome, is far less frequent than the resistance driver that is generated by alternative splicing—a more accessible change of state of a dynamic, heterogeneous process (Wan and Larson, 2018). Many such examples may exist in which the frequent occurrence of non-genetic alterations is selected in a population rather than additional point mutations with a much lower likelihood of occurrence, even in cases in which the point mutation leads to higher long-term fitness.

Multiple fields would benefit by considering the effect size of variants within cancers. Basic research could focus on those mutations with high cancer effects as they are more essential to understanding the mechanisms underlying cancer. In precision medicine, the effect sizes of mutations could help tumor boards select precision therapeutic drugs for patients, especially for off-label usage in a cancer type for which no direct clinical trial efficacy data can be compared. Effect sizes can guide decisions regarding which precision therapeutic clinical trials are likely to be successful, and effect size could help prioritize pharmaceutical development of drugs that directly target high cancer-effect mutations, which are more likely to exhibit clinical benefit in human clinical trials. Large clinical trials testing precision-medicine strategies, including NCI-MATCH (Conley and Doroshow, 2014) and ASCO's TAPUR Study (Mangat et al., 2018), could benefit from using the relative effect sizes of mutations to stratify patients for targeted therapies rather than relying on correlated but less precise measures like mutation prevalence. Such approaches could improve the efficacy of these trials and allow for prospective clinical evaluation of the importance of effect size. Since targeted therapy trials are by their nature limited in sample size, projects such as AACR Project GENIE (AACR Project GENIE Consortium, 2017), which host collaborative data repositories of clinical sequencing data matched with outcomes aggregated from several cancer centers, provide researchers with a necessary increase in ability to determine the utility of targeted therapies, identify biomarkers of response, and test theories like cancer effect size.

1.3. Epistasis among cancer drivers

Scaled selection coefficients that have been calculated without reference to pre-existing germline or coincident somatic mutations (Cannataro et al., 2018) constitute averages across tumors. Epistatic interactions with pre-existing germline or coincident somatic mutations complicate the use of generalized scaled selection coefficients for tumor-specific precision medicine (Forneris et al., 2017; Weigelt and Reis-Filho, 2014). Depending on the epistatic relationship of the mutation as well as the presence of one or more partner mutations, the selective advantage incurred by a mutation in a tumor can be significantly altered.

In antagonistic epistasis, the presence of one mutation sharply reduces the selective advantage for the other mutation in the cancer cell. Antagonistic epistasis typically results in a pattern of mutual exclusivity. It often arises as a consequence of mutations to proteins that affect the function of genes within a linear or near-linear pathway (Wilkins et al., 2018). In synergistic epistasis, the presence of multiple mutations increases the selective advantage attributable to each of the mutations. Synergistic epistasis typically

results in a pattern of co-occurrence. Both mutual exclusivity and co-occurrence of mutations can be found using gene-essentiality screens as long as the mutations are functional and associated with cell proliferation (Mina et al., 2020). However, mutual exclusivity and co-occurrence are not direct measures of epistasis, and cannot on their own be used to conclude that there is evidence of antagonistic or synergistic epistasis (Park and Lehner, 2015; van de Haar et al., 2019). For one thing, the statistical conclusion that mutual exclusivity is present can be caused by differences in driver mutation frequencies between tumor subtypes (van de Haar et al., 2019). When tumor subtypes are characterized by different sets of driver mutations, the high frequency of those mutations in their subtypes and low frequency in other subtypes would lead to high measures of mutual exclusion and could be interpreted as epistatic when it is not the case. The misinterpretation of mutual exclusivity as epistasis is complicated by mutation load in the subtypes. A driver mutation in a subtype with a low mutation load may appear to be epistatic through mutual exclusion with other genes (van de Haar et al., 2019). Van de Haar et al. (2019) measured the association between the mutation frequency and tumor mutation load which they termed mutation load association (MLA), and they found that genes with low MLA—genes that were mutated more frequently in tumors with a low mutation load—tended to be cancer genes. Mutual exclusivity was also found to be more commonly statistically detected in those low MLA genes. Stratification by tumor subtype reduced the correlation of mutual exclusivity detection in low MLA genes and greatly reduced the number of detected mutually exclusive pairs overall. Correspondingly, an elevation in some tumors but not other tumors of a specific mutational pattern (e.g. APOBEC mutagenesis associated with HPV infection in head-and-neck cancer; Cannataro et al., 2019) that increases the frequency of two distinct oncogenic mutations can lead to co-occurrence. Mutually exclusive patterns of mutation arising from differential carcinogenic exposure can lead to mutual exclusivity of mutation that is unrelated to epistasis. The strength of the effect of epistasis, observed through these patterns, varies widely—depending not only on the organism and environment but also the cancer type, necessitating a comprehensive analysis across types (Hall et al., 2019; Park and Lehner, 2015).

Knowledge of pairwise epistasis through observation of tumor sequence representation requires high sample sizes (effectively, sample sizes that are the square of those needed to conclude the cancer driver status of a mutation). Therefore, knowledge of its existence in patients through biochemical studies can be especially informative and can help with the development of effective therapeutics. Antagonistic epistasis, for instance, suggests that there is a possible evolutionary path toward drug resistance: a drug that successfully abrogates the effect of one mutation that is part of a mutually exclusive pair may engender a novel selective pressure on a new mutation arising in its mutually exclusive partner (Wilkins et al., 2018). This altered selective pressure can also be estimated using phylogenetic analyses comparing pre- vs post-treatment tumor sequences and can be used to confirm inferences of epistatic relationships, further encouraging molecular biological investigation and the development of combination therapies. Targeting drug development toward mutations that are synergistically epistatic would likely have strong benefits (abrogating cancer fitness gain from both mutations) and have lower chances of the evolution of drug resistance. Analysis of subsets of tumors with specific driver mutations (Cannataro et al., 2018) can reveal epistatic relationships pointing towards putative synthetic lethal mutant phenotypes (for antagonistic epistasis) or synergistic clinical effects (for synergistic epistasis). Experimental confirmation and cross-validation with evolutionary dependencies from experimental cyclopedias such as the Cancer Dependency Map (Boehm et al., 2021) can provide additional justification for pursuit of therapies that exploit these epistatic relationships via precision combination therapy (Wilkins et al., 2018). Generally, a better awareness of epistasis can more accurately inform which treatments are least or most helpful—knowledge that can help with crucial precision-medicine decision making.

Given consideration of cancer's special characters, their evolution over time, and the complicating effects of epistasis, the next steps for the evolutionary study of cancer include stage-specific and epistatic estimates of cancer effects for not just SNVs but also diverse copy number variations (Beroukhim et al., 2010; Pladsen et al., 2020), epigenetic changes (Chatterjee et al., 2018), multinucleotide variants (Kaplanis et al., 2019; Srinivasan et al., 2021), giant-cell evolution (Pienta et al., 2020; Shabo et al., 2020), karyotypic chaos (Heng and Heng, 2020; Pellestor and Gatinois, 2020), and other factors associated with cancer development.

1.4. Longitudinal studies and metastatic migration histories

Longitudinal studies with multi-regional sampling or sampling of distant metastases are especially valuable for timing important periods of cancer growth and change. The first large-scale study of multiple samples from multiple cases examined 40 patients and 13 types of cancer, demonstrated early and multiple origins of metastatic lineages within primary tumors, and used molecular evolutionary calibrations to create cancer chronograms (Zhao et al., 2016). Other studies have also traced driver mutations through time (Gerstung et al., 2020; Jamal-Hanjani et al., 2017). The chronograms supply timing information regarding the somatic genetic evolution of cancer, which can be matched with events in the clinical time course projecting which driver mutations were occurring when, whether they were occurring early or late, and perhaps most importantly, relating these changes to their specific clinical context. Deriving cancer chronograms as in Zhao et al. (2016), it likely will become possible to link changes in therapy with key events in cancer progression such as the evolution of resistance and its associated mutations. Key phenotypic events can be tracked by adaptive therapy strategies that take into account the evolutionary characteristics of cancer progression—for instance, treatment with relatively weak drug doses to limit cancer growth but not create a selective pressure for resistance (Enriquez-Navas et al., 2016; West et al., 2020). The effects of adaptive therapies are modeled based on the dynamic evolution of cancer and enable prediction of patients' trajectories (e.g. Zhang et al., 2017). Moving forward, adaptive trials may be informed not only by current clinical measurements and an understanding of the historical response of other patients (West et al., 2019) but also by inference of the somatic evolutionary history of each patient, using cancer chronograms.

The clonal evolutionary history inferred from somatic genetic variation within patients, when analyzed alongside the tumors' physical locations, can be used to map the spatiotemporal dynamic of cancer cell migrations (Chroni et al., 2019; El-Kebir et al., 2018; Kumar et al., 2020). Such maps reveal the origin and early progression of metastatic clones which are not medically detected or visible until later stages of cancer development when the patient seeks medical attention. Sophisticated phylogenetic and phylogeography methods of analysis have shown promising results in mapping clone migration from the primary tumor to the origination of new metastases, migration between metastases, and migration from secondary tumors back to the primary tumors (Alves et al., 2019; Chroni et al., 2019; Kumar et al., 2020). For example, the application of PathFinder—a Bayesian approach to map tumor migration histories—predicted multiple instances of metastasis-to-metastasis cancer cell migrations in a patient

inflicted with basal-like breast cancer (Kumar et al., 2020). This evidence of migration stood in stark contrast to the initial proposal that all the metastases (Lung, Brain, Lever, Rib, and Kidney) were directly seeded by the primary tumor (Hoadley et al., 2016). Escalating sequencing efforts are poised to enable high-resolution discovery of clonal heterogeneity at increasingly higher numbers of tumor sites. Soon, analysis of such data from many patients will be the key to deciphering migratory origins of genetic heterogeneity in metastatic tumors. This information will add to our understanding of the processes that influence tumor aggressiveness, resistance, and escape from therapy due to the sharing and flow of clones across tumors.

1.5. Genotype-by-environment interactions

Cancer follows principles of ecological fitness in which genetically-diverse cancer cell populations are shaped through evolutionary selection by the environments in which they reside. Environmental conditions, such as resource availability, local geography, and predation from the immune system select for cancer cell phenotypes that promote survival and eventual reproduction (proliferation). The phenotypes that enable survival and reproduction are driven by the underlying genotype. Yet, while the potential genotypes that enable survival and reproduction are vast, these genotypes converge on a smaller number of phenotypes. The well-established concept of gene-by-environment interaction serves as a guiding framework for understanding how different cancer genotypes converge on distinct cellular phenotypes in response to their environments. Adaptive topographies for a character in different environments illustrate the possible differences in the evolutionary processes influencing selection (Via and Lande, 1985; Yi and Dean, 2019). Different environments produce different evolutionary landscapes, so the pattern of selection for a character may vary depending on the environment. Adaptive topographies enable us to understand the dynamics of cancer's special characters. This may allow us to develop therapies that address not only the cancer characters themselves but also the fitness landscapes in which specific cancer characters are selected and enriched.

A study of the yeast *Saccharomyces cerevisiae* analyzed the genetic and environmental response to copper levels (Hodgins-Davis et al., 2012). Copper acts as a nutrient at low levels but as a toxin at high levels, so the effect of the environment on gene expression can be analyzed across a definable fitness-viable continuum. Hodgins-Davis et al. (2012) examined a span of copper levels from low to high that was just tolerable enough that 5450 divergent strains could reliably be cultured in the laboratory. Examining well-measured, expressed genes in these strains across this span of copper levels, the expression of 729 genes in the yeast strains changed dependent on the strain genotype alone, while expression of only 114 genes changed dependent only on the environment but not the genotype. Only 60 genes demonstrated independent effects of both genotype and environment. Importantly, though, a large majority—1606—genes, were reliant on the combination of the effects of genes and environment (Hodgins-Davis et al., 2012). Gene expression variation is consistent with a house-of-cards model of stabilizing selection across yeast, fruit flies, and nematode model organisms (Hodgins-Davis et al., 2015); the frequencies of genetic, environmental, and gene-environment interactions in gene expression found in these model organisms (Hodgins-Davis and Townsend, 2009) may pertain to cancer cells as well. Abstracting these results from a model microorganism to cancer biology, these studies reveal the importance of understanding both the microenvironmental and genetic effects in tandem to properly characterize tumors. Not only are the microenvironmental differences among tumors important (e.g. Peltanova et al., 2019), but interactions between genetics and the microenvironment are likely to be responsible for a significant amount of gene expression variation in tumors. Accounting for these interactions may result in significantly improved predictions.

Just as the microenvironment can influence gene expression, changes to the somatic genotype can influence the microenvironment. Nearly all of the mutations that are most commonly observed across cancers are involved in either promoting survival or inducing proliferation, two features that define cancer cell fitness. Efforts to assign mutations to cancer hallmarks have begun to reveal how diverse cancer genotypes converge on hallmark phenotypes (Iannuccelli et al., 2020; Iorio et al., 2018). However, while these mutations alter cell-intrinsic cancer phenotypes, many of these mutations also shape the dynamics of the cell-extrinsic interactions between cancer cells and their environments. For example, gain-of-function mutations in p53 can induce interferon beta in cancer-associated fibroblasts (Madar et al., 2013), modify the interaction of cancer cells with the tumor extracellular matrix (Amelio and Melino, 2020), and shift macrophages from tumor suppressive to tumor permissive through the release of microRNA-loaded exosomes (Cooks et al., 2018). Cancer mutations can have substantial impacts on the immune landscape, with distinct oncogenic mutations inducing enrichment of specific immune subsets (Wellenstein and de Visser, 2018).

Gene-by-environment interactions in cancer are radically altered by therapy, with cells possessing different underlying genotypes responding in divergent ways to therapy. For example, prostate cancer cells treated with second-generation hormone therapies, such as abiraterone acetate or enzalutamide, are often genetically-altered—through copy number amplification, mutation, epigenetic rewiring, or chromosome rearrangements—to bypass these therapies (Watson et al., 2015). Phenotypically, persistence of androgen receptor signaling induces a dormancy-like phenotype in which prostate cancer cells upregulate p38/MAPK signaling (Ware et al., 2020). Clinically, a majority of patients display continued androgen receptor signaling, as exhibited by long-term clinical responses and continued expression of prostate-specific antigen, an androgen receptor-regulated gene (Alumkal et al., 2020). On the contrary, prostate cancer cells can also exhibit TP53 and RB1 gene loss, which promotes a neuroendocrine-like phenotype in which the cancer cell becomes indifferent to androgen receptor signaling (Ku et al., 2017; Mu et al., 2017). These patients exhibit little to no response to hormone therapy and an aggressive disease course (Akamatsu et al., 2018; Hirano et al., 2004). Differing genotypes—in androgen receptor signaling or TP53/RB1—induce divergent cellular behavior in response to the powerful, systemic environmental variable of hormone therapy.

One of the most relevant treatment strategies that directly addresses the interaction between cancer cells and their microenvironment is immune-checkpoint inhibition. Immune-checkpoint inhibition acts by blocking immunosuppressive “checkpoint” molecules on cancer cells (Pardoll, 2012). Blockade of immune-checkpoint molecules prevents cancer-cell immune-cell interactions and re-activates the immune system to eradicate cancer cells (Pardoll, 2012). Response to immune-checkpoint blockade differs based on genotype: alterations in genes that control the immune response (JAKs; Zaretsky et al., 2016), loss of antigen presentation (Rooney et al., 2015; β2 microglobulin, HLA-A, B, C; Zaretsky et al., 2016), and apoptosis (CASP8; Rooney et al., 2015) are enriched during acquired resistance to immune checkpoint blockade (Zaretsky et al., 2016) while amplification of chromosomal regions encoding PD-L1/PD-L2 and ALOX12B/15B are associated with improved cytolytic activity (Rooney et al., 2015). Additionally, larger-scale phenomena including specific chromosomal events

and high clonal mutation burdens (TMBs) have been shown to be effective biomarkers for checkpoint inhibition therapy in several cancer types (Bai et al., 2020; Litchfield et al., 2021). For instance, it has been demonstrated in a pan-cancer study that loss of chromosome 9 typically deletes *TRAF2*, thereby improving the efficacy of checkpoint inhibition (Litchfield et al., 2021).

Building on the relationship between the microenvironment and gene expression, Gaffney et al. (2019) studied the expression of several genes in multiple different cancer tissue types (Gaffney et al., 2019). They sought to deconvolve the expression of different genes that are typically immune-related genes that may be checkpoints. Specifically, they focused on checkpoints whose inhibition might be complementary to PD-1 and CTLA-4, which are currently in widespread use in cancer with promising results (Herbst et al., 2020; Kooshkaki et al., 2020; Larkin et al., 2019; Mazieres et al., 2021; Ready et al., 2020; Schadendorf et al., 2015). They sought to find T cells expressing a checkpoint gene other than PD-1 and CTLA-4 which could be targeted in patients whose T cells were not successfully targetable with those inhibitors. Several genes—such as *CD6*, *CD96*, and *TIGIT*—featured high expression across multiple tumor types, indicating multiple possibilities for inhibitor therapy development (Gaffney et al., 2019). This study further emphasizes the necessity of understanding genetics in the context of the tumor microenvironment to develop therapies.

These interactions highlight the importance of accounting for considerations beyond tumor genetic sequencing. Genes are subject to transcriptional, translational, and epigenetic regulation, all of which contribute to oncogenesis (Biswas and Rao, 2017; Vaklavas et al., 2017), can be modified by a variety of internal and external factors, and are influenced by epistatic and microenvironmental interactions. Just as germline genetic determinism fails to predict human development, somatic germline determinism is incapable of explaining the intricacies of human pathology (Resnik and Vorhaus, 2006). The changes that lead to cancer can occur not only via mutation of the somatic genotype but also via extreme alterations of cellular phenotype. Such phenotypic changes are not necessarily preceded by genetic modifications; they can occur stochastically (Mooney et al., 2016) and can be epigenetically heritable (Carlos Guerrero-Bosagna, 2012). Thus, while genetic data provides a strong basis for our understanding of how cancer evolves, knowledge of transitions of regulating, modifying, epistatic, and environmental factors are essential to the interpretation and exploitation of the evolutionary trajectory of cancer with an aim toward understanding mechanisms and developing therapies.

2. Conclusion

To make rapid progress in these crucial areas of the evolution of cancer, an essential question we will have to answer is how we synthesize these diverse areas of study: molecular evolutionary biology and the many approaches within it, pharmacology, clinical investigations, and more. Differences in jargon and disagreements over the main concerns can prevent effective communication and collaboration, slowing the inclusion of molecular evolutionary paradigms into therapeutic and clinical applications. Evolution establishes the foundation upon which this synthesis can occur. Basic research, pharmacological innovations, and clinical trials can be built on and understood through evolutionary principles, enabling us to bring these diverse fields under a single, comprehensive perspective. Thus, evolutionary biologists, clinicians, and everybody who has insight into how cancer is a process of evolution will benefit from increased communication and the establishment of a research community. A scientific community that encourages the discussion of ideas across disciplinary boundaries is likely to make meaningful and rapid progress in cancer research.

Author statement

JPT conceived the review; JPT, SK, JAS, and KD acquired funding; KD and JPT drafted the manuscript; KD, JPT, JAS, and SK made additional contributions to the manuscript, edited it, and contributed to its revision.

Declaration of interests

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: JPT is consulting for Agios Pharmaceuticals, Servier Pharmaceuticals, and Black Diamond Therapeutics. All other declare no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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