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Human cancers comprise an heterogeneous array of diseases with different progression patterns and responses to therapy. However, they all develop within a host context that constraints their natural history. As it occurs with the diversity of organisms, one can conjecture that there is order in the cancer multiverse. Is there a way to capture the broad range of tumor types within a space of the possible? Here we define the oncospace, a coordinate system that integrates the ecological, evolutionary and developmental components of cancer complexity. The spatial position of a tumor results from its departure from the healthy tissue along these three axes, and progression trajectories inform about the components driving malignancy across cancer subtypes. We postulate that the oncospace topology encodes new information regarding tumorigenic pathways, subtype prognosis and therapeutic opportunities: treatment design could benefit from considering how to nudge tumors towards empty evolutionary deserts in the oncospace.

Keywords: cancer morphospace; microenvironmental complexity; genome instability; developmental abnormalities

There is an internal logic to the genesis and transformation of morphologies and in that logic we may learn about the constraints on the normal.

Pere Alberch - *The logic of Monsters* (1989)

I. INTRODUCTION

Cancer is a highly heterogeneous disease, and even within a specific cancer type there is heterogeneity in the tempo and mode of progression and natural history. Part of the variability depends on the genetic features of the host, the abnormal genetics and metabolism of the cancerous tissue (1) and, when treated, the diverse response to different therapies (2). Cancer can be seen as a distorted execution of developmental programs, that has been freed from the organismal-level constraints that foster collective stability.

However, given the amount of heterogeneity among cancer types, from their genomes to their natural history, one could easily reach a somewhat obvious conclusion: cancer types are not constrained to a given finite repertoire of possibilities. Is that the case? Within the context of developmental constraints, the Catalan evolutionary biologist Pere Alberch argued that this might not be so (3). In his paper "The Logic of Monsters" Alberch summarised compelling evidence that, even within the domain of teratologies, it is possible to perceive a discrete, underlying organization: there is a deep order that allows to define a taxonomy of "anomalies".

Is there also a logic in the abnormal patterns of carcinogenesis leading to different tumor types? Throughout the past century, different approaches have attempted to define a tumor classification scheme, with the purpose of optimizing cancer diagnosis, prognosis, and rational therapy, and hence enlightening our understanding of the disease (4). Classifications have also played an increasingly important role in guiding translational cancer research and stratification of patients for clinical trials. However, most classifications (see (5) as an exception) are limited to the molecular or cell-level attributes of cancerous *agents* and do not capture the system-level properties, or *agencies*, that drive and direct tumor growth.

It is widely agreed that the process of tumor formation follows *evolutionary* and *ecological rules* (13), and that (anomalous) *developmental cues* shape tumour phenotypes into a caricature of normal tissues (14). How can we capture the different outcomes obtained by the interaction of these three agencies? The standard evolutionary perspective on carcinogenesis considers a landscape where rogue clones evolve under selection pressures imposed by the host organism (15). A tumour is then understood as an heterogeneous cloud of genotypes surrounding a fitness peak. However, the fitness map does not capture the developmental architecture of each tumour class nor its ecological composition, and populating the fitness landscape with different tumor families might not render any relevant topology.

We here suggest that a space of cancer types can be defined by weighting the relevance of the three previous components of tumour complexity. Our proposed cancer *oncospace* (see Box 1) can reveal disease trajectories and patterns of clustering that highlight the presence of a constrained organisation. Occupied domains also uncover large regions where no cancer types are to be found. As discussed below, there is a rationale for this structure

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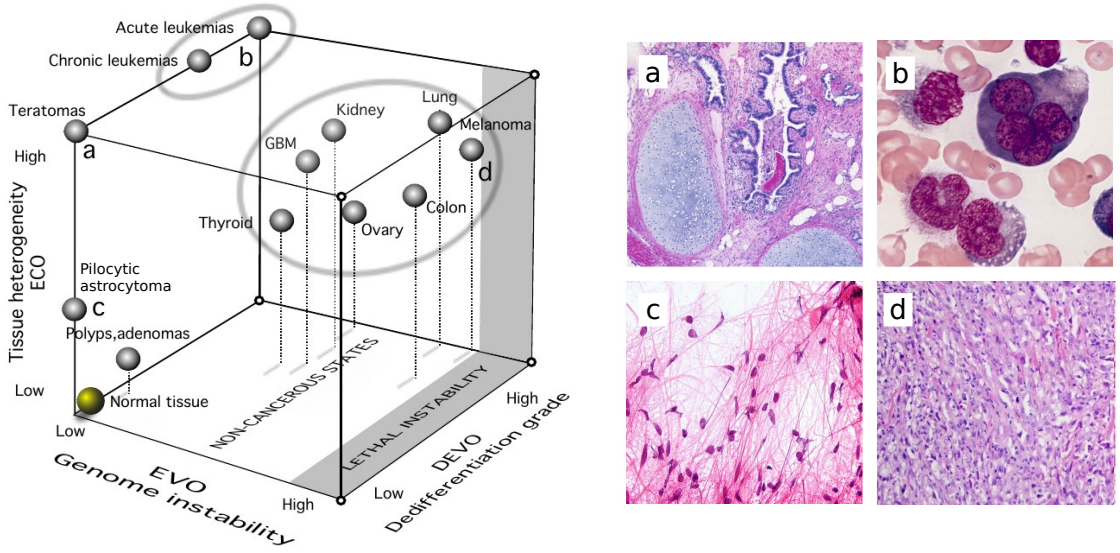

FIG. 1 **The oncospace for human cancers**. Why, and how, are cancers so different or similar to one another (**a-d**)? Qualitative pan-cancer oncospaces targeting these questions can be build by merging available data on mutational footprints (6), stromal and immune infiltrates (7; 8) and histopathological or stemness grading (9; 10). Even in such a coarse-grained scenario, insight results from understanding how clusters of tumors highlight families with common carcinogenic trajectories, while separation between cancer types might give a qualitative explanation for their differences (**(a)** Mature cystic teratoma, **(b)** Acute erythroid leukemia, **(c)** Pilocytic astrocytoma, **(d)** Skin cutaneous melanoma). Here the two encircled subsets correspond to liquid (left) and solid (right) malignant tumors, while empty regions raise questions on why given configurations are not seen in human cancers.

BOX 1: Morphospaces – The geometry of biological complexity

A systems-level approach to the discrete nature of biological order is provided by the so-called *morphospaces*. They are built upon a set of dimensions that encapsulate properties of the studied system, such as different geometrical attributes (11). Phenotypes, therefore, sit upon points in the space, creating a characteristic topology that provides novel information of the underlying laws of the categorized system (12). Across different domains of biology, morphospaces do not only highlight the relative position between studied agents, but may also uncover both evolutionary and developmental trajectories or the existence of voids, unoccupied regions in the *space of the possible* that hold information of dynamical processess and structural constraints (12).

that might provide an opportunity for therapeutic novelty, by uncovering how to nudge tumours towards empty regions in the oncospace.

II. THE ONCOSPACE: AN INTEGRATIVE COORDINATE SYSTEM

The oncospace is an heuristic, comparative approach that allows to define a global picture of cancerous diseases within the bounds of a three-dimensional space (Fig. 1). The three axes provide a metric for the location of each tumor type at a given time point in their life-history. The normal tissue state is located on the lower left corner of our space[1]. These axes capture (i) complexity of the cancer ecosystem and its composition, (ii) evolutionary footprints in the unstable cancer genome, and (iii) aberrations in developmental architectures present in the tumor.

[1] Healthy tissues belong themselves to a large class of systems displaying a wide range of structural motifs, functional features, turnover rates or regeneration properties. However, a common set of traits are also in place involving multicellularity and histomorphological features associated to a stable, well-defined functional state.

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BOX 2: From qualitative to quantitative oncospaces

1. Measuring Ecological Complexity: Ecological aberrations at the tissue-level can be measured by taking into account the cellular heterogeneity of the tumor microenvironment. A possible metric can be obtained by taking the inverse of *tumor purity* (7), the estimated percentage of cancer cells in a tissue biopsy. Low purities are indicative of tumors highly infiltrated by other cell types (such as a strong immune infiltrate or a complex stromal component) that actively alter the normal interactions and signaling of the original tissue (8).

2. Measuring Evolutionary Complexity: Evolutionary footprints of cancer pervade multiple layers of the genome (6). These can be summarized into microsatellite mutations, epigenetic alterations and changes at the chromosomal scale (16). The link between these and *evolvability* is, however, not totally understood, and key questions linking instability to phenotypic exploration remain open (17). As a first approach, weighting available measures of mutational load, copy number changes and methylation degree allows a measurement of how each tumor type is affected by oncogenic mutation-selection processes.

3. Measuring Developmental Complexity: Developmental complexity has historically been measured by *Dedifferentiation Grade*: an histopathological classification of a neoplasm based on the resemblance of the tumoral tissue to its normal counterpart. This observations, that already provide a direct gradient between Devo-normal and highly undifferentiated or stem-like cancers, are rapidly being improved by the advent of refined image recognition techniques (10). Further research on sequencing opportunities is also unraveling genetic and epigenetic signatures capturing the degree of tumor stemness (9) or its methylation status (18).

A. Ecological complexity

Within tumours, a set of different cells coexist in a complex ecological network of interactions (19). This ecological dimension unfolds once the selection barriers of tissue homeostasis and stable multicellularity are trespassed by cancer. To a large extent, cancer types can be understood in terms of so called *novel ecosystems*. These are defined as unique species assemblages, resulting from alteration by humans, able to cross an ecological threshold that facilitates a new ecosystem trajectory (20; 21). As it occurs in cancer, novel systems often persist surrounded by the historical community within which they have emerged and are typically resilient and resistant to removal strategies).

A first layer of complexity in these cancer ecosystems comprises tumor cell populations harbouring different phenotypes, hence defining multiple *clones* or *species* (15). As in natural ecosystems, ecological interactions such as competition, mutualism and antagonism promote diversity while shaping the landscape of somatic cancer evolution (22). Abnormal growth occurs within a given host ecological context and interactions between growing tumors, host tissue, blood vessels, immune cells and the resulting network of chemical communications are best characterized through complex ecological dynamics (23; 24).

This cellular heterogeneity at the tissue-level often correlates with a worse prognosis and therapy resistance (25). A wide array of ecological interactions and processes deviate from tissue homeostasis to foster tumor diversity. Examples involve angiogenesis and the resulting tumor vascular network as a carrier of resources (26) or the role of spatial restrictions in shaping phenotype-specific niches or density-independent strategies (27). In our oncospace, a well-defined corner is provided by teratomas, which are genetically stable, highly differentiated systems characterized by an heterogeneous ecosystem of cellular populations.

B. Evolutionary complexity

Cancer is also a disease of Darwinian evolution (15). The complex ecological environment of tissue homeostasis defines multiple selective barriers to novel, evolved phenotypes (15). As cells tend to loose their multicellular machinery, selfish replicator phenotypes evolve able to modulate immune interactions (28), metabolic pathways (29) or the capacity to metastasize (30). Cancer evolution is also observed in the clinics, with most advanced malignancies evolving the capacity to resist or circumvent a wide arrange of therapies (31).

What are the underlying mechanisms of variation in cancer? Oncogenic aberrations, demonstrating the footprints of evolution in the human genome, are known to happen virtually at any level of its complex packaged structure. More than a century ago, early observations of the karyotype of cancer cells indicated the possibility of chromosomal aberrations initiating tumor growth (32). Decades later, the discovery of DNA and the advent of the genomics era identified cancer as a disease of the genes (33). Modern observations of aberrant chromatin architectures point towards the possibility of epigenet-

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ics as a complementary or alternative driver of phenotypic changes (34). Importantly, evolutionary dynamics in cancer can led to runaway effects through the accumulation of genome instability: because the failure of control checkpoints trigger further losses of stability, it has been argued that some unstable cancers might evolve to the edges of viability (35).

C. Developmental complexity

Pathologists of the mid-19th century already observed striking similarities between tumor cells and normal embryonic tissues (36). More than a hundred years later, the observation of cancer cells with a stem-like phenotype led to the Cancer Stem Cell (CSC) model where a hierarchical but aberrant tissue architecture maintains tumor progression (37). Tumors grow to become *caricatures of normal tissue development* (14), perhaps as a result of the ontogenetic process where both developmental and ecological rules interact.

Beyond the CSC model, evidence of cellular plasticity and spontaneous dedifferentiation (38) indicates that the developmental landscapes of cancer might be much more complex than fixed hierarchical architectures. Recent evidence for complex phenotypic plasticity includes non-mutational switching between well-defined cellular modules in glioblastoma (39) or lineage plasticity driving therapy resistance in prostate and lung cancers (40).

A clear image of how development is integrated in oncogenesis follows from understanding the dynamical nature of the Waddington landscape (41). In it, initially embryonic cells *roll down* into valleys as they differentiate and specialize. The number and existence of attractor states in the landscape results from the multiple configurations of gene-regulatory networks (42). In this context, genome instability and chromatin alterations translate into changes in the topology of the landscape itself, thus mediating the creation and accessibility of so-called *cancer attractors* (42).

III. ONTOGENETIC PATHS AND THERAPY IN THE ONCOSPACE

In their original formulation, mosphospaces also allowed for understanding ontogenetic (development-related) trajectories within the limits of the space of the possible (11). Benign tumors somehow adjust to this concept, moving across the oncospace as they grow and develop completely predictable histopathological traits. For malignant cancers ontogeny strongly departs from the standard picture of development: ecology, evolution and development are inevitably intertwined, and histopathological trajectories remain unpredictable for many tumor types.

Our perspective indicates that, by collecting accurate data across cancer subtypes (Box 2), the oncospace can uncover unknown ontogenetic tumor pathways. As for colorectal cancers where well-known trajectories can be observed (Fig. 2a, (43)), mapping complex tumor progression into the oncospace will provide both a formal classification scheme and a research method for less-understood oncogenic processes.

The gravest corollary of ontogenetic trajectories is treatment failure. Resistance to successive lines of therapy giving rise to relapse after a period of apparent remision is a major cause of cancer mortality. In theory, it could be argued that cancers have multiple escape paths for a given treatment, each involving ecological, evolutionary or developmental innovations. However, clinical observations indicate that pathways to resistance appear much more constrained (45).

Morphospaces not only highlight possible developmental paths, but also allow the study of morphologies that do not exist and the meanings of such voids (12). We propose that populating an oncospace with the pre- and post-treatment tumor coordinates might contribute to our understanding of cancer drug resistance. In our context, regions of the oncospace occupied by cancer subtypes indicate genotype or phenotype states that are *evolutionary attainable*: given an external selective pressure, it is reasonable to expect a tumor to move towards another preferred configuration and survive (see e.g. (46), Fig. 2a).

On the opposite side, empty regions in the oncospace push us to question what lies beyond existing cancer configurations, and what would happen to tumors if nudged towards such voids. Could it be that *evolutionary forbidden* or *lethal* boundaries exist (Fig. 2b-d, see e.g. (35))? Or else that constraints explain escape trajectories such as phenotypic switching, as seen for example in cell transdifferentiation of certain pulmonary and prostatic cancers (46)?

Potential examples of *critical boundary* therapies include mutagenic therapies (47) or Adaptive Therapy (AT) (48). In the first, the presence of viability limits to genome instability indicates that already unstable tumors could be pushed towards a region where excessive mutational load results in loss of identity and self-arrest (35). AT, on the other hand, proposes to avoid *competitive release*, a threshold scenario where high-dosage therapy eliminates all but resistant cells in a tumor. AT proposes to control tumor growth by maintaining tumors in an intermediate Eco region, where sufficient clones maintain resistant growth at bay through competition (48).

IV. CONCLUSIONS AND PROSPECTS

The evolutionary ecology of cancer has attracted attention over the last two decades, shaping an emerging field

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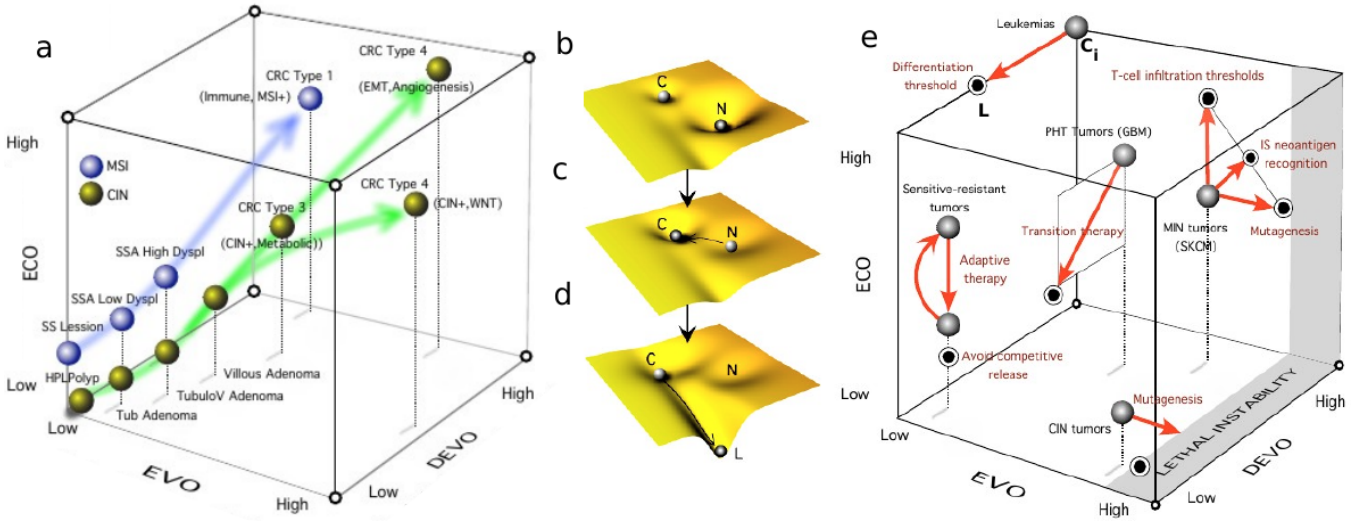

FIG. 2 **Trajectories, attrractors and breakpoints in cancer therapies**. Quantitative oncospaces can be build with cancer type-specific data on the three dimensions simultaneously. In **(a)**, available data on colorectal cancer (CRC) subtypes ((43) and references therein) and their precursors (44) allows us to build the space of colorectal malignancies. This space highlights the two well-differentiated CRC malignancy life-histories (MSI and CIN) (43), prompting the possibility that oncospaces can uncover ontogenetic trajectories for other tumor types. Similar to trajectories from normal (N) to cancer attractors (C) (42) **(b-c)**, we could expect displacements following treatment **(d)** towards lethal states (L): a therapy displacing C to some non-viable set of conditions). Obtaining data for these trajectories **(e)** could help us visualize therapies that, by nudging tumors away from the tumor success trajectories in **(a)**, can exploit lethal tipping points leading to cure.

where understanding tumorigenesis involves considering several scales of complexity. Key concepts from evolutionary theory such as fitness landscapes (49) or Muller ratchets (50), along with community ecology concepts such as succession or niche construction (24) are being increasingly integrated in the oncology narrative. Theoretical models have been successful at exploiting these concepts not just as accurate descriptions of tumor complexity, but as essential elements to understand cancer.

In parallel, the remarkable developmental similarities between cancers and embryonic tissues has a long historical record, particularly given the importance for classification diagnosis and the role of differentiation plasticity in treatment resistance (37; 38). But the three components turn to be relevant to oncogenesis, and a systems view bringing together the ecological, evolutionary and developmental coordinates of cancer is much needed.

The present perspective establishes the *oncospace*, a spatial scheme able to shed light on subtype stratification and treatment opportunities. The use of these three agencies as axes to construct the tumoral oncospace reflects an attempt to capture oncogenesis as a result from the integration of the three dynamic processes. Beyond the potential capacity to uncover new histopathological life-histories, the prospect that arises is that the spatial position of a given tumor in the oncospace can be modified by intervention.

Further insight will follow from applying our framework across tumors types, as already available metrics (Box 2) are obtained simultaneously for each biopsy. We hypothesize that precise analyses covering a wide range of disease subtypes will allow the construction of oncospaces that render novel intuition on tumorigenic pathways and treatment design. This could improve subtype stratification, uncover tumor progression pathways and shed light into the mechanisms of cancer drug resistance.

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