BBA - Reviews on Cancer 1868 (2017) 484–499

Contents lists available at ScienceDirect

BBA - Reviews on Cancer

journal homepage: www.elsevier.com/locate/bbacan

Review

Cancer as an ecomolecular disease and a neoplastic consortium

Santiago Ramón y Cajal[a,b,c,*], Claudia Capdevila[a], Javier Hernandez-Losa[a,b,c], Leticia de Mattos[a], Abhishek Ghosh[d], Julie Lorent[e], Ola Larsson[e], Trond Aasen[a,c], Lynne-Marie Postovit[f], Ivan Topisirovic[d]

[a] Translational Molecular Pathology, Vall d'Hebron Research Institute (VHIR), Universitat Autònoma de Barcelona, Passeig Vall d'Hebron 119-129, 08035 Barcelona, Spain
[b] Pathology Department, Vall d'Hebron Hospital, 08035 Barcelona, Spain
[c] Spanish Biomedical Research Network Centre in Oncology (CIBERONC), Spain
[d] Lady Davis Institute, JGH, SMBD, Gerald-Bronfman Department of Oncology, McGill University QC, Montreal H3T 1E2, Canada
[e] Department of Oncology-Pathology, Science for Life Laboratory, Karolinska Institutet, 171 65 Solna, Sweden
[f] Cancer Research Institute of Northern Alberta Department of Oncology, University of Alberta, Edmonton, AB, T6G 2E1, Canada

ARTICLE INFO

Keywords:
Cancer
Ecomolecular
Consortium
Paradigms
Systems biology
Heterogeneity

ABSTRACT

Current anticancer paradigms largely target driver mutations considered integral for cancer cell survival and tumor progression. Although initially successful, many of these strategies are unable to overcome the tremendous heterogeneity that characterizes advanced tumors, resulting in the emergence of resistant disease. Cancer is a rapidly evolving, multifactorial disease that accumulates numerous genetic and epigenetic alterations. This results in wide phenotypic and molecular heterogeneity within the tumor, the complexity of which is further amplified through specific interactions between cancer cells and the tumor microenvironment. In this context, cancer may be perceived as an "ecomolecular" disease that involves cooperation between several neoplastic clones and their interactions with immune cells, stromal fibroblasts, and other cell types present in the microenvironment. This collaboration is mediated by a variety of secreted factors. Cancer is therefore analogous to complex ecosystems such as microbial consortia.

In the present article, we comment on the current paradigms and perspectives guiding the development of cancer diagnostics and therapeutics and the potential application of systems biology to untangle the complexity of neoplasia. In our opinion, conceptualization of neoplasia as an ecomolecular disease is warranted. Advances in knowledge pertinent to the complexity and dynamics of interactions within the cancer ecosystem are likely to improve understanding of tumor etiology, pathogenesis, and progression. This knowledge is anticipated to facilitate the design of new and more effective therapeutic approaches that target the tumor ecosystem in its entirety.

1. Causes and consequences of cancer cell heterogeneity

Malignant tumors are enormously diverse. More than 250 clinicopathological types and thousands of varieties of neoplasia have so far been described. Moreover, cells within the same tumor are morphologically, phenotypically, and genetically heterogeneous, with further post-treatment diversification in metastases and recurrent lesions [1–3]. This inter- and intratumor heterogeneity manifests as a dramatic discrepancy in clinical features, prognoses, and therapeutic responses. Morphological patterns and other histological features that distinguish tumor types are already used to predict differences in prognosis (e.g. solid or macropapillary patterns are associated with worse survival in patients with lung adenocarcinoma) [4]. The same applies for a number of molecular alterations, some of which are used to guide clinical decisions [5,6]. Finally, intratumor heterogeneity, and the extent to which it occurs, can also be used as a prognostic indicator [7–10]. Hence, heterogeneity between and within tumors can affect clinical outcomes and guide therapeutic approaches.

2. Genomic heterogeneity

Recent studies using next-generation sequencing and single cell-based technologies have uncovered tremendous intratumor heterogeneity at the molecular level. For example, several studies have characterized the genomic landscape of primary tumors and metastatic lesions within the same patient [11,12,1,3–7,13]. These analyses

* Corresponding author at: Vall d'Hebron Research Institute (VHIR), Universitat Autònoma de Barcelona, Passeig Vall d'Hebron 119-129, 08035 Barcelona, Spain.
E-mail address: sramon@vhebron.net (S. Ramón y Cajal).

http://dx.doi.org/10.1016/j.bbcan.2017.09.004
Received 9 March 2017; Received in revised form 19 September 2017; Accepted 20 September 2017
Available online 23 September 2017
0304-419X/

revealed a constellation of genetic alterations in primary tumors and identified distinct clonal and subclonal architectures within both primary lesions and metastases, which indicated a number of seemingly different evolutionary routes that cancer cells can undertake within the same tumor [3,6–9]. Clear examples of genetic intratumor heterogeneity have been documented for neoplasia of the breast [14], lung [15,16], and kidney [17].

Indeed, in a manner analogous to the role of biodiversity in natural ecosystems, genetic diversity in cancer is thought to promote tumor fitness and is therefore a predictor of poor clinical outcomes [7–10]. Hence, it is important to understand how this intratumor heterogeneity occurs, as well as its significance in disease progression. The acquisition and maintenance of the "hallmarks of cancer" [18,19] are thought to occur stochastically with the accumulation of genetic alterations that are selected according to their contribution to cancer cell fitness, that is, whether they are driver or passenger events. This mirrors the Darwinian, step-wise, and reiterative process of clonal expansion, genetic diversification, and clonal selection of fitter populations [20]. One such example is cell competition, whereby fitter cells (winners) eliminate the surrounding cells (losers) by apoptosis [21]. There is however increasing evidence for a non-linear, branched evolution of neoplasia [7,16,22]. In this model, distinct, sometimes complementary, phenotypes emerge within a tumor, and each of these phenotypes is selected for simultaneously. The clones still originate from a common ancestor. However, in contrast to linear evolution, divergent clones evolve in parallel, resulting in multiple lineages that collectively contribute to the malignancy. This process of branched evolution appears to be especially applicable in the context of heterogeneous microenvironments because different selection forces may be operating concurrently in different areas of the tumor. In addition, it has recently been proposed that heterogeneity within certain tumor types may also occur via the "Big Bang" model, in which many mutations are acquired very early during tumor progression. In the absence of strong selective pressures at the initial stages of tumor progression, these mutations are likely to coexist. Theoretically, this state is maintained until a given stressor selects for the fittest clones. In this model, complete clonal sweeps are thought to be rare and the clones that survive stress may thus not have been the most dominant in the original tumor [23,24].

Regardless of its origin, genomic heterogeneity within tumors presents a challenge to both diagnosis and therapy. Genomic heterogeneity is associated with several important caveats when attempts are made to classify and prognosticate cancers. In recent decades, considerable effort has been directed toward generating a comprehensive catalog of the genes that initiate or cause cancer progression (drivers) and distinguishing them from genes that are a simple by-product of somatic evolution (passengers), for which a number of bioinformatic tools have been developed [25]. Even in those cases where potentially druggable alterations are found, the implementation of this framework is contradictory to the widely heterogeneous nature of most tumors because such studies are performed on restricted cell populations isolated from a small part of the tumor that are unlikely to reflect the full spectrum of the heterogeneity within a given neoplasia. As such, intratumor heterogeneity significantly confounds the interpretation of massive sequencing studies performed using single tumor samples, as minor clones may be masked and molecular studies may not be representative of the tumor as a whole. This makes it challenging to target single cancer-driving mutations because these mutations may be present in some but not all cancer cells in the same tumor. Furthermore, during cancer evolution, one driving genetic lesion may be replaced by another as it is becoming apparent that mutations essential for cancer development may not be required for disease progression [26].

Consistent with this tenet, even those tumors with a potent driver mutation show a temporal clinical response of months or years, followed by clinical relapse when that mutation is targeted. This eventual treatment failure is thought to be a consequence of the involvement of alternative genes or the activation of redundant pathways, as well as the inability of single drugs to target the entire subset of malignant cells [3,10,27]. For example, almost half of melanomas harbor BRAF-activating mutations (most commonly BRAFV600E), which lead to constitutive activation of the mitogen activated protein kinase (MAPK) pathway. BRAF inhibitors such as vemurafenib and dabrafenib are used to treat metastatic melanomas and initially cause tumor regression. However, resistance ensues, often due to downstream activation of MEK. To circumvent this, MEK inhibitors have been developed and used in combination with BRAF inhibitors. This extended the response to about a year, but alternative modes of resistance emerged, leading to recurrence [28]. Similar targeted therapies have been developed for a number of other oncogenes and cancers, but their clinical efficacy is usually lower than expected. Moreover, several important drivers have not yet been targeted. For instance, no effective therapies have been found for KRAS mutation-driven tumors, even though > 20% of all cancers harbor mutations in this gene and its aberrant activation is associated with resistance to anti-epidermal growth factor receptor (EGFR) therapies and other anticancer agents [29]. We posit that this is largely due to the tremendous genetic heterogeneity present in most tumors, which is further compounded by a variety of epigenetic mechanisms [30].

Finally, many genetic alterations vary widely from one patient to another (referred to as intertumor heterogeneity), making it difficult to form overarching conclusions regarding the importance of specific alterations. These caveats are further compounded in advanced disease, in which genetic alterations vary enormously between primary tumors and metastases and/or are affected by chemo- or radiotherapy.

3. Epigenetic heterogeneity

As proposed by Kolch et al. [30], genetic events are likely triggering elements of tumorigenesis, but much of the enormous plasticity of cancer cells to evolve different phenotypes, as well as their ability to adapt to challenging environments and withstand therapy, is encoded by constant perturbations in epigenetic programs and the rewiring of signaling networks, which display high flexibility and nonlinearity.

Indeed, overlaid onto genomic heterogeneity is epigenetic heterogeneity [31]. Unlike mutations, epigenetic changes do not affect the primary DNA sequence, but involve interactions among cells and their microenvironments, which lead to heritable changes in otherwise reversible phenomena such as chromatin modifications. In cancers, epigenetic heterogeneity can manifest as cellular hierarchies, similar to those observed in stem cell-associated systems, as well as the manifestation of cellular plasticity.

According to the hierarchical model of cancer, either a stem cell acquires a set of mutations that gives rise to a stem cell-like counterpart, referred to as a "cancer stem cell", or a cancer cell acquires stem cell-like properties [32]. Cancer stem cells can self-renew and give rise to the progeny of more differentiated cancer cells with a variety of different phenotypes. Consequently, they engender a hierarchy of cells that are all derivatives of the original mutated progenitor, contributing to the cellular heterogeneity of tumors [32]. The first study to describe the hierarchical model of cancer, led by Dick and colleagues [33], was based on a human acute myeloid leukemia model. This paradigm has since been extended to malignancies as diverse as breast cancer, glioma, and colon cancer [34–37]. Hence, hierarchical structures likely contribute to tumor heterogeneity in most cancer types. Interestingly, strategies for disrupting pathways that are thought to maintain stem-like and niche cell phenotypes such as inhibition of Wnt production have been proposed [38].

Epigenetic heterogeneity may also be acquired via "phenotypic plasticity". Phenotypically, plastic cancer cells can move back and forth through a continuum of cell fate specifications, from well-differentiated cell types to those with stem cell-like phenotypes [39]. For example, non-invasive epithelial-like $CD44^+/CD24^+$ breast cancer populations can give rise to highly invasive mesenchymal-like $CD44^+/CD24^-$ cells

Box 1
Big data in cancer.

All genomic interaction studies are currently performed by bioinformatics experts, whose role is becoming increasingly important. The methods used are diverse, and several computational data evaluation models have been described. For example, in some types of cancer, the main databases include the Catalogue of Somatic Mutations in Cancer (COSMIC), which encompasses more than 1.5 million individual mutations in 25,606 genes from almost 950,000 samples. Also important is the quantity of data held by the consortium formed by the Cancer Genome Project, the International Cancer Genome Consortium (ICGC), The Cancer Genome Atlas (TCGA), and the Encyclopedia of DNA Elements (ENCODE), which also investigates various structural and regulatory units of the human genome. Several platforms are used to analyze this huge quantity of data. These include Bionimbus, Bioconductor, CytoScape, and OncoDrive, which were designed to enable scientists to exchange databases and construct algorithms and mathematical models of cancer. With all of these databases, the main objective is to understand molecular alterations, mechanisms, and interactions between the different alterations and biochemical pathways in order to identify the real drivers of tumor progression.

Therefore, massive data are being incorporated from different types of tumors. These include histopathologic, immunohistochemical, molecular, and proteomic data, as well as data on microRNA. Data are also obtained from spectrophotometry, liquid chromatography, metabolomics, nuclear medicine and imaging, circulating tumor cells, and tumors implanted in murine models. Although these databases significantly contributed to the field of cancer biology, several issues such as misinterpretation of DNA damage during sample handling as bona fide somatic mutations in cancer specimens have been recognized (add PMID: 28209900).

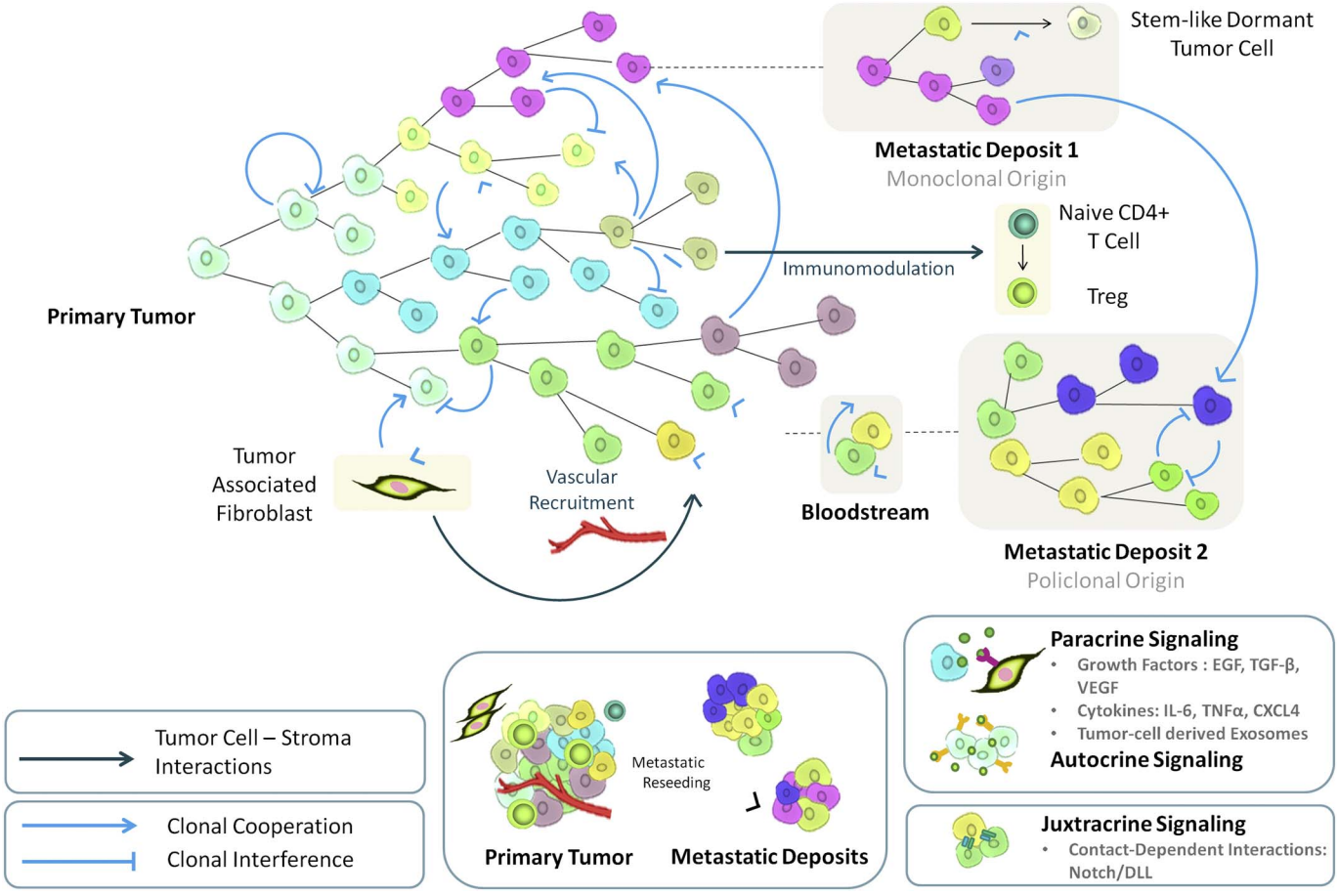

Fig. 1. Clonal interference and cooperation in tumor evolution. A regulatory architecture for intratumor heterogeneity.
This scheme illustrates how several clones are formed during tumor progression (each clone is indicated with a different color). Clones need to cooperate among themselves and with stromal and inflammatory cells. These interactions can be via paracrine, autocrine, or juxtacrine signaling. Metastases are formed by some clones that probably also need to cooperate among themselves to be able to grow in the metastatic niche.

both in vitro and in vivo [40]. While the emergence of cancer stem cells is a feature of plasticity, other phenomena such as epithelial-to-mesenchymal transition (EMT) also occur [41]. EMT is characterized by a loss of epithelial cell markers, such as epithelial (E)-cadherin, and the acquisition of mesenchymal markers, such as vimentin and neural (N)-cadherin [41]. In cancer, EMT is induced by a variety of transcription factors, signaling proteins, and aberrant regulation of various microRNAs (miRNAs) [42]. For example, upon exposure to tobacco, normal human bronchial epithelial cells undergo EMT, due to aberrant epigenetic silencing of miR-200 and miR-205 tumor suppressors [43,44]. EMT also correlates with an upregulation of pluripotency markers such as Nanog and Nodal [45,46], suggesting that cells that have undergone EMT may represent those with more stem cell-like phenotypes. Several studies have shown that plasticity can be induced

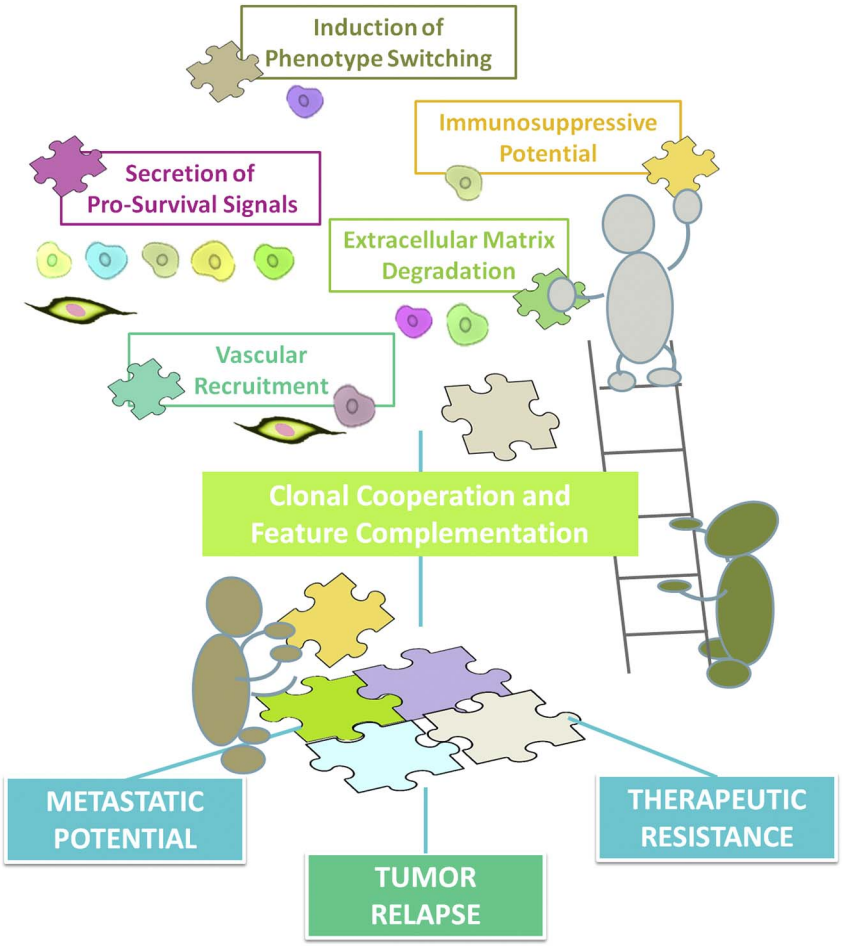

Fig. 2. Clonal cooperation in cancer. Emergent properties.
The clones needed to form the malignant tumor are selected based on oncogenic properties that have developed and may be shared with other clones not containing these properties, including shared use of proangiogenic factors or prosurvival signals secreted by some clones. We visualize this cooperation as pieces of a jigsaw puzzle, which, when completed, reveals the full picture, as a real emergent property.

by stresses such as hypoxia and chemotherapy, pointing to an adaptive mechanism that is driven by the microenvironment and can reset the equilibrium of a tumor to favor continued adaptation and progression [47–49]. Hence, differences in the tumor microenvironment that occur during progression or in response to therapies may also drive epigenetic heterogeneity concomitant with plasticity. This plasticity of cancer may generate and/or accelerate the selection of cellular clones with complementary features that lead to therapy resistance and favor cancer dissemination.

Similar to genomic heterogeneity, epigenetic heterogeneity can also limit the efficacy of targeted therapies. For example, chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (ALL), which are associated with clone-specific BCR-ABL fusion [50], can be successfully treated by inhibiting BCR-ABL with imatinib. However, resistance and recurrence occur in some BCR-ABL$^+$ patients treated with imatinib. This is partly due to the inability of the drug to eradicate leukemic stem cells [50,51]. Leukemic stem cells appear to be epigenetically rewired to not always manifest oncogene addiction to BCR-ABL as compared to more differentiated progeny. This leads to residual disease persistence in patients treated with imatinib, highlighting the importance of understanding epigenetic heterogeneity for the success of the anticancer treatment [52,53].

4. Epigenetic changes and genomic instability go together

Genetic and epigenetic mechanisms also continuously engage and disengage a multitude of signaling pathways, resulting in dynamic restructuring of key cellular networks [54,30]. As one can imagine, mutations may activate specific pathways. However, the outcome of this activation depends on cellular context and epigenetic receptivity. Many such examples of the orchestration and modular activation of multiple signaling pathways have been described [30], including crosstalk between tyrosine kinase receptors. The function of EGFR is affected by gene amplifications and mutations, as well as the availability of other tyrosine kinase receptors for dimerization [30,55]. As such, the consequences of an EGFR mutation would depend on the epigenetically regulated expression of other receptors. EGFR activity is thought to be mostly mediated by the MAPK/ERK and PI3K signaling pathways [30]. However, the effects of EGFR on downstream signaling pathways appear to be modular. For instance, heterodimerization of EGFR with other receptors of the EGFR family such as HER2 and HER3 bolsters the activation of both MAPK/ERK and PI3K pathways [30]. EGFR has also been reported to engage AXL, which is transactivated by EGFR through heterodimerization. AXL, in turn, can be stimulated by platelet-derived growth factor and interact with additional receptors, including MET [30]. These examples illustrate the potential diversification of EGFR signaling in the context of neoplasia. They also highlight an important caveat that must be considered when deriving targeted therapies against this frequently mutated protein.

Cellular plasticity can also be influenced by the interplay between genomic and epigenetic mechanisms. For example, during EMT, signals from ligands, including TGF-β, lead to the orchestrated expression of transcription factors such as Snail-1, Slug, and ZEB-1, which repress the expression of specific epithelial genes (e.g. E-cadherin) while inducing the expression of mesenchyme-specific genes (e.g. vimentin) [56]. Several interconnecting positive and negative feedback loops comprising ERK, WNT, microRNAs, and other pathways have been proposed to govern complex perturbations in gene expression that underpin EMT [57–60]. Collectively, it is becoming obvious that the interplay between genomic, epigenetic, and signaling alterations in

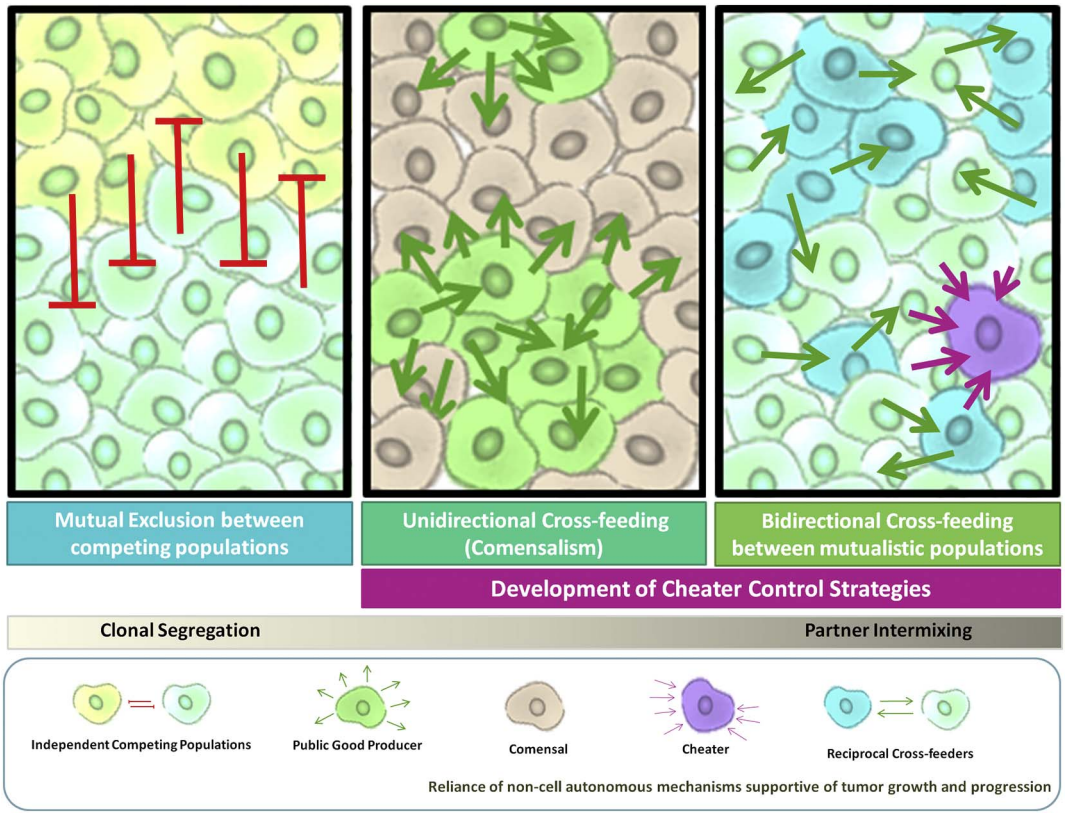

Fig. 3. Spatial and functional architecture in cancer. Clonal segregation and partner intermixing.
In malignant and invasive cells, clones may have bidirectional cross-feeding between mutualist populations. At the primary tumor, other clone strategies may be found such as competing populations and even unidirectional cross-feeding.

cancer may be infinitely more complex than initially anticipated, whereby genetic, epigenetic, and signaling perturbations diversify cells within the same tumor bed and lead to immense intratumor heterogeneity (see Box 1 big data and Box 1 ecological diversity).

5. Cancer as a consortium of cooperating malignant clones and microoenviromental cells

For several decades, authors such as Heppner [19,61–64] have been stressing that tumor progression requires the cooperation of several transformed cellular clones, as well as the active involvement of the microenvironment.

Thus, cancer could be considered a multicellular community. In ecology, the biological functions associated with interspecies interactions must be concomitantly more beneficial to the component species than their respective costs [65]. Complex multicellular systems, such as cancer, are thus likely to function in a similar fashion to microbial consortia (see Box 6 microbial consortium), wherein a spatial architecture and distribution of cellular clones ensures greater and mutual benefits. Positive and negative clonal cooperation (clonal interference), mediated both directly at the level of cellular contacts and indirectly via microenvironmental factors, cytokines, and/or exosomes, is therefore likely to play a major role in cancer evolution (see Figs. 1, 3). Tumor cells are thought to require a certain number of molecular alterations—just three according to Vogelstein [66,67]—to overcome senescence and acquire neoplastic properties. However, to generate metastases, a cancer cell must be able to overcome anoikis, invade and survive in the peripheral blood, and eventually grow in a remote organ. It is unlikely that these processes are achieved in isolation in a single clone. A more plausible explanation is that the metastatic potential of cancer cells is generated in cancer cell consortia, which facilitate tumor progression in an “ecomolecular” way in which several clones cooperate. These clones are synergistic and share the molecular and biochemical alterations required to generate an invasive tumor. Based on these observations, we propose that cancer should be perceived as an “ecomolecular” disease that involves cooperation between several neoplastic clones and their interactions with immune cells, stromal fibroblasts, and other cell types present in the microenvironment. Cancer is therefore analogous to complex ecosystems such as microbial consortia.

Clonal cooperation within cancer cell populations can explain phenomena such as the recently described cooperative invasion in melanoma [68] or circulating tumor cell (CTC) clusters [69] (see also Fig. 2). Interestingly, CTC clusters appear to display enhanced metastatic potential compared with single cells [70]. Polyclonal CTC clusters have been demonstrated in metastatic murine models [68,69,71,72], whereby seeding of different malignant cellular clones within CTC clusters can occur in parallel or at different moments (indirect clonal cooperation) [69–71]. These data support the concept of clonal cooperation and suggest that, in tumor growth, synergism between several complementary clones and local factors is needed for survival and invasion. Malignant cells can then stay quiescent for an extended period of time (“dormancy”). These cell populations evolve a self-induced latency state that allows them to evade immune response while promoting their long-term survival in micrometastatic deposits [73]. SOX transcription factors and the Wnt pathway have been proposed to “wake up” these clones [74]. However, accordingly to the idea of ecomolecular disease and tumor consortia, cooperation between several tumor clones may be required to trigger tumor growth in the metastatic niche. Furthermore, other studies have shown that this cooperation can also occur between malignant and non-malignant cell types [75,76]. For example, association with surrounding normal cells, including

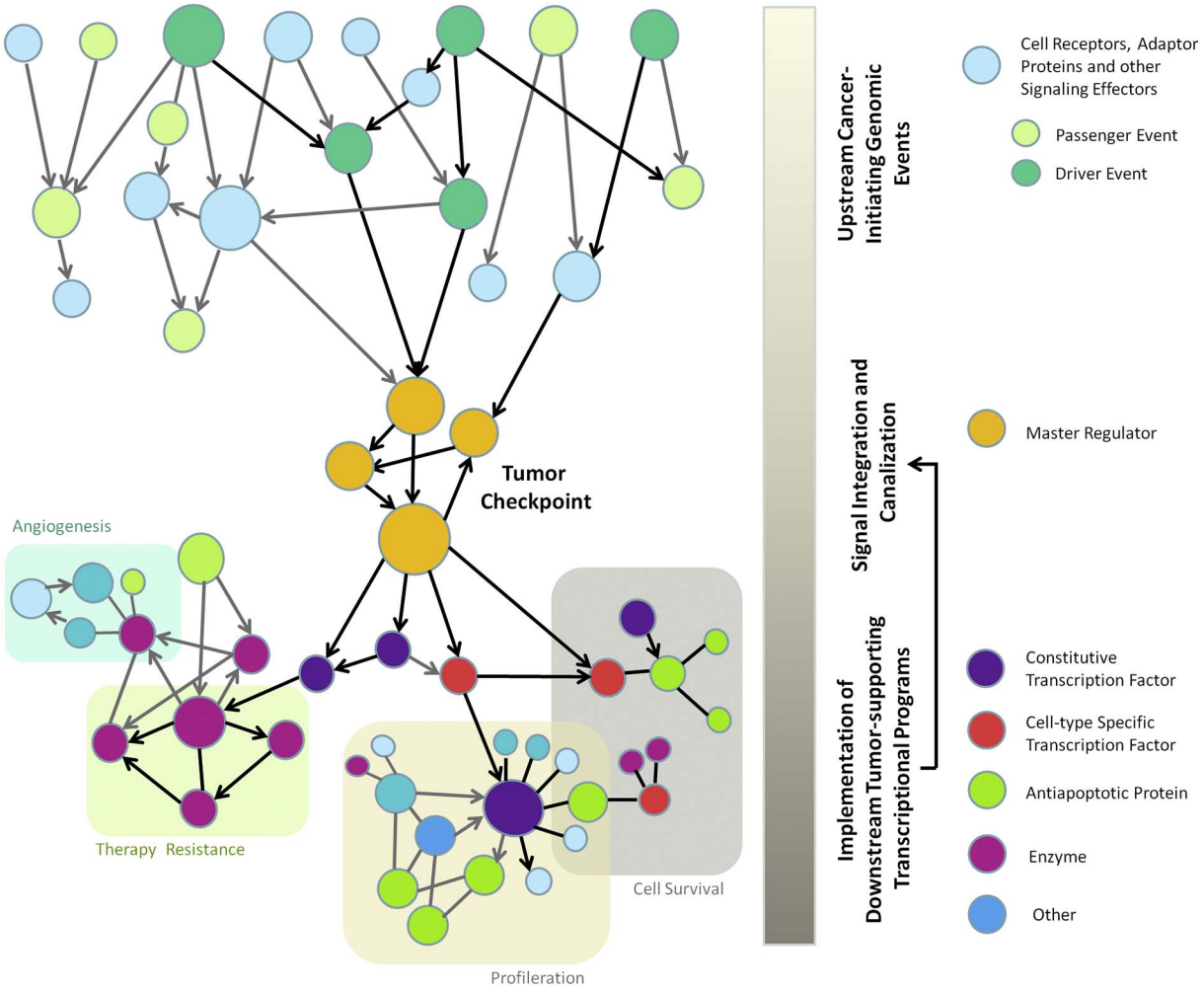

Fig. 4. Establishment and maintenance of the tumor cell state. Master regulators, tumor checkpoints, and tumor-supporting transcriptional signatures.
According to the hallmarks of Hanahan and Weinberg, tumor transformation and progression requires the disruption of several biochemical pathways. Large numbers of genetic alterations are observed in malignant tumors and numerous positive and negative feedback loops in and between those pathways. It therefore seems logical to look for central nodes, hubs, or funnel factors that control cell proliferation or the resistance of malignant cells to several cellular stresses. Systems biology is emerging as a powerful tool to identify the factors that commonly change within one tumor and in separate tumors among independent patients.

platelets, macrophages, and fibroblasts, increases the metastatic potential of cancer cells [75,76]. Notably, paraneoplastic phenomena are sometimes years ahead of the clinical detection of a malignant tumor. For example, paraneoplastic syndromes such as eosinophilia and thrombocytosis, as well as certain neurological disorders, can anticipate the early detection of tumors at an incipient clinical stage [77].

Clonal cooperation in cancer can be expanded to explain why a minimum number of cells is required for a clone to have sufficient biological fitness, a phenomenon known as the Allee effect [9,78]. The Allee effect explains why isolated cells often cannot grow in vitro or in human tumor explants and why rates of cancer initiation, invasion, and metastasis are relatively low when individual or a relatively low number of cells are used. This can be at least partly explained by an ability of clonal cooperation to bolster tumor growth, especially in situations of microenvironmental stress. For instance, autocrine production of growth-promoting and prosurvival factors may be insufficient to support neoplastic growth unless they are present in large quantities (i.e. from a greater number of cells). This is referred to as cooperative feeding and may be one of the major determinants of the Allee effect in cancer. The acquisition of driver events and the continuous shaping of the genomic landscape of a tumor could be understood either under the lens of the classical clonal theory or more recent evolutionary and developmental paradigms [23,24,79,80]. Herein, we propose that these theoretical frameworks should also include inter-clonal relationships other than competition (e.g. mutualism and commensalism) and consider sources of variability not necessarily contingent upon the genomic status of the cancer cell (i.e. epigenetic, post-transcriptional, and signaling pathway remodeling) [63].

Cancer cells interact with the microenvironment. The tumor microenvironment consists of various cell types, such as endothelial and immune cells, as well as inflammatory cells, fibroblasts, adipocytes, and mesenchymal stem cells. These cells are surrounded by heterogeneously deposited extracellular matrices and signaling proteins and are affected by changing biophysical properties such as pH and oxygenation [18,45,81,82]. A plethora of mechanisms ensure the adaptation of somatic cells to the multicellular development program of the organism, whereas deregulation of these mechanisms allows cancer cells to thrive and progress despite negative microenvironmental cues. Indeed, cancer cells actively enroll their healthy counterparts in tumor progression-supporting behaviors. Hence, the microenvironment is an active mediator of tumor progression and must be accounted for when cancer is conceptualized, prognosticated, and treated.

Environmental factors such as limited oxygen supply or lack of nutrients bolster the expression of multiple cytokines, pro-stromal, and inflammatory factors and thereby promote the recruitment of endothelial cells, macrophages, fibroblasts, and an array of inflammatory cells to hypoxic areas of the tumor [83,84]. Hypoxia is a potent activator of both metastasis and therapy resistance and, as described above,

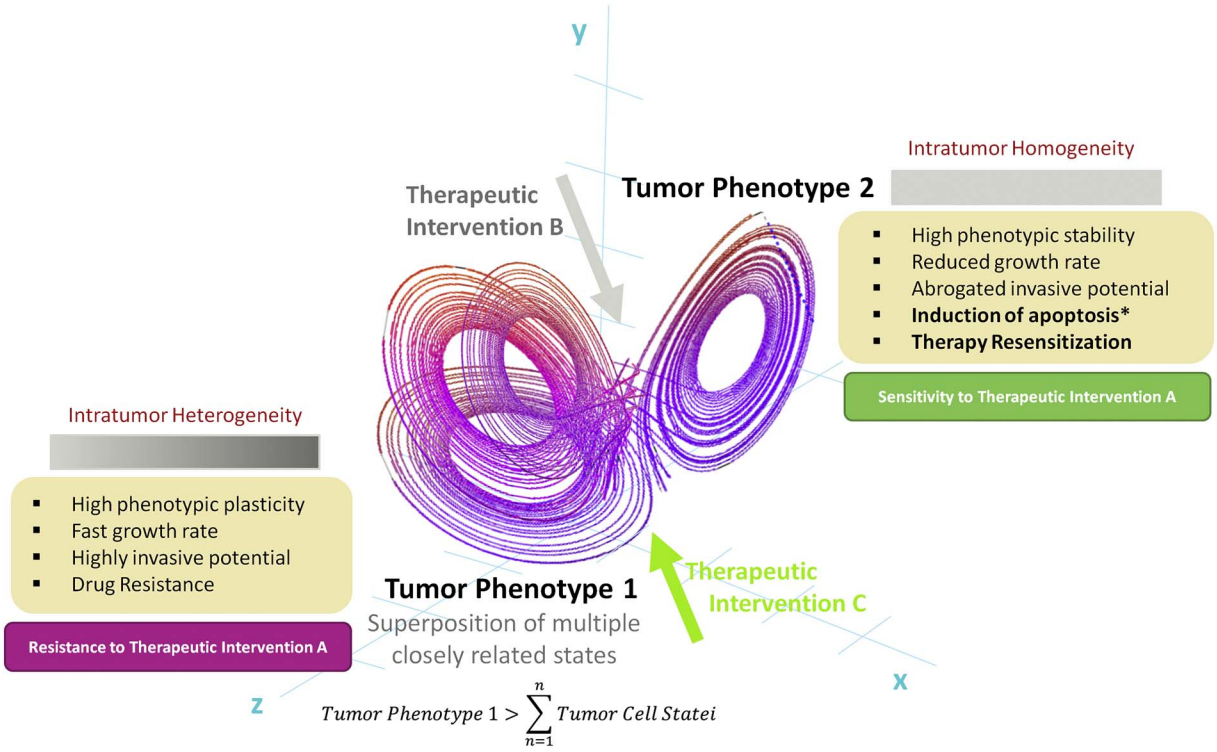

Fig. 5. Domesticating the chaos. A proposal for network rewiring in tumor cells.
In the complex interplay of the pathways activated in cancer, new therapeutic approaches have to be defined. According to chaos theory, it would be difficult to control each pathway, but there are options, such as reorientation of the signals to a pathway that is druggable. Thus, the networks responsible for the maintenance of a particular highly heterogeneous tumor phenotype would be shifted toward more manageable homogeneous states.

Box 2
Application of the theories of "ecological" diversity to the study of tumors.

Intratumor heterogeneity is increasingly studied by employing models used in ecology. Well-known indices have been applied to the study of breast cancer by various groups, including that of Polyak, in order to better understand the genetic and phenotypic diversity of breast cancer metastases. Such indices include the Shannon entropy index, which was described for the study of animal species and quantification of entropy, that is, to reflect information and uncertainty and to try to predict variations in the homogeneity. Also used has been the Simpson index, a diversity index that aims to validate the percentage of individuals who belong to a specific type of species by sub-classifying them into variants.

Use of mathematical approaches in conjunction with the Shannon entropy and the Simpson diversity index aim to better explain the molecular heterogeneity and diversity of tumors [63,64,125]. Other authors [126] have proposed the use of the quadratic entropy index (Rao) or index of ecological diversity, which has been studied in plant genealogy.

can induce stem cell phenotypes concomitant with the expression of cytokines such as IL-6. By changing the cytokine milieu, hypoxia promotes the acquisition of an immunosuppressive microenvironment, allowing cancer cells to evade destruction [85,86]. Alterations in cytokine secretion also promote metastasis by recruiting cells such as M2 macrophages that can facilitate invasion and cancer spread. Consistently, numerous studies have shown that hypoxia [87,88] and leucocytes [75] promote metastasis.

In addition to extracellular stimuli, an important determinant in tumor evolution involves interactions with the immune system (see Box 5). Indeed, the immune system can prevent, control, shape, and promote cancer through the process of immunoediting, during which tumor cells continually evolve in response to interactions with the immune compartment [85,89–91]. Immunoediting involves three phases: elimination, in which the immune system recognizes and eradicates cancer cells; equilibrium, in which the tumor is kept in check, or dormant, by co-existing with the immune system without growing; and escape, in which the tumor grows and can no longer be suppressed. Immune surveillance can be escaped via several mechanisms, including a reduction in tumor-associated antigens, resistance to apoptosis and immune suppression through the secretion of cytokines and metabolic factors, and suppressor cell recruitment and activation. Moreover, an altered transcriptional landscape in malignant cells increases immunogenic diversity by generating alternative protein isoforms [92]. The expression of alternative isoforms is associated with reduced signatures of T cell cytolytic activity and poor patient survival. Hence, epigenetic modifications, leading to altered isoform expression, could be how cancer cells adapt to and evade the immune system. These concepts highlight the importance of immune cells in tumor evolution and have been reviewed extensively elsewhere [85,89–91].

Based on these findings, we propose that cancer cells, through clonal interactions and crosstalk with their microenvironment, constitute a neoplastic consortium that functions analogously to that of their microbial counterparts. Mapping and dissection of the molecular underpinnings of neoplastic consortia will undoubtedly enhance understanding of cancer biology and provide the basis for more effective cancer treatments.

6. Cancer as an emergent property

The concept of emergent properties is commonly equated to that of a famous saying by Aristotle, “The whole is greater than the sum of its parts”, or more recently to the principle postulated by Kurt Koffka, “The whole is other than the sum of its parts” (see Box 6).

Emergent behavior is often unpredictable and unprecedented and may represent a new level in the evolution of the system. Emergent properties arise when a number of single components (e.g. pixels on a television screen, bees within a beehive, the subcellular machinery of the cell) interact in an environment and lead to complex collective behaviors that are difficult to grasp by simply monitoring the individual components of the system.

Cancer can be studied in a similar way to the pixels on a television screen: a single pixel reveals nothing: it is the sum of all of the pixels that conveys the meaning of an image. In other words, neoplasia is not the result of single genomic alterations or even multiple genomic alterations in a single cell, but the sum of all of the molecular changes undergone by a community of tumor cells, including those affecting signal transduction and gene regulatory networks, as well as the environment within which malignant cells reside. Similar concepts have been postulated in the neural networks theory [93], in which the synchronized activity of a set of neurons enables the perception of images and sounds to give rise to cerebral and cognitive functions. This is in opposition to concepts underlying current precision medicine strategies. Most precision-based approaches are based on the premise that an entire tumor can be eradicated by taking out a single driving factor. The rather disappointing outcomes of recent trials and single-cell studies demonstrating tremendous clonal heterogeneity suggest that Gestalt-like models should be considered to enhance the understanding of cancer complexity [11,12].

In a similar manner, we propose that cancer must be understood within the framework of a series of genetic alterations that appear to be coordinated with other molecular events, such as the epigenetic status of the cell, rewiring of signaling networks, and microenvironmental factors. This is analogous to the model in which individual pixels cooperate to form a complete picture—reuniting a minimum number of conditions to configure a circuit that provides cancer cells with required growth autonomy. But this paradigm must consider that the complexity of cancer is also likely to rely on interactions between tumor cell clones and associated normal cells. This complete set of properties, some of which differ between cell populations in the tumor, allows neoplasia to act as a cooperative and coordinated community, facilitating invasion and disease spread, and ultimately leading to the patient's demise. Thus, understanding of how these consortia of stromal and inflammatory cells interact with tumor cells is critical for developing more effective treatments [75,94–96].

7. Employing systems biology approaches to grasp the complexity of cancer ecosystems

Systems biology encompasses tools that hold great promise for deciphering the vulnerabilities of the tumor ecosystem as a whole. These studies are based on the premise that multiple oncogenic events converge on a relatively limited number of cellular networks (see Box 3 topologic analysis), which may contain essential or synthetically lethal clinically targetable hubs or factors [26,97] such as the eIF4F complex (see Box 4 central nodes). Targeting of these central nodes of cancer-specific networks (e.g. protein synthesis machinery) is thought to provide a sufficient therapeutic window to selectively target cancer ecosystems while causing minimal toxicity in normal tissues, which indeed is observed in preclinical studies. Nonetheless, many contemporary systems biology approaches do not consider intratumor heterogeneity. This is relevant as key functional nodes within the metabolic, signal transduction, and gene expression networks responsible for supporting the tumor phenotype are critically dependent on the heterogeneity of the tumor. Critical nodes of cancer-specific networks should thus be studied within specific cancer ecosystems. This aspect still represents a major challenge.

Given the large amount of data amassed on tumors in recent years at the clinical, morphological, and molecular levels, there is heightened interest in the development of powerful bioinformatics methods and well-curated databases to boost understanding of the complexity of tumor ecosystems. These data may also help to classify tumors according to histopathological, biochemical, and genomic features and thus facilitate tailoring of diagnosis and clinical management to the biological profile of a patient's tumor. Accordingly, multidimensional molecular and gene expression data, which are associated with the response to antitumor treatments and clinical progress, are thought to facilitate the selection of patients who are more likely to respond to targeted or “precision” therapies [98,99]. Several approaches that encompass deep-learning are being developed to harness information on intratumor heterogeneity and to identify and diagnose multiple tumor types [178,179] by integrating radiological, histological, gene expression, and in situ hybridization data.

There are ongoing large collaborative efforts such as the Cancer Cell Map Initiative [100] and others taken on by groups such as the Califano laboratory at Columbia University [26,101]. Consistent with the role of epigenetic and signaling programs in cancer development and progression, these efforts suggest that a functionally relevant characterization of all of the molecular alterations described in a patient's tumor will only be possible in the context of a topological study of all of the pathways and networks involved in tumorigenesis. According to such efforts, it appears that genomic and gene expression profiling—at both steady-state mRNA and proteome levels—must be appropriately integrated to identify the clinically targetable factors driving tumor progression in each individual patient. However, most current precision therapies target the mutated genes in a given tumor type, whereby it is thought that suppression of drivers will shut down downstream pathways that provide cancer cells with a selective growth advantage. However, the presence of evolutionary tolerable mutations in driver genes, in conjunction with the well-established ability of cancer cells to rewire their signaling pathways and intratumor heterogeneity, complicates such approaches.

Multi-institutional efforts are crucial to the development of more efficient treatment strategies. For example, the DARWIN trial (Deciphering Antitumor Response With Intratumor Heterogeneity; NCTO2183883) intended to define the relationship between driver clonality and the potential benefit of targeted therapy by assessing ctDNA and CTC and the TRACER trial (TRAcking Non-small Cell Lung Cancer Evolution Through Therapy [Rx]; NCTO1888601). Herein, several regions of tumor were sequenced before and after relapse in order to define the genomic landscape of tumors throughout evolution and to understand the impact of tumor heterogeneity on therapy responses [102,103]. This information is now being used to further refine clinical trials and to try to individualize treatments as much as possible in stratified patient groups. For example, in the emerging “N-of-1 trial” [104], the trial data are obtained from a single patient to determine the optimal intervention for that individual. However, these trials need increased attention in light of the era of personalized medicine.

VIPER analysis [97] and multiple concerted disruption [105] aim to integrate data on DNA alterations (mutations, amplifications, translocations, methylations, and deletions) with mRNA expression and protein levels. Although these approaches are likely to produce some meaningful data, given the complex relationships within the tumor microenvironment, it will also likely be pertinent to understand the dynamics of DNA alterations in relation to mRNA and protein levels occurring as a result of the interactions within the tumor ecosystem. Finally, these data should also be appropriately integrated with patients' clinical and family history. Collectively, − omics data generation, analysis, and interpretation, and their clinical applications, will require a joint effort from experts in diverse disciplines such as

Box 3
Topological analysis and study of biochemical and genetic alterations.

Several representative examples explore the interplay among biochemical pathways and clinicopathological data. The database Gene X Press includes gene modules that affect the activity of a tumor, such as those of the Gene Ontology project, which describes the potential pathways and abnormalities in tumors resulting from specific genetic alterations. In addition, Gene Microarray Pathway Profiler and Signaling Pathway Impact Analysis consider the position of a gene in a pathway. Similarly, some models associate genes in both cis and trans, making it possible to identify genes known as "masters". Study of cancer-related pathways has been proposed to consolidate understanding of biological mechanisms by means of algorithms. One example is the Pathway Recognition Algorithm, which uses integration data from oncogenomic models, allowing the number of copies of genes to be contrasted with mRNA expression, methylation, and microRNA expression.

medicine, biology, mathematics, statistics, bioinformatics, and systems biology [30,106,107] (see Box 1 big data and Box 2 ecological diversity).

The availability of system-wide data in a variety of cancers is facilitating the development of approaches that go beyond the classic, reductionist paradigms, which are limited to the association of single genes with cellular phenotypes and functions. Systems biology approaches consider the interplay between multiple molecular factors that underpin the development of a particular phenotype. Accordingly, rather than a genetic disease, cancer is now being perceived as a "disease of networks" [100]. Therefore, to fully grasp the complexity of the tumor ecosystem, the networks driving cancer need to be mapped and their dynamics and evolution over time need to be deciphered. Emerging data show that these cancer networks are constantly rewired in part by clonal interactions, changing microenvironments, and the acquisition of novel molecular alterations that are largely induced by anticancer treatments [106,108]. Hence, minor subpopulations that are not readily detectable in bulk tumors or that manifest the ability to adapt to hostile environments may emerge following treatments that specifically target cancer-driving mutations present in the predominant tumor subpopulations. These subpopulations are likely to result in refractory disease inasmuch as they do not harbor the vulnerabilities identified in the majority of the tumor.

In our opinion, these studies suggest that a shift in cancer treatment paradigms may be warranted. Interactions in the tumor ecosystem do not occur randomly: they appear to follow a series of principles. They contain highly connected core nodes known as "hubs". Hubs interconnect various pathways and are considered essential for the maintenance and integrity of the entire network and cellular ecosystems, whether healthy or pathogenic. These "network hubs" are usually encoded by well-conserved genes that play a role in key cellular activities [106–111]. Analogous to the "butterfly effect" in chaos theory, small alterations in these hubs can lead to major alterations in cellular functions (e.g. proliferation and invasion), whereby the differential reliance of cancer and normal cells on a given "network hub" is expected to provide a sufficient therapeutic window (see Box 7).

Therefore, systems biology approaches in cancer research hold a promise of identifying networks that are crucial for cancer cell survival and disease progression in the context of tumor ecosystems. These approaches are also thought to allow modeling and prediction of the response to drugs and the identification of key nodes or essential cancer networks [26,97]. Furthermore, recently developed methods exploit data-centered mathematical and computational methods, such as deep learning and evolutionary optimization algorithms, which are expected to facilitate mapping of the interactions between networks in systems of immense complexity such as the cancer ecosystem, as well as to detect similarities and discrepancies between different cancer ecosystems [30,108–111].

Thus, the application of current systems biology approaches and the development of novel approaches to study cancer may prove important in the following areas. **(1) Provision of detailed system level-aided and clinically oriented subclassifications of cancer types.** In this regard, the use of deep-learning approaches appears promising. **(2) Mapping of oncogenic networks and identification of their critical nodes to overcome the effects associated with intratumor heterogeneity.** A comprehensive understanding of the cellular networks that are altered in the tumorigenic state and in individual patients will be especially important to the study of the actions and interactions of cytotoxic drugs and other small molecule inhibitors with the cellular machinery. A large number of pharmacokinetic and pharmacodynamics factors, including drug half-life, potency, and efficiency of target inhibition or activation, as well as other parameters, will be required to accurately predict and guide therapeutic decisions (systems pharmacology). **(3) Informing future preclinical research and design of**

Box 4
Are central nodes of oncogenic networks targetable and could they overcome intratumor heterogeneity?

Compared with targeting of functionally redundant upstream regulators, targeting of central nodes of signaling networks that integrate multiple oncogenic signals may represent a valid strategy to overcome the capacity of neoplastic cells to rewire and become drug resistant [26]. Protein synthesis is frequently dysregulated in neoplasia. Differences in translational programs between normal and cancer cells are thought to provide a sufficient therapeutic window to selectively target cancer cells while causing minimal toxicity in normal tissues [127,128]. The eukaryotic translation initiation factor 4F (eIF4F) complex, which comprises a cap-binding subunit eIF4E, scaffolding protein eIF4G, and DEAD box RNA helicase eIF4A, recruits mRNA to the ribosome [129]. It is activated by the vast majority of oncogenes (e.g. c-MYC, HER2, PI3KCA) and inactivated by tumor suppressors (e.g. TSC1/2, PTEN) [128]. An increase in eIF4F levels is observed in the vast majority of cancers, where it results in a selective increase in the translation of mRNAs encoding pro-oncogenic factors such as cyclins, c-myc, and BCL-2 family members while not affecting the synthesis of housekeeping proteins such as actins and tubulins [130]. Elevated eIF4F levels are associated with chemoresistance and poor prognosis [131–133]. Moreover, activation of the eIF4F complex through multiple pathways diminishes the efficacy of a wide variety of oncogenic kinase inhibitors, including those targeting EGFR, HER2, PI3K, MAPK, and mTOR [134–146]. Given that the eIF4F complex plays a crucial role in cancer cell survival, irrespective of driver mutations or pathway rewiring [143], targeting of eIF4F may provide a means to address issues related to both intratumor heterogeneity and drug resistance [143,147,148,149,150]. Indeed, several preclinical studies have confirmed the validity of approaches that interfere with eIF4F assembly and/or function [145,149–154].

Box 5
Tumor microenvironment and therapeutic strategies.

Several therapeutic strategies have been proposed to target different cells in the tumor microenvironment. For example, cancer-associated fibroblasts (CAFs) take on hallmarks of transformation and are important mediators of cancer progression [155]. The tumor-supporting attributes of CAFs are acquired after exposure to tumor-derived factors such as TGF-β and become essential for tumor growth and metastasis. This is thought to at least in part be caused by the ability of CAFs to contribute essential growth factors within the cancer ecosystem and to chaperone cancer cells through the vasculature [156].

The interplay between cancer cells and the immune system is also highly important. Tumors achieve evasion via a number of mechanisms, including the expression of checkpoint proteins such as programmed cell death protein-1 (PD-1) and cytotoxic T lymphocyte-associated protein-4 (CTLA-4), as well as through the downregulation of immune-stimulating antigens [91]. Immuno-oncology therapies target such phenomena by stimulating the immune system via either passive or active approaches [89].

Active therapies include adoptive T cell transfer, vaccines, antigen-presenting cells such as dendritic cells, and oncolytic viruses [89]. Passive therapies are broadly aimed at fighting tumors by modifying signaling pathways that promote immunosuppression [89]. These approaches include checkpoint inhibitors such as ipilimumab (which targets CTLA4) and pembrolizumab and nivolumab (which target PD1R) as well as small molecules targeting immune modulators as diverse as cyclooxygenase-2 (COX-2) and chemokine receptor type-4 (CXCR-4) [89]. The most successful passive therapies thus far are the checkpoint inhibitor therapies. These therapies have been shown to eradicate some tumors by altering the tumor ecosystem in a manner that allows immune cells to regain control [89,155,157–159].

A promising approach to the treatment of malignant tumors is to target factors that confer them resistance to cellular stress. It is thought that acute stress (e.g. starvation, oxidative stress, chemotherapy, hypoxia) induces adaptation mechanisms in the translation machinery that are largely independent of the genetic and epigenetic makeup of cancer cells [160]. Although the best-explained mechanism of translational adaptation to stress comprises reduction in ternary complex recycling via eIF2αphosphorylation [161], recently emerging data show that various types of chemotherapeutics induce eIF4E phosphorylation via MAP kinase-interacting kinases (MNKs) [162]. MNKs are activated by ERK or stress-induced p38 kinase [163,164]. Phospho-eIF4E tends to selectively affect the translation of mRNAs encoding for secreted factors, cytokines, and matrix metalloproteinases, which play a major role in the interaction of cancer cells with their microenvironment [165]. Indeed, cancer cells whose eIF4E cannot be phosphorylated have severely impeded metastatic potential [166]. Therefore, eIF4E phosphorylation may be an essential mechanism of adaptation to stress downstream of p38 and ERK, and recently developed MNK inhibitors are showing early but promising results in combination with traditional therapeutic approaches. Moreover, levels of phospho-eIF4E appear to be consistently elevated in the vast majority of cells in the tumor [162]. Accordingly, it is expected that, during acute adaptation to chemotherapy-induced stress, phospho-eIF4E levels will be uniformly increased throughout the tumor and metastases, which suggests that MNK inhibitor and chemotherapeutic combinations may help to overcome issues associated with intratumor heterogeneity. Notably, the anticancer effects of MNK inhibitors have been shown in a number of preclinical models [167–171].

phase I clinical trials by anticipating therapy response in silico and predicting the best targets for each patient and tumor (personalized cancer therapy or precision medicine).

Altogether, the application of systems biology in cancer research may revolutionize the way we assess the molecular and biochemical changes in a single tumor and permit therapeutic approaches based on central targets. Nevertheless, some pitfalls or limitations can be envisioned. The great value of the available data and curated databases only materializes following detailed post hoc analyses. In-depth understanding of the properties of the system studied is required to use the data in such databases, and the heterogeneity in data quality, which is particularly observed during the developmental phase of -omics methods, is a major challenge that needs to be considered. For example, a recent method that has gathered substantial interest as providing a link between transcriptomes and proteomes is ribosome profiling [112]. Recently, there were concerns raised regarding biases in ribosome profiling data that could be associated with technical artifacts in cDNA library preparation and sequencing [113]. Therefore, although one of

Box 6
Microbial consortia as a paradigm for cancer understanding.

Clonal interrelationships have been extensively studied in microbial ecology, as exemplified by the microbial consortia. In microbiology, microbial populations inhabiting varying environments and/or responding to stress can cooperate with each other by forming well-structured communities in both space, time, and function [172–174,65]. Notably, the constitution of microbial consortia is an area of considerable interest in the biotechnological industry because such communities, while remarkably complex, show promise in overcoming the limitations imposed by approaches based on the use of a single strain [146]. In this regard, significant efforts have been made to engineer synthetic ecologic consortia, in which the interplay among members is expected to lead to a more sustainable, productive, predictable, and stable design [65].

The microbial interactions within consortia are mainly mediated by secreted factors, including metabolites. To this end, the stability of consortia depends on aspects as variable as cellular density, medium viscosity, and the localization and availability of resources and other metabolic products [65,174]. Spatial distribution of the involved populations (assortment), including cheaters (species that have access to group benefits but do not contribute to the other members of the group), is also thought to play a major role in the function of microbial consortia [65,174]. Cooperative interrelationships between microbes in consortia are commonly classified as non-reciprocal (commensalism) or reciprocal (mutualism) [65]. While competing populations with no metabolic interdependence tend to segregate (competitive exclusion), mutualism tends to drive partner intermixing [174]. Several studies have demonstrated that spatial self-organization, sometimes conditioned by phenomena as unpredictable as genetic drift, may provide a solution for the stability of intraspecific cooperation without the need for specific molecular mechanisms of partner recognition. This suggests that mapping of the spatial organization of a given consortium is likely to provide insights into its function.

Box 7
Emergent properties and the chaos theory in cancer research.

Emergent properties represent one of the most significant challenges for the engineering of complex systems. The system is different from the "sum" of its component parts, which in the context of cancer research hinders approaches centered on the study of cancer cells in isolation.

For example, a plethora of factors are involved in tumor progression and metastasis (e.g. genetic interactions, stromal cells, histiocytes, lymphocytes, and environmental conditions). Such complex interplay of large numbers of factors is challenging to predict, even with the most sophisticated software available today. Hence, this very feature of "chaos" should be accounted for in order to fully understand cancer.

The application of chaos theory may thus greatly help to explain the formation and progression of malignant tumors. In the three-body problem, Henri Poincaré [175] observed that the behavior of the heavenly bodies was extremely complicated and that this made it impossible to make long-term projections about their trajectories. He wrote, "A very small cause that escapes us determines a considerable effect which we cannot ignore, and then we say that the effect is due to chance….but it is not always so." He also observed that, "it may happen that small differences in the initial conditions produce very great ones in the final phenomenon. A small error in the former will produce an enormous error in the latter. Prediction becomes impossible and we have a fortuitous phenomenon." Chaos theory was postulated in the decades following the work of Poincaré. It is somewhat paradigmatic that in the 1960s, with the advent of the first computers, the meteorologist Edward Lorentz began to design calculations to predict the evolution of the weather. Based on a seemingly banal experiment, he realized that if he entered numbers into a new computer with three decimal places instead of six, the results were totally different. For years, Lorentz tried to find an explanation, and his efforts laid the foundation for what we now know as chaos theory. He also established the term "butterfly effect", in which small initial variations may produce enormous final variations, as pointed out by Poincaré. In the context of tumor biology, one can imagine how this might manifest: a small early event could be amplified and then even redirected by varietal competing factors.

Chaos theory brings an alternative approach to study of the complexity of tumor systems and is likely applicable to systems biology. For example, a recently published study [176] provides a very graphic summary of the discordance between massive sequencing studies, data analysis, and evaluation of data, depending on the platform used to interpret them. After comparing thousands of variants from several large numbers of tumors using various sets of transcripts with the platforms REFSEQ, ENSEMBLE, the annotation test, ANNOVAR, and other software packages, the authors came to an interesting conclusion: the results were highly variable and depended on the set of transcripts and software platform used. Moreover, the same sequences compared using different software applications showed discrepancies of $> 30\%$.

Given that, in principle, it was already impossible with the three-body problem to determine and predict the evolution of orbits, it is rather plausible that such a prediction may be even more "chaotic" in cellular models and biological systems with tens, if not thousands, of variables. However, chaos, while unpredictable, can be determined. In other words, chaos is not random, but has an underlying order. In this sense, especially at the physical level, but also at the biochemical level, modeling of enzyme behavior has permitted advances in attempts to predict what was previously perceived as the unpredictable. Chaos theory postulates the existence of clearly deterministic concepts that depend on the initial conditions and on the number of initial variables. In fact, recent research indicates that it might be possible to "train" chaos. For instance, Ott, Grebogy, and Yorke drew up a mathematical algorithm that could transform chaos into simple regular processes [177]. This mathematical approach has already been used in medicine. Ott, Grebogy, and Yorke also noted that, "it is not necessary to completely understand the chaotic process to regulate it". The proposed algorithm targets the direction of the process and tries to modify it with small adjustments to ensure that it "gets back on track". Therefore, chaotic systems are very flexible and can interrelate and modulate each other. This concept of chaos theory can be applied to one of the examples set out above, namely, control of cell stress and thus the promotion of factors mediating resistance to cell damage.

the advantages of -omics methods is commonly assumed to be their unbiased nature, this should always be questioned as hidden biases may be at play and distort interpretations. Moreover, application of -omics methods should be adapted to the underlying question so that the most complete understanding can be obtained. Thus, to accurately progress or understand cancer from a systems biology perspective, the methodology should be carefully and critically chosen. In addition, to avoid artifacts, rigorous validation of findings obtained using systems biology methods by orthogonal and well-established molecular biology and biochemistry techniques is also warranted.

8. Final considerations

It is clear that cancer cells vary from patient to patient as well as among themselves, even within the same tumor bed. Such heterogeneity can be a limiting factor in the identification of a single molecular marker associated with tumor aggressiveness, response to therapy, and prognosis. In this regard, CTCs or cell-free ctDNA in plasma and in cerebrospinal fluid and other biological fluids [114] may constitute a non-invasive source of genetic material that may allow identification of the genetic characteristics of tumors [115–119] and help to reveal their clonal relationships and hierarchical organization [120].

Efficiently applied systems biology studies, in conjunction with standard molecular biology and biochemical methods, may help to change many of the paradigms in cancer research by providing a way to assess multiple variables in a high-throughput and tumor ecosystem-wide manner. Furthermore, tumors constantly evolve new phenotypes, which enable cancer cells to withstand therapy, invade, and metastasize. In this sense, systems biology approaches can be used for modeling tumor evolution and experimentally testing these models, which will hopefully result in new tools to predict disease progression in the clinic [121–124].

We therefore propose the following considerations:

1. Tumor progression is characterized not only by the sequential accumulation of molecular aberrations, but also by the diversification and coexistence of various tumor cell clones with unique molecular profiles and distinctive behaviors. It is highly likely that these clones display synergistic properties that together contribute to the development of aggressive and invasive tumors. Factors released by the clones or environmental cells could then maintain the capabilities of

the consortium and could be new cancer treatment targets.
2. Interrelationships between molecular pathways and complex biological processes are not linear. Small adjustments can lead to disproportionate changes with major consequences.
3. Cancer is a dynamic system, in which the whole is different than the sum of the parts. Neoplastic ecosystems are quantitatively and qualitatively different to normal tissue systems and may exhibit less "ordered" hierarchy. Cancer networks are also modulated over time; consequently, prediction of their behavior is highly complex, if not impossible, within the framework of the current cancer biology paradigms.
4. Due to intratumor heterogeneity, most molecular data obtained in a small tumor sample are unlikely to be representative of the entire landscape of the tumor and/or metastases. Multisampling and longitudinal studies, as well as topologic and systems biology analyses, are needed to establish a more reliable correlation between real drivers and clinical response.
5. In light of recent findings on the complexity of tumor consortia, we envisage a slow accumulation of advances that will make cancer a chronic disease and reduce mortality by improving early diagnosis, identifying new therapeutic targets, and permitting immunotherapy advances. Significant improvements may be achieved in the long term if researchers can identify key target nodes supporting tumors (i.e. master regulators and funnel factors) that are largely independent of genetic makeup and microenvironment [26] (see also Fig. 4).
6. The biochemical alterations involved, while complex, are directly associated with spontaneous events that produce marked cellular biochemical and biological changes enabling cancer cell survival and tumor progression. This "chaotic advantage" of the biochemical regulation of the tumor may be exploitable by redirecting the action of the apparent "chaos", for example, by modulating factors involved in the cellular stress response. In such a framework, it will be vital to bring together research professionals (molecular biologists, bioinformatics, mathematicians, systems biology specialists) who can certify and validate the findings of systems biology studies and, perhaps even more importantly, establish standards for study design and database curation.

In summary, we propose that cancer is a complex consortium, characterized by collaboration among various cells (e.g. different cancer cell clones and inflammatory and stromal cells), which in concert result in the emergent properties of cancer. These emergent properties of cancer confer a malignant clinical phenotype of invasiveness and metastatic potential. Ecological, evolutionary, and molecular alterations of neoplasia are dynamic and change as the disease progresses. This highlights the importance of studying different areas of the tumor, during progression, recurrences, and metastases. Cancer biology, then, seems amenable to the application of ecological and evolutionary principles. It is thus expected that the effective treatments will be those that avoid or even exploit the clonal diversity of the tumor while still being selective [9]. The collaboration between tumor and non-tumor cells (e.g. via cell-cell interactions, metabolites, cytokines, and exosomes) in cancer ecosystems may open new lines of research that enable progress in the study of advanced cancers, whose survival expectations are still abysmal (see Fig. 5).

Funding

SRYC acknowledges support from Fondo de Investigaciones Sanitarias (P1170185 and PI 14/01320), Redes temáticas de Investigación Cooperativa en Salud (RTICC, RD 12/0036/0057), Generalitat de Catalunya (AGAUR, 2014, 1131), and CIBERONC (CB16/12/00363). TA acknowledges support from Instituto de Salud Carlos III grant PI16/00772 and grant CPII16/00042, co-financed by the European Regional Development Fund (ERDF). OL acknowledge support from the Swedish Cancer Society. Research in Topisirovic's laboratory is supported in part by grants from the Canadian Cancer Society Research Institute and Prostate Cancer Canada. IT is a Junior 2 Research Scholar of the Fonds de Recherche du Québec – Santé (FRQ-S). LMP is an Alberta Innovates Health Solutions (AIHS) Chair in Cancer.

Conflict of interest

None.

Transparency document

The http://dx.doi.org/10.1016/j.bbcan.2017.09.004 associated with this article can be found, in the online version.

References

[1] W.D. Travis, E. Brambilla, M. Noguchi, A.G. Nicholson, K. Geisinger, Y. Yatabe, et al., Diagnosis of lung cancer in small biopsies and cytology: implications of the 2011 International Association for the Study of Lung Cancer/American Thoracic Society/European respiratory society classification, Arch. Pathol. Lab. Med. 137 (5) (2013) 668–684.
[2] E.V. Denisov, N.V. Litviakov, M.V. Zavyalova, V.M. Perelmuter, S.V. Vtorushin, M.M. Tsyganov, et al., Intratumoral morphological heterogeneity of breast cancer: neoadjuvant chemotherapy efficiency and multidrug resistance gene expression, Sci. Rep. 4 (2014) 4709.
[3] J. Rosai, Rosai and Ackerman's Surgical Pathology, 10th Edition, (2012).
[4] S. Murakami, H. Ito, N. Tsubokawa, T. Mimae, S. Sasada, T. Yoshiya, et al., Prognostic value of the new IASLC/ATS/ERS classification of clinical stage IA lung adenocarcinoma, Lung Cancer 90 (2) (2015) 199–204 [Internet]. Elsevier Ireland Ltd. Available at: https://doi.org/10.1016/j.lungcan.2015.06.022.
[5] V.T. DeVita, T.S. Lawrence, S.A. Rosenberg, DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology, Wolters Kluwer Health, 2014.
[6] R.M. Webster, Combination therapies in oncology, Nat. Rev. Drug Discov. 15 (2) (2016) 81–82 [Internet]. Nature Publishing Group. Available at: http://dx.doi.org/10.1038/nrd.2016.3\n10.1038/nrd.2016.3.
[7] M. Gerlinger, A.J. Rowan, S. Horswell, J. Larkin, D. Endesfelder, E. Groonros, et al., Intratumor Heterogeneity and Branched Evolution Revealed by Multiregion Sequencing, N. Engl. J. Med. 366 (10) (2012) 883–892.
[8] E.C. de Bruin, N. McGraham, M. Salm, D.C. Wedge, L. Yates, M. Jamal-Hankani, et al., Spatial and temporal diversity in genomic instability processes defines lung cancer evolution, Science 346 (6206) (2014) 251–256 (80-).
[9] K.S. Korolev, J.B. Xavier, J. Gore, Turning ecology and evolution against cancer, Nat. Rev. Cancer 14 (5) (2014) 371–380 [Internet]. Nature Publishing Group. Available at. http://www.ncbi.nlm.nih.gov/pubmed/24739582.
[10] C.T. Hiley, C. Swanton, Spatial and temporal cancer evolution: causes and consequences of tumour diversity, Clin. Med. 14 (suppl 6(6)) (2014) (Northfield Il). (s33–7).
[11] I. Tirosh, B. Izar, S.M. Prakadan, M.H.W. Ii, D. Treacy, J.J. Trombetta, et al., Dissecting the multicellular exosystem of metastatic melanoma by single-cell RNA-seq, Science 352 (6282) (2016) 189–196 (80-).
[12] X. Zhang, S.L. Marjani, Z. Hu, S.M. Weissman, X. Pan, S. Wu, Single-Cell sequencing for precise cancer research: Progress and prospects, Cancer Res. 76 (6) (2016) 1305–1312.
[13] E.V. Denisov, N.V. Litviakov, M.V. Zavyalova, V.M. Perelmuter, S.V. Vtorushin, M.M. Tsyganov, et al., Intratumoral morphological heterogeneity of breast cancer: neoadjuvant chemotherapy efficiency and multidrug resistance gene expression, Sci Rep 4 (2014) 4709 [Internet]. Available at: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3988480&tool=pmcentrez&rendertype=abstract.
[14] L.G. Martelotto, C.K. Ng, S. Piscuoglio, B. Weigelt, J.S. Reis-Filho, Breast cancer intra-tumor heterogeneity, Breast Cancer Res. 16 (3) (2014) 210 [Internet]. Available at: http://breast-cancer-research.biomedcentral.com/articles/10.1186/bcr3658.
[15] C. Abbosh, N.J. Birkbak, G.A. Wilson, M. Jamal-Hanjani, T. Constantin, R. Salari, et al., Phylogenetic ctDNA analysis depicts early stage lung cancer evolution, Nature (2017) [Internet]. Available at: http://www.nature.com/doifinder/10.1038/nature22364.
[16] M. Jamal-Hanjani, G.A. Wilson, N. McGranahan, N.J. Birkbak, T.B.K. Watkins, S. Veeriah, et al., Tracking the Evolution of Non–Small-Cell Lung Cancer, N. Engl. J. Med. (2017) [Internet]. NEJMoa1616288. Available at: http://www.nejm.org/doi/10.1056/NEJMoa1616288.
[17] M. Gerlinger, S. Horswell, J. Larkin, A.J. Rowan, M.P. Salm, Genomic architecture and evolution of clear cell renal cell carcinomas defined by multiregion sequencing, Nat. Genet. 46 (3) (2014) 225–233.
[18] D. Hanahan, R.A. Weinberg, The Hallmarks of Cancer, 100(7) Cell Press, 2000, pp. 57–70.
[19] D. Hanahan, R.A. Weinberg, Hallmarks of cancer: the next generation, Cell (2011) 646–674.
[20] M. Greaves, C.C. Maley, Clonal evolution in cancer, Nature. 481 (7381) (2012)

306–313.
[21] A. Di Gregorio, S. Bowling, T.A. Rodriguez, Cell competition and its role in the regulation of cell fitness from development to cancer, Dev. Cell 38 (6) (2016) 621–634 [Internet]. Elsevier Inc. Available at: https://doi.org/10.1016/j.devcel.2016.08.012.
[22] S. Ling, Z. Hu, Z. Yang, F. Yang, Y. Li, Q. Chen, et al., Extremely high genetic diversity in a single tumor points to prevalence of non-Darwinian cell evolution, Proc. Natl. Acad. Sci. 113 (5) (2016) E6496–505 [Internet]. Available at: http://www.pnas.org/lookup/doi/10.1073/pnas.1600151113.
[23] A. Sottoriva, H. Kang, Z. Ma, T.A. Graham, M.P. Salomon, J. Zhao, et al., A Big Bang model of human colorectal tumor growth, Nat. Genet. 47 (3) (2015) 209–216 [Internet]. Nature Publishing Group. Available at: https://doi.org/10.1038/ng.3214.
[24] M. Robertson-Tessi, A.R.A. Anderson, Big Bang and context-driven collapse, Nat Genet 47 (3) (2015) 196–197 [Internet]. Available at: http://dx.doi.org/10.1038/ng.3231\nhttp://www.nature.com/doifinder/10.1038/ng.3231.
[25] L. Ding, M.C. Wendl, J.F. McMichael, B.J. Raphael, Expanding the computational toolbox for mining cancer genomes, Nat. Rev. Genet. 15 (July) (2014) 556–570 [Internet]. Nature Publishing Group. Available at: http://www.nature.com/doifinder/10.1038/nrg3767\nhttp://www.ncbi.nlm.nih.gov/pubmed/25001846.
[26] A. Califano, M.J. Alvarez, The recurrent architecture of tumour initiation, progression and drug sensitivity, Nat. Rev. Cancer (2016) 1–15. Advance On (December 2016).
[27] C.E. Meacham, S.J. Morrison, Tumour heterogeneity and cancer cell plasticity, Nature 501 (7467) (2013) 328–337.
[28] P. Queirolo, F. Spagnolo, BRAF plus MEK-targeted drugs: a new standard of treatment for BRAF-mutant advanced melanoma, Cancer Metastasis Rev. 36 (1) (2017) 35–42 [Internet]. Available at: https://doi.org/10.1007/s10555-017-9660-6.
[29] M. Malumbres, M. Barbacid, RAS oncogenes: the first 30 years, Nat. Rev. Cancer 3 (6) (2003) 459–465.
[30] W. Kolch, M. Halasz, M. Granovskaya, B.N. Kholodenko, The dynamic control of signal transduction networks in cancer cells, Nat. Publ. Group 15 (9) (2015) 515–527 [Internet]. Nature Publishing Group. Available at: https://doi.org/10.1038/nrc3983.
[31] H. Easwaran, H. Tsai, S.B. Baylin, Cancer epigenetics: tumor heterogeneity, plasticity of stem-like states, and drug resistance, Mol. Cell 54 (5) (2014) 716–727 [Internet]. Elsevier Inc. Available at: https://doi.org/10.1016/j.molcel.2014.05.015.
[32] J. Rosen, C. Jordan, The increasing complexity of the cancer stem cell paradigm, Science 324 (5935) (2009) 1670–1673 (80-) [Internet]. Available at: http://www.sciencemag.org/content/324/5935/1670.short.
[33] T. Lapidot, C. Sirard, J. Vormoor, B. Murdoch, T. Hoang, J. Caceres-Cortes, et al., A cell initiating human acute myeloid leukaemia after transplantation into SCID mice, Nature 367 (6464) (1994 Feb 17) 645–648 [Internet]. Available at: https://doi.org/10.1038/367645a0.
[34] J.E. Visvader, G.J. Lindeman, Cancer stem cells: current status and evolving complexities, Cell Stem Cell 10 (6) (2012) 717–728 [Internet]. Elsevier. Available at: https://doi.org/10.1016/j.stem.2012.05.007.
[35] M. Al-Hajj, M.S. Wicha, A. Benito-Hernandez, S.J. Morrison, M.F. Clarke, Prospective identification of tumorigenic breast cancer cells, Proceedings of the National Academy of Sciences of the United States of America, 2003, pp. 3983–3988.
[36] S.K. Singh, C. Hawkins, I.D. Clarke, J.A. Squire, J. Bayani, T. Hide, et al., Identification of human brain tumour initiating cells, Nature 432 (November) (2004) 396–401 [Internet]. Available at: https://doi.org/10.1038/nature03128.
[37] L. Ricci-Vitiani, D.G. Lombardi, E. Pilozzi, M. Biffoni, M. Todaro, C. Peschle, et al., Identification and expansion of human colon-cancer-initiating cells, Nature 445 (7123) (2007) 111–115 [Internet]. Available at: http://www.nature.com/doifinder/10.1038/nature05384.
[38] T. Tammela, F.J. Sanchez-Rivera, N.M. Cetinbas, K. Wu, N.S. Joshi, K. Helenius, et al., A Wnt-producing niche drives proliferative potential and progression in lung adenocarcinoma, Nature 545 (7654) (2017) 355–359 [Internet]. Nature Publishing Group. Available at: http://www.nature.com/doifinder/10.1038/nature22334.
[39] D.F. Quail, M.J. Taylor, L.-M. Postovit, Microenvironmental Regulation of Cancer Stem Cell Phenotypes, Curr. Stem Cell Res. Ther. 7 (3) (2012) 197–216.
[40] M.J. Meyer, J.M. Fleming, M.A. Ali, M.W. Pesesky, E. Ginsburg, B.K. Vonderhaar, Dynamic regulation of CD24 and the invasive, CD44posCD24negphenotype in breast cancer cell lines, Breast Cancer Res. 11 (6) (2009) R82 [Internet]. Available at: https://doi.org/10.1186/bcr2449.
[41] S.A. Mani, W. Guo, M.J. Liao, E.N. Eaton, A. Ayyanan, A.Y. Zhou, et al., The epithelial-mesenchymal transition generates cells with properties of stem cells, Cell 133 (4) (2008) 704–715 [Internet]. Available at: https://doi.org/10.1016/j.cell.2008.03.027.
[42] R. Kalluri, R. Weinberg, a. The basics of epithelial-mesenchymal transition, Eur. J. Clin. Investig. 119 (6) (2009) 1420–1428.
[43] C.S. Tellez, D.E. Juri, K. Do, A.M. Bernauer, C.L. Thomas, L.A. Damiani, et al., EMT and stem cell-like properties associated with miR-205 and miR-200 epigenetic silencing are early manifestations during carcinogen-induced transformation of human lung epithelial cells, Cancer Res. 71 (8) (2011) 3087–3097.
[44] J.H. Taube, J.I. Herschkowitz, K. Komurov, A.Y. Zhou, S. Gupta, J. Yang, et al., Core epithelial-to-mesenchymal transition interactome gene-expression signature is associated with claudin-low and metaplastic breast cancer subtypes, Proc Natl Acad Sci 107 (35) (2010) 15449–15454 [Internet]. Available at: http://www.pnas.org/cgi/doi/10.1073/pnas.1004900107.
[45] K. Polyak, R.A. Weinberg, Transitions between epithelial and mesenchymal states: acquisition of malignant and stem cell traits, Nat. Rev. Cancer 9 (4) (2009 Apr) 265–273 [Internet]. Nature Publishing Group. Available at: https://doi.org/10.1038/nrc2620.
[46] D.F. Quail, G.M. Siegers, M. Jewer, L.-M. Postovit, Nodal signalling in embryogenesis and tumourigenesis, Int. J. Biochem. Cell Biol. 45 (4) (2013) 885–898 [Internet]. Available at: http://www.sciencedirect.com/science/article/pii/S1357272512004177.
[47] D.R. Pattabiraman, R.A. Weinberg, Tacking the cancer stem cells - what challenges do they pose? Nat Rev Drug Discov. 13 (7) (2014) 497–512.
[48] M. Cojoc, K. Mäbert, M.H. Muders, A. Dubrovska, A role for cancer stem cells in therapy resistance: cellular and molecular mechanisms, Semin. Cancer Biol. 31 (2015) 16–27 [Internet]. Elsevier Ltd. Available at: https://doi.org/10.1016/j.semcancer.2014.06.004.
[49] C.L. Chaffer, I. Brueckmann, C. Scheel, A.J. Kaestli, P.A. Wiggins, L.O. Rodrigues, et al., Normal and neoplastic nonstem cells can spontaneously convert to a stem-like state, Proc. Natl. Acad. Sci. U. S. A. 108 (19) (2011) 7950–7955 [Internet]. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21498687.
[50] T.O. Hare, M.S. Zabriskie, A.M. Eiring, M.W. Deininger, Pushing the Limits of Targeted Therapy in Chronic Myeloid Leukaemia, 12 (2012) (August).
[51] F. Notta, C.G. Mullighan, J.C. Wang, A. Poeppl, S. Doulatov, L.A. Phillips, et al., Evolution of human BCR-ABL1 lymphoblastic leukaemia-initiating cells, Nature 469 (7330) (2011) 362–367 [Internet]. Nature Publishing Group. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21248843.
[52] A.S. Corbin, A. Agarwal, M. Loriaux, J. Cortes, M.W. Deininger, B.J. Druker, Human Chronic Myeloid Leukemia Stem Cells Are Insensitive to Imatinib Despite Inhibition of BCR-ABL Activity, 121 (2011) (1).
[53] X. Jiang, Y. Zhao, C. Smith, M. Gasparetto, A. Turhan, A. Eaves, et al., Chronic Myeloid Leukemia Stem Cells Possess Multiple Unique Features of Resistance to BCR-ABL Targeted Therapies, (2007), pp. 926–935.
[54] M.C. Lloyd, J.J. Cunningham, M.M. Bui, R.J. Gillies, J.S. Brown, R.A. Gatenby, Darwinian dynamics of intratumoral heterogeneity: Not solely random mutations but also variable environmental selection forces, Cancer Res. 76 (11) (2016) 3136–3144.
[55] S.D.M. Santos, P.J. Verveer, P.I.H. Bastiaens, Growth Factor-induced MAPK Network Topology Shapes Erk Response Determining PC-12 Cell Fate, 9 (2007) (3).
[56] B. De Craene, G. Berx, Regulatory networks defining EMT during cancer initiation and progression, Nat. Rev. Cancer 13 (2) (2013) 97–110 [Internet]. Nature Publishing Group. Available at: http://www.nature.com/doifinder/10.1038/nrc3447.
[57] C.R.S. Banerji, S. Severini, C. Caldas, A.E. Teschendorff, Intra-tumour signalling entropy determines clinical outcome in breast and lung cancer, PLoS Comput. Biol. 11 (3) (2015) 1–23.
[58] X. Dai, A. Chen, Z. Bai, Integrative investigation on breast cancer in ER, PR and HER2-defined subgroups using mRNA and miRNA expression profiling, Sci Rep 4 (2014) 6566 [Internet]. Available at: http://www.nature.com/srep/2014/141023/srep06566/full/srep06566.html.
[59] L. Ding, T.J. Ley, D.E. Larson, C.A. Miller, D.C. Koboldt, J.S. Welch, et al., Clonal evolution in relapsed acute myeloid leukaemia revealed by whole-genome sequencing, Nature 481 (7382) (2012) 506–510 Nature Publishing Group.
[60] S. Lamouille, J. Xu, R. Derynck, Molecular mechanisms of epithelial-mesenchymal transition, Nat. Rev. Mol. Cell Biol. 15 (3) (2014) 178–196.
[61] G. Heppner, Tumor Heterogeneity, Cancer Res. 44 (6) (1984) 2259–2265.
[62] G.H. Heppner, B.E. Miller, Therapeutic implications of tumor heterogeneity, Semin. Oncol. 16 (2) (1989) 91–105 [Internet]. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom = pubmed & id = 2652316 & retmode = ref & cmd = prlinks\npapers3://publication/uuid/9666CA38-4116-49C2-85A6-84D735D76F16.
[63] A. Marusyk, V. Almendro, K. Polyak, Intra-tumour heterogeneity: a looking glass for cancer? Nat. Rev. Cancer 12 (5) (2012) 323–334.
[64] D.P. Tabassum, K. Polyak, Tumorigenesis: it takes a village, Nat. Rev. Cancer 15 (8) (2015) 473–483 [Internet]. Nature Publishing Group. Available at: http://www.nature.com/doifinder/10.1038/nrc3971.
[65] A.E. Escalante, M. Rebolleda-Gómez, M. Benítez, M. Travisano, Ecological perspectives on synthetic biology: insights from microbial population biology, Front. Microbiol. 6 (2015) 1–10 (FEB).
[66] C. Tomasetti, L. Marchionni, M.A. Nowak, G. Parmigiani, B. Vogelstein, Only three driver gene mutations are required for the development of lung and colorectal cancers, Proc. Natl. Acad. Sci. U. S. A. 112 (1) (2015) 118–123 [Internet]. Available at: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid = 4291633&tool = pmcentrez&rendertype = abstract.
[67] B. Vogelstein, K.W. Kinzler, The path to cancer - three strikes and you're out, N. Engl. J. Med. 373 (20) (2015) 1895–1898 [Internet]. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26559568.
[68] A. Chapman, L.F. del Ama, J. Ferguson, J. Kamarashev, C. Wellbrock, A. Hurlstone, Heterogeneous tumor subpopulations cooperate to drive invasion, Cell Rep. 8 (3) (2014) 688–695 [Internet]. The Authors. Available at: https://doi.org/10.1016/j.celrep.2014.06.045.
[69] K.J. Cheung, A.J. Ewald, J. Massagué, A.C. Obenauf, J.E. Talmadge, I.J. Fidler, et al., A collective route to metastasis: Seeding by tumor cell clusters, Science 352 (6282) (2016) 167–169 [Internet]. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27124449.
[70] N. Aceto, A. Bardia, D.T. Miyamoto, M.C. Donaldson, B.S. Wittner, J.A. Spencer, et al., Circulating tumor cell clusters are oligoclonal precursors of breast cancer metastasis, Cell 158 (5) (2014) 1110–1122 [Internet]. Elsevier Inc. Available at:

https://doi.org/10.1016/j.cell.2014.07.013.
[71] R. Maddipati, B.Z. Stanger, Pancreatic cancer metastases harbor evidence of polyclonality, Cancer Discov. 5 (10) (2015) 1086–1097.
[72] K.J. Cheung, V. Padmanaban, V. Silvestri, K. Schipper, J.D. Cohen, A.N. Fairchild, et al., Polyclonal breast cancer metastases arise from collective dissemination of keratin 14-expressing tumor cell clusters, Proc. Natl. Acad. Sci. 113 (7) (2016) 201508541 [Internet]. Available at: http://www.pnas.org/lookup/doi/10.1073/pnas.1508541113\nhttp://www.ncbi.nlm.nih.gov/pubmed/26831077\nhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid = PMC4763783.
[73] S. Malladi, D.G. MacAlinao, X. Jin, L. He, H. Basnet, Y. Zou, et al., Metastatic Latency and Immune Evasion through Autocrine Inhibition of WNT, Cell 165 (1) (2016) 45–60.
[74] S. Malladi, D.G. MacAlinao, X. Jin, L. He, H. Basnet, Y. Zou, et al., Metastatic Latency and Immune Evasion through Autocrine Inhibition of WNT, Cell 165 (1) (2016) 45–60.
[75] K.E. de Visser, T. Tüting, How neutrophils promote metastasis, Science 352 (6282) (2016) 145–146 (80-).
[76] R. Leblanc, O. Peyruchaud, Metastasis: new functional implications of platelets and megakaryocytes, Blood 128 (1) (2016) 24–31 [Internet]. Available at: http://www.bloodjournal.org/cgi/doi/10.1182/blood-2016-01-636399.
[77] L.C. Pelosof, D.E. Gerber, Paraneoplastic syndromes: an approach to diagnosis and treatment, Mayo Clin. Proc. 85 (9) (2010) 838–854 [Internet]. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20810794.
[78] T. Hillen, J. Lowengrub, Feedback control in a stem cell model can cause an Allee effect, Bull. Math. Biol. 78 (4) (2011) 1–12 [Internet]. Available at: https://doi.org/10.1007/s11538-016-0161-5.
[79] L. Persano, E. Rampazzo, G. Basso, G. Viola, Glioblastoma cancer stem cells: role of the microenvironment and therapeutic targeting, Biochem. Pharmacol. 85 (5) (2013 Mar 1) 612–622 [Internet]. Elsevier Inc. [cited 2014 Dec 18]. Available at http://www.ncbi.nlm.nih.gov/pubmed/23063412.
[80] B. Beck, C. Blanpain, Unravelling cancer stem cell potential, Nat. Rev. Cancer 13 (10) (2013) 727–738 [Internet]. Nature Publishing Group. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24060864.
[81] D.F. Quail, J.A. Joyce, Microenvironmental regulation of tumor progression and metastasis, Nat. Med. (2013) 1423–1437.
[82] K. Polyak, I. Haviv, I.G. Campbell, Co-evolution of tumor cells and their microenvironment, Trends Genet. 25 (1) (2009 Jun 13) 30–38 [Internet]. Elsevier. Available at: https://doi.org/10.1016/j.tig.2008.10.012.
[83] B. Muz, P. de la Puente, F. Azab, A.K. Azab, The role of hypoxia in cancer progression, angiogenesis, metastasis, and resistance to therapy, Hypoxia 3 (83) (2015) [Internet]. Available at: https://www.dovepress.com/the-role-of-hypoxia-in-cancer-progression-angiogenesis-metastasis-and–peer-reviewed-fulltext-article-HP ..
[84] W.M. Elshamy, A. Sinha, N. Said, Aggressiveness niche: Can it be the foster ground for cancer metastasis precursors? Stem Cells Int. 2016 (2016).
[85] M. Mohme, S. Riethdorf, K. Pantel, Circulating and disseminated tumour cells - mechanisms of immune surveillance and escape, Nat. Rev. Clin. Oncol. 14 (3) (2017 Mar) 155–167 [Internet]. Nature Publishing Group, a division of Macmillan Publishers Limited. All Rights Reserved. Available at: https://doi.org/10.1038/nrclinonc.2016.144.
[86] M.Z. Noman, M. Hasmim, Y. Messai, S. Terry, C. Kieda, B. Janji, et al., Hypoxia: a key player in antitumor immune response. A Review in the Theme: Cellular Responses to Hypoxia, Am. J. Phys. Cell Phys. 309 (9) (2015) C569–79 [Internet]. Available at: http://ajpcell.physiology.org/lookup/doi/10.1152/ajpcell.00207.2015.
[87] E.B. Rankin, A.J. Giaccia, Hypoxic control of metastasis, Science 352 (6282) (2016) 175–180 (80-).
[88] D.M. Gilkes, G.L. Semenza, D. Wirtz, Hypoxia and the extracellular matrix: drivers of tumour metastasis, Nat. Rev. Cancer 14 (6) (2014) 430–439 [Internet]. Nature Publishing Group. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24827502\nhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid = PMC4283800.
[89] J. Kamta, M. Chaar, A. Ande, D.A. Altomare, S. Ait-Oudhia, Advancing cancer therapy with present and emerging immuno-oncology approaches, Front Oncol 7 (April) (2017) 1–15 [Internet]. Available at: http://journal.frontiersin.org/article/10.3389/fonc.2017.00064/full.
[90] D. Mittal, M.M. Gubin, R.D. Schreiber, M.J. Smyth, New insights into cancer immunoediting and its three component phases—elimination, equilibrium and escape, Curr Opin Immunol 27 (2014) 16–25 [Internet]. Available at: http://www.sciencedirect.com/science/article/pii/S0952791514000053.
[91] Teng MWL, J. Galon, W.-H. Fridman, M.J. Smyth, From mice to humans: developments in cancer immunoediting, Eur. J. Clin. Investig. 125 (9) (2015 Sep 1) 3338–3346 [Internet]. American Society for Clinical Investigation. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4588291/.
[92] A. Qamra, M. Xing, N. Padmanabhan, J.J.T. Kwok, S. Zhang, X. Chang, et al., Epigenomic promoter alterations amplify gene isoform and immunogenic diversity in gastric adenocarcinoma, Cancer Discov. (2017) [Internet]. (June):CD – 16–1022. Available at: http://cancerdiscovery.aacrjournals.org/lookup/doi/10.1158/2159-8290.CD-16-1022.
[93] R. Yuste, From the neuron doctrine to neural networks, Nat. Rev. Neurosci. 16 (8) (2015) 487–497 [Internet]. Nature Publishing Group. Available at: http://www.nature.com/doifinder/10.1038/nrn3962\nhttp://dx.doi.org/10.1038/nrn3962.
[94] Y. Liu, V. Devescovi, S. Chen, C. Nardini, Multilevel omic data integration in cancer cell lines: advanced annotation and emergent properties, BMC Syst. Biol. 7 (2013) 14.
[95] R. Fronza, M. Tramonti, W.R. Atchley, C. Nardini, Joint analysis of transcriptional and post- transcriptional brain tumor data: searching for emergent properties of cellular systems, BMC Bioinf. 12 (1) (2011) 86 [Internet]. BioMed Central Ltd. Available at: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid = 3078861&tool = pmcentrez&rendertype = abstract.
[96] S. Turajlic, C. Swanton, Metastasis as an evolutionary process, Science 352 (6282) (2016) 162–175 (80-).
[97] M.J. Alvarez, Y. Shen, F.M. Giorgi, A. Lachmann, B.B. Ding, B.H. Ye, et al., Functional characterization of somatic mutations in cancer using network-based inference of protein activity, Nat. Genet. 48 (8) (2016) 838–847 [Internet]. Available at: http://www.nature.com/doifinder/10.1038/ng.3593\nhttp://www.ncbi.nlm.nih.gov/pubmed/27322546.
[98] M. Russo, G. Siravegna, L.S. Blaszkowsky, G. Corti, G. Crisafulli, L.G. Ahronian, et al., Tumor heterogeneity and Lesion-specific response to targeted therapy in colorectal cancer, Cancer Discov. 6 (2) (2016) 147–153.
[99] R.A. Gatenby, J.J. Cunningham, J.S. Brown, Evolutionary triage governs fitness in driver and passenger mutations and suggests targeting never mutations, Nat Commun 5 (2014) 5499 [Internet]. Nature Publishing Group. Available at: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid = 4260773&tool = pmcentrez&rendertype = abstract.
[100] N.J. Krogan, S. Lippman, D.A. Agard, A. Ashworth, T. Ideker, The cancer cell map initiative: defining the Hallmark networks of cancer, Mol. Cell 58 (4) (2015) 690–698 [Internet]. Elsevier Inc. Available at: https://doi.org/10.1016/j.molcel.2015.05.008.
[101] M.S. Carro, W.K. Lim, M.J. Alvarez, R.J. Bollo, X. Zhao, E.Y. Snyder, et al., The transcriptional network for mesenchymal transformation of brain tumours, Nature 463 (7279) (2010) 318–325 [Internet]. Nature Publishing Group. Available at: https://doi.org/10.1038/nature08712.
[102] M. Jamal-Hanjani, A. Hackshaw, Y. Ngai, J. Shaw, C. Dive, S. Quezada, et al., Tracking genomic cancer evolution for precision medicine: the lung TRACERx study, PLoS Biol. 12 (7) (2014) 1–7.
[103] M. Jamal-Hanjani, S.A. Quezada, J. Larkin, C. Swanton, Translational implications of tumor heterogeneity, Clin. Cancer Res. 21 (6) (2015) 1258–1266.
[104] E.O. Lillie, B. Patay, J. Diamant, B. Issell, E.J. Topol, N.J. Schork, et al., The n-of-1 clinical trial: the ultimate strategy for individualizing medicine? Pers. Med. 8 (2) (2011) 161–173.
[105] R. Chari, B.P. Coe, E.A. Vucic, W.W. Lockwood, W.L. Lam, An integrative multidimensional genetic and epigenetic strategy to identify aberrant genes and pathways in cancer, BMC Syst. Biol. 4 (67) (2010) [Internet]. Available at: http://www.biomedcentral.com/1752-0509/4/67\nhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid = 2880289 & tool = pmcentrez & rendertype = abstract.
[106] H.M.J. Werner, G.B. Mills, P.T. Ram, Cancer Systems Biology: a peek into the future of patient care? Nat. Rev. Clin. Oncol. Nature Publishing Group 11 (3) (2014) 167–176.
[107] C. Kiel, L. Serrano, Structural data in synthetic biology approaches for studying general design principles of cellular signaling networks, Structure 20 (11) (2012) 1806–1813 [Internet]. Elsevier Ltd. Available at: https://doi.org/10.1016/j.str.2012.10.002.
[108] N.T.L. Tran, L. Deluccia, A.F. Mcdonald, C. Huang, Cross-Disciplinary Detection and Analysis of Network Motifs, (2015), pp. 49–60.
[109] A. Hilfinger, J. Paulsson, Systems biology: defiant daughters and coordinated cousins, Nature 519 (7544) (2015) 422–423 [Internet]. Available at: http://www.nature.com/nature/journal/vaop/ncurrent/full/nature14210.html?WT.ec_id = NATURE-20150312\nhttp://www.nature.com/doifinder/10.1038/nature14210.
[110] J.J. Hornberg, F.J. Bruggeman, H.V. Westerhoff, J. Lankelma, Cancer: a systems biology disease, Mol. BioSyst. 83 (2006) 81–90 (2–3 SPEC. ISS.).
[111] K. Saetzler, C. Sonnenschein, A.M. Soto, Systems biology beyond networks: Generating order from disorder through self-organization, Semin. Cancer Biol. 21 (3) (2011) 165–174 [Internet]. Elsevier Ltd. Available at: https://doi.org/10.1016/j.semcancer.2011.04.004.
[112] N.T. Ingolia, S. Ghaemmaghami, J.R.S. Newman, J.S. Weissman, Genome-wide analysis in vivo of translation with nucleotide resolution using ribosome profiling, Science 324 (5924) (2009) 218–223 (80-) [Internet]. Available at: http://www.sciencemag.org/content/306/5703/1895.short.
[113] P.B.F. O'Connor, D.E. Andreev, P.V. Baranov, Comparative survey of the relative impact of mRNA features on local ribosome profiling read density, Nat. Commun. 7 (2016) 12915 [Internet]. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27698342\nhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid = PMC5059445.
[114] L. De Mattos-Arruda, R. Mayor, C.K.Y. Ng, B. Weigelt, F. Martínez-Ricarte, D. Torrejon, et al., Cerebrospinal fluid-derived circulating tumour DNA better represents the genomic alterations of brain tumours than plasma, Nat. Commun. 6 (2015) 8839 [Internet]. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26554728.
[115] C. Alix-Panabières, K. Pantel, Clinical applications of circulating tumor cells and circulating tumor DNA as liquid biopsy, Cancer Discov. 6 (5) (2016) 479–491.
[116] L. De Mattos-Arruda, J. Cortes, L. Santarpia, A. Vivancos, J. Tabernero, J.S. Reis-Filho, et al., Circulating tumour cells and cell-free DNA as tools for managing breast cancer, Nat. Rev. Clin. Oncol. 10 (7) (2013 Jul) 377–389 [Internet]. Nature Publishing Group, a division of Macmillan Publishers Limited. All Rights Reserved. Available at: https://doi.org/10.1038/nrclinonc.2013.80.
[117] T. Forshew, M. Murtaza, C. Parkinson, D. Gale, D.W.Y. Tsui, F. Kaper, et al., Noninvasive identification and monitoring of cancer mutations by targeted deep sequencing of plasma DNA, Sci. Transl. Med. 4 (136) (2012 May 30) [Internet].

136ra68 LP–136ra68. Available at: http://stm.sciencemag.org/content/4/136/136ra68.abstract.
[118] M. Murtaza, S.-J. Dawson, D.W.Y. Tsui, D. Gale, T. Forshew, A.M. Piskorz, et al., Non-invasive analysis of acquired resistance to cancer therapy by sequencing of plasma DNA, Nature 497 (7447) (2013 May 2) 108–112 [Internet]. Nature Publishing Group, a division of Macmillan Publishers Limited. All Rights Reserved. Available at: https://doi.org/10.1038/nature12065.
[119] G. Siravegna, S. Marsoni, S. Siena, A. Bardelli, Integrating liquid biopsies into the management of cancer, Nat. Rev. Clin. Oncol. (2017 Mar 2) [Internet]. Nature Publishing Group, a division of Macmillan Publishers Limited. All Rights Reserved. advance online publication. Available at: https://doi.org/10.1038/nrclinonc.2017.14.
[120] M. Murtaza, S.-J. Dawson, K. Pogrebniak, O.M. Rueda, E. Provenzano, J. Grant, et al., Multifocal clonal evolution characterized using circulating tumour DNA in a case of metastatic breast cancer, Nat. Commun. 6 (2015) 8760 [Internet]. Nature Publishing Group. Available at: http://www.nature.com/doifinder/10.1038/ncomms9760.
[121] B. Zhao, J.R. Pritchard, D.A. Lauffenburger, M.T. Hemann, Addressing genetic tumor heterogeneity through computationally predictive combination therapy, Cancer Discov. 4 (2) (2014) 166–174.
[122] S. Aparicio, E. Mardis, Tumor heterogeneity: next-generation sequencing enhances the view from the pathologist's microscope, Genome Biol. 15 (9) (2014) 463 [Internet]. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25315013.
[123] G.D. Lianos, A. Mangano, S. Rausei, C. Katsios, D.H. Roukos, Tumor heterogeneity-based resistance guides personalized cancer medicine, Future Oncol. 10 (12) (2014) 1889–1892 [Internet]. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25386806.
[124] M. Gerlinger, N. McGranahan, S.M. Dewhurst, R.A. Burrell, I. Tomlinson, C. Swanton, Cancer: evolution within a lifetime, Annu. Rev. Genet. 48 (2014) 215–236 [Internet]. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25292359.
[125] V. Almendro, H.J. Kim, Y.-K. Cheng, M. Gönen, S. Itzkovitz, P. Argani, et al., Genetic and phenotypic diversity in breast tumor metastases, Cancer Res 74 (5) (2014) 1338–1348 [Internet]. Available at: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3963810&tool=pmcentrez&rendertype=abstract.
[126] S.J. Potts, J.S. Krueger, N. Landis, D. Eberhard, D. Young, S.C. Schmechel, et al., Evaluating tumor heterogeneity in immunohistochemistry-stained breast cancer tissue, Lab Investig 92 (9) (2012) 1342–1357 [Internet]. Available at: https://doi.org/10.1038/labinvest.2012.91.
[127] J.W.B. Hershey, N. Sonenberg, M.B. Mathews, Principles of translational control: an overview, Cold Spring Harb. Perspect. Biol. 4 (12) (2012) 1–10.
[128] M. Bhat, N. Robichaud, L. Hulea, N. Sonenberg, J. Pelletier, I. Topisirovic, Targeting the translation machinery in cancer, Nat. Rev. Drug Discov. 14 (4) (2015) 261–278 [Internet]. Nature Publishing Group. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25743081.
[129] A.G. Hinnebusch, The scanning mechanism of eukaryotic translation initiation, Annu. Rev. Biochem. 83 (2014) 779–812 [Internet]. Available at: http://www.annualreviews.org/doi/full/10.1146/annurev-biochem-060713-035802?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub=pubmed&.
[130] J. Chu, M. Cargnello, I. Topisirovic, J. Pelletier, Translation initiation factors: reprogramming protein synthesis in cancer, Trends Cell Biol. 26 (12) (2016) 918–933 [Internet]. Elsevier Ltd. Available at: https://doi.org/10.1016/j.tcb.2016.06.005.
[131] H.G. Wendel, E. De Stanchina, J.S. Fridman, A. Malina, S. Ray, S. Kogan, et al., Survival signalling by Akt and eIF4E in oncogenesis and cancer therapy, Nature 428 (6980) (2004) 332–337 [Internet]. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15029198\nhttp://www.nature.com/nature/journal/v428/n6980/pdf/nature02369.pdf.
[132] H.G. Wendel, A. Malina, Z. Zhao, L. Zender, S.C. Kogan, C. Cordon-Cardo, et al., Determinants of sensitivity and resistance to rapamycin-chemotherapy drug combinations in vivo, Cancer Res. 66 (15) (2006) 7639–7646.
[133] F. Rojo, L. Najera, J. Lirola, J. Jiménez, M. Guzmán, M. Dolors Sabadell, et al., 4E-binding protein 1, a cell signaling hallmark in breast cancer that correlates with pathologic grade and prognosis, Clin. Cancer Res. 13 (1) (2007) 81–89.
[134] C. Mateus, E. Routier, M. Thomas, C. Basmadjian, N. Ribeiro, C. Robert, eIF4F is a Nexus of Resistance to Anti-BRAF and Anti-MEK Cancer Therapies, (2014).
[135] B. Allal, T. Filleron, S. Pierredon, P. Zindy, Y. Berg, A. Cammas, et al., Formation of the eIF4F Translation – Initiation Complex Determines Sensitivity to Anticancer Drugs Targeting the EGFR and HER2 Receptors, 71(12) (2011), pp. 4068–4073.
[136] N. Ilic, T. Utermark, H.R. Widlund, T.M. Roberts, PI3K-targeted therapy can be evaded by gene amplification along the MYC-eukaryotic translation initiation factor 4E (eIF4E) axis, Proc. Natl. Acad. Sci. 108 (37) (2011) E699–708 [Internet]. Available at: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3174675&tool=pmcentrez&rendertype=abstract\nhttp://www.pnas.org/cgi/doi/10.1073/pnas.1108237108.
[137] T. Alain, M. Morita, B.D. Fonseca, A. Yanagiya, N. Siddiqui, M. Bhat, et al., eIF4E/4E–BP Ratio Predicts the Efficacy of mTOR Targeted Therapies, 72(24) (2012), pp. 6468–6476.
[138] C. Bi, X. Zhang, T. Lu, X. Zhang, X. Wang, B. Meng, et al., Inhibition of 4EBP phosphorylation mediates the cytotoxic effect of mTOR kinase inhibitors in aggressive B-cell lymphomas, (2017).
[139] C.L. Cope, R. Gilley, K. Balmanno, M.J. Sale, K.D. Howarth, M. Hampson, et al., Adaptation to mTOR kinase inhibitors by amplification of eIF4E to maintain cap-dependent translation, J. Cell Sci. 127 (Pt 4) (2014) 788–800 [Internet]. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24363449.
[140] S. Mallya, B.A. Fitch, J.S. Lee, L. So, M.R. Janes, D.A. Fruman, Resistance to mTOR kinase inhibitors in lymphoma cells lacking 4EBP1, 9 (2) (2014) 1–10.
[141] L. So, J. Lee, M. Palafox, S. Mallya, C.G. Woxland, M. Arguello, et al., The 4E–BP – eIF4E Axis Promotes Rapamycin-sensitive Growth and Proliferation in Lymphocytes, 9(430) (2016), pp. 1–14.
[142] Y. Zhan, M.S. Dahabieh, A. Rajakumar, M.C. Dobocan, V. Kempen, C. Goncalves, et al., The Role of eIF4E in Response and Acquired Resistance to Vemurafenib in Melanoma, (2015), p. 135.
[143] G. Armengol, F. Rojo, J. Castellví, C. Iglesias, M. Cuatrecasas, B. Pons, et al., 4E-binding protein 1: a key molecular "funnel factor" in human cancer with clinical implications, Cancer Res. 67 (16) (2007) 7551–7555.
[144] J. Castellvi, A. Garcia, F. Rojo, C. Ruiz-Marcellan, A. Gil, J. Baselga, et al., Phosphorylated 4E binding protein 1: a hallmark of cell signaling that correlates with survival in ovarian cancer, Cancer 107 (8) (2006) 1801–1811.
[145] A. Martínez, M. Sesé, J.H. Losa, N. Robichaud, N. Sonenberg, T. Aasen, et al., Phosphorylation of eIF4E confers resistance to cellular stress and DNA-damaging agents through an interaction with 4E-T: a Rationale for novel therapeutic approaches, PLoS One 10 (4) (2015) 1–23.
[146] E. Martinez-Saez, V. Peg, A. Ortega-Aznar, F. Martinez-Ricarte, J. Camacho, J. Hernandez-Losa, et al., peIF4E as an independent prognostic factor and a potential therapeutic target in diffuse infiltrating astrocytomas, Cancer Med. 5 (9) (2016) 2501–2512.
[147] J.R. Graff, B.W. Konicek, J.H. Carter, E.G. Marcusson, Targeting the eukaryotic translation initiation factor 4E for cancer therapy, Cancer Res. 68 (3) (2008) 631–634.
[148] J. Pelletier, J. Graff, D. Ruggero, N. Sonenberg, Targeting the eIF4F translation initiation complex: a critical nexus for cancer development, Cancer Res. 75 (2) (2015) 250–563.
[149] J. Tamburini, A.S. Green, V. Bardet, N. Chapuis, S. Park, L. Willems, et al., Protein Synthesis is Resistant to Rapamycin And Constitutes a Promising Therapeutic Target in Acute Myeloid Leukemia, 114(8) (2017), pp. 1–3.
[150] Y. Ramon, S. Cajal, L. De Mattos-Arruda, N. Sonenberg, J. Cortes, V. Peg, The intra-tumor heterogeneity of cell signaling factors in breast cancer: p4E-BP1 and peIF4E are diffusely expressed and are real potential targets, Clin. Transl. Oncol. 16 (11) (2014) 937–941.
[151] M. Bordeleau, F. Robert, B. Gerard, L. Lindqvist, S.M.H. Chen, H. Wendel, et al., Therapeutic suppression of translation initiation modulates chemosensitivity in a mouse lymphoma model, 118 (7) (2008).
[152] Z. Nasr, F. Robert, J.A.P. Jr, W.J. Muller, J. Pelletier, eIF4F suppression in breast cancer affects maintenance and progression, Nat. Publ. Group 32 (7) (2012) 861–871. Available at: https://doi.org/10.1038/onc.2012.105.
[153] Y. Feng, A.B Pinkerton, L. Hulea, T. Zhang, M.A Davies, S. Grotegut, et al., SBI-0640756 Attenuates the Growth of Clinically Unresponsive Melanomas by Disrupting the eIF4F Translation Initiation Complex, Cancer Res. 75 (24) (2015) 5211–5218.
[154] B. Pons, V. Peg, M.Á. Vázquez-Sánchez, L. López-Vicente, E. Argelaguet, L. Coch, et al., The effect of p-4E-BP1 and p-eIF4E on cell proliferation in a breast cancer model, Int. J. Oncol. 39 (5) (2011) 1337–1345.
[155] J.A. Joyce, Therapeutic targeting of the tumor microenvironment, Cancer Cell 7 (6) (2005) 513–520.
[156] S. Kuzet, C. Gaggioli, Fibroblast activation in cancer : when seed fertilizes soil, [Internet], Cell Tissue Res. (2016) 607–619. Available at: https://doi.org/10.1007/s00441-016-2467-x.
[157] J.D. Wolchok, F.S. Hodi, J.S. Weber, J.P. Allison, W.J. Urba, C. Robert, et al., Development of ipilimumab: a novel immunotherapeutic approach for the treatment of advanced melanoma, Annals of the New York Academy of Sciences, 2013, pp. 1–13.
[158] C. Barnhart, Pembrolizumab: first in class for treatment of metastatic melanoma, J. Adv. Practition. Oncol. (2015) 234–238.
[159] R. Asmar, J. Yang, R.D. Carvajal, Clinical utility of nivolumab in the treatment of advanced melanoma, Ther. Clin. Risk Manag. (2016) 313–325.
[160] N. Robichaud, N. Sonenberg, Translational control and the cancer cell response to stress, Curr. Opin. Cell Biol. 45 (2017 Apr) 102–109 [Internet]. Available at: http://www.sciencedirect.com/science/article/pii/S0955067417300583.
[161] G. Leprivier, B. Rotblat, D. Khan, E. Jan, P.H. Sorensen, Stress-mediated translational control in cancer cells, Biochim. Biophys. Acta, Gene Regul. Mech. 1849 (7) (2015 Jul) 845–860 [Internet]. Available at: http://www.sciencedirect.com/science/article/pii/S1874939914002752.
[162] N. Siddiqui, N. Sonenberg, Signalling to eIF4E in cancer, Biochem. Soc. Trans. 43 (5) (2015) 763–772 [Internet]. Available at: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4613458&tool=pmcentrez&rendertype=abstract.
[163] A.J. Waskiewicz, A. Flynn, C.G. Proud, J.A. Cooper, Mitogen-activated protein kinases activate the serine/threonine kinases Mnk1 and Mnk2, 16 (8) (1997) 1909–1920.
[164] R. Fukunaga, T. Hunter, MNK1, a New MAP Kinase-activated Protein Kinase, Isolated by a Novel Expression Screening Method for Identifying Protein Kinase Substrates, 16(8) (1997), pp. 1921–1933.
[165] L. Furic, L. Rong, O. Larsson, I.H. Koumakpayi, K. Yoshida, A. Brueschke, et al., eIF4E phosphorylation promotes tumorigenesis and is associated with prostate cancer progression, Proc. Natl. Acad. Sci. U. S. A. 107 (32) (2010) 14134–14139 [Internet]. Available at: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2922605&tool=pmcentrez&rendertype=abstract.
[166] N. Robichaud, S.V. del Rincon, B. Huor, T. Alain, L.A. Petruccelli, J. Hearnden, et al., Phosphorylation of eIF4E promotes EMT and metastasis via translational control of SNAIL and MMP-3, Oncogene 34 (16) (2015 Apr 16) 2032–2042 [Internet]. Macmillan Publishers Limited. Available at: https://doi.org/10.1038/onc.2014.146.

[167] R. Lock, R. Ingraham, O. Maertens, A.L. Miller, N. Weledji, E. Legius, et al., Cotargeting MNK and MEK kinases induces the regression of NF1-mutant cancers, J. Clin. Invest. 126 (6) (2016) 2181–2190.
[168] B.W. Konicek, J.R. Stephens, A.M. Mcnulty, N. Robichaud, R.B. Peery, C.A. Dumstorf, et al., Therapeutic Inhibition of MAP Kinase Interacting Kinase Blocks Eukaryotic Initiation Factor 4E Phosphorylation and Suppresses Outgrowth of Experimental Lung Metastases, Cancer Res. 71 (5) (2011) 1849–1857.
[169] J.B. Bell, F.D. Eckerdt, K. Alley, L.P. Magnusson, H. Hussain, Y. Bi, et al., MNK Inhibition Disrupts Mesenchymal Glioma Stem Cells and Prolongs Survival in a Mouse Model of Glioblastoma, 14 (2016) (October).
[170] S. Lim, T. Yih, M. Zhang, M.R. Janes, K. Nacro, J. Hill, et al., Targeting of the MNK – eIF4E Axis in Blast Crisis Chronic Myeloid Leukemia Inhibits Leukemia Stem Cell Function, (2013), pp. 2298–2307.
[171] J.K. Altman, A. Szilard, B.W. Konicek, P.W. Iversen, B. Kroczynska, H. Glaser, et al., Inhibition of Mnk Kinase Activity by Cercosporamide and Suppressive Effects on Acute Myeloid Leukemia Precursors, 121(18) (2017), pp. 3675–3682.
[172] H. Ducasse, A. Arnal, M. Vittecoq, S.P. Daoust, B. Ujvari, C. Jacqueline, et al., Cancer: An emergent property of disturbed resource-rich environments? Ecology meets personalized medicine, Evol. Appl. 8 (6) (2015) 527–540.
[173] F. Thomas, D. Fisher, P. Fort, J.-P. Marie, S. Daoust, B. Roche, et al., Applying ecological and evolutionary theory to cancer: a long and winding road, Evol. Appl. 6 (1) (2013) 1–10 [Internet]. Available at: http://onlinelibrary.wiley.com/doi/10.1111/eva.12021/abstract.
[174] Á.T. Kovács, Impact of spatial distribution on the development of mutualism in microbes, Front. Microbiol. 5 (NOV) (2014) 1–5.
[175] J. Barrow-Green, Poincaré and the three body problem, AMS Bookstore, Providence RI, 1997 ISBN 0-8218-0367-0.
[176] McCarthy DJ, P. Humburg, A. Kanapin, M.A. Rivas, K. Gaulton, J.-B. Cazier, et al., Choice of transcripts and software has a large effect on variant annotation, Genome Med. 6 (3) (2014) 26 [Internet].
[177] B.I. Epureanu, E.H. Dowell, On the optimailty of the Ott-Grebogi-Yorke control scheme, Physica D 116 (1–2) (1998) 1–7.
[178] Z. Han, B. Wei, Y. Zheng, Y. Yin, K. Li, S. Li, Breast Cancer Multi-classification from histopathological images with structured deep learning model, Sci Rep 7 (1) (2017 Jun 23) 4172.
[179] M.E. Vandenberghe, M.L. Scott, P.W. Scorer, M. Söderberg, D. Balcerzak, C. Barker, Relevance of deep learning to facilitate the diagnosis of HER2 status in Breast Cancer, Sci Rep 7 (2017 Apr 5) 45938.