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IDEAS & SPECULATIONS

Insights & Perspectives

Do microenvironmental changes disrupt multicellular organisation with ageing, enacting and favouring the cancer cell phenotype?

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Abstract

Cancer is a singular cellular state, the emergence of which destabilises the homeostasis reached through the evolution to multicellularity. We present the idea that the onset of the cellular disobedience to the metazoan functional and structural architecture, known as the cancer phenotype, is triggered by changes in the cell's external environment that occur with ageing: what ensues is a breach of the social contract of multicellular life characteristic of metazoans. By integrating old ideas with new evidence, we propose that with ageing the environmental information that maintains a multicellular organisation is eroded, rewiring internal processes of the cell, and resulting in an internal shift towards an ancestral condition resulting in the pseudo-multicellular cancer phenotype. Once that phenotype emerges, a new local social contract is built, different from the homeostatic one, leading to tumour formation and the foundation of a novel local ecosystem.

KEYWORDS
ecological oncology, multicellular organisation, oncogenesis

THE CELLULAR SOCIAL CONTRACT BEHIND THE MULTICELLULAR ARCHITECTURE

The internal environment of metazoan cells, bounded by the cellular membrane, has coevolved with their local external environment.[1] However, these cells have maintained, encrypted in the space of possible strategies, a behaviour from their single-celled[2,3] and pseudo-multicellular ancestors.[4] The transition to multicellularity is vital in order to comprehend the emergence of the cancerous phenotype as a breaking down of the metazoan homeostatic architecture.[5] The premise for this concept is that the most evolutionarily successful state of a multicellular organism is one governed by the division of labours between cellular lineages in a condensed state. Here, homeostasis is achieved through the cooperative metabolic replication of different cell lineages. A set of rules, a "multicellular algorithm", as it were, underlies cooperation and regulation of conflicts between coexisting lineages. Through that algorithm, the multicellular entity's functional and structural architecture emerges (Figure 1).

Oncogenesis involves overriding some rules of the multicellular architecture. In particular, the local rupture of the social contract that maintains multicellular functioning.[6,7] The metaphor of the social contract as a necessary condition for multicellularity is explicit in that it is associated to a state characterised by the maintenance and persistence, through regulatory pathways, of interacting and functionally heterogeneous metabolic networks of coexisting cell lineages that favor the collective over the individual scale.[8–12] Oncogenic cells find a way to hack the norm. They progressively erode the homeostatic social contract enacting their own to persist and differentiate; thus, generating the tumor ecosystem or microenvironment, reminiscent of a pseudo-multicellular state.[4] However, which are the conditions that lead to this eroding and re-writing of the social contract? To answer this question, we need to analyse the oncogenetic process.

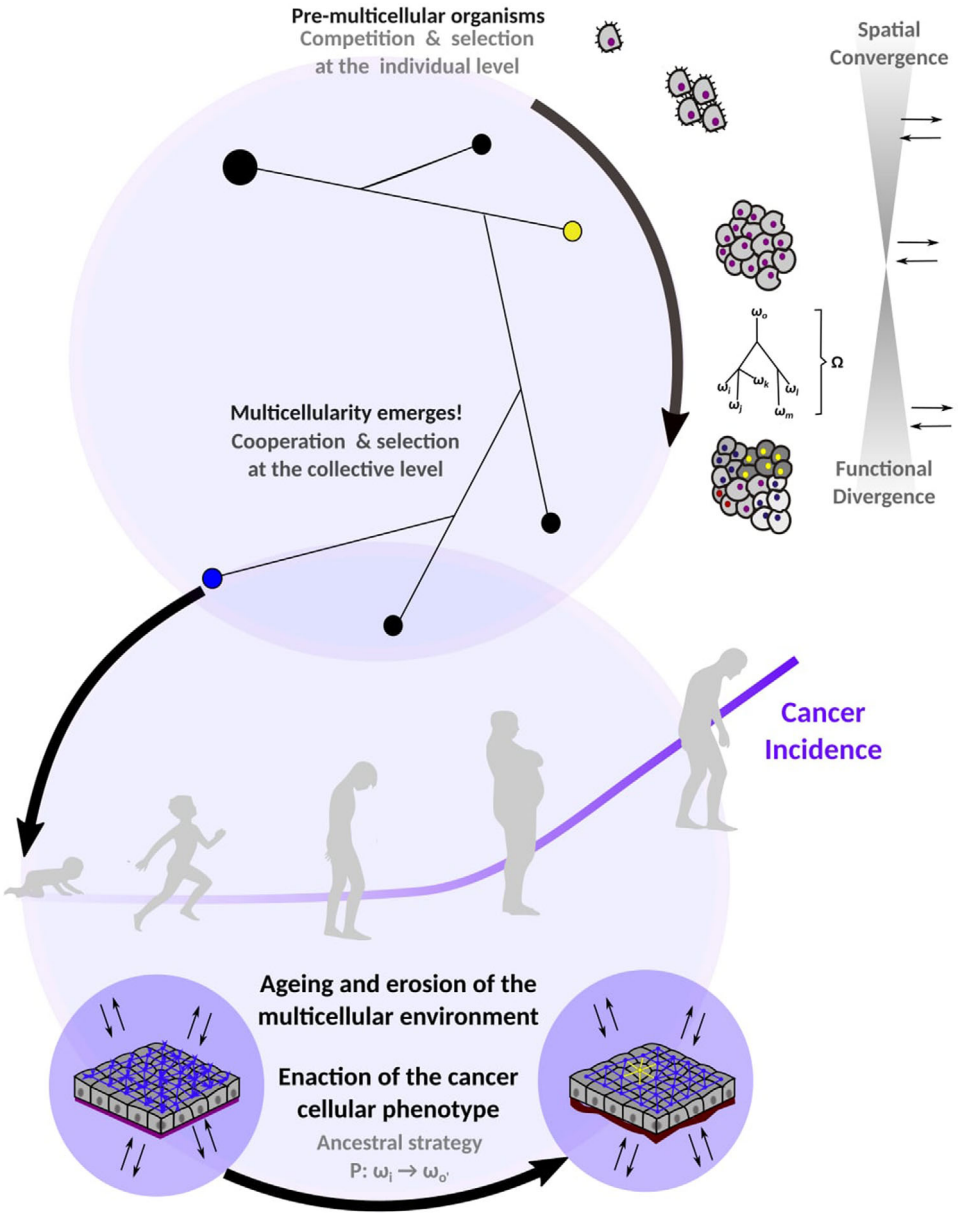

FIGURE 1 The emergence of the cancer phenotype in response to the erosion of the spatial and functional structure reached under the multicellular organization. In an evolutionary context, the external environment of cells promotes the spatial convergence of the individualized cells into aggregates. Mechanisms related to the selection of varieties and the resolution of conflicts lead to functional divergence and multicellularity. These steps append possible cellular strategies to the evolutionary history of the cell stored in Ω. With ageing, the erosion of the multicellular environment is transduced and interpreted by cells, enacting the cancer strategy and reorganizing the spatial and functional structure. In the figure, double arrows represent the interaction between the system and the environment, that is, co-determination

IS IT ALL ABOUT GENES? ECO-EVOLUTIONARY HYPOTHESES FOR CANCER EMERGENCE

In physiological terms, the cancer phenotype is a cellular strategy characterized by a myriad of hallmarks and innovations [13] often viewed as a mosaic of characters determined by mutational steps and clonal expansion. Such a view is envisioned under the somatic mutation theory,[14,15] which emphasises the onset of cancer as an endogenously mutation-driven process. The somatic mutations model states that each cancer cell has a history of accumulation of mutations and epi-mutations in somatic cells. In other words, with each stochastic mutational event, a cell might display a new strategy, navigating through its fitness landscape.[16,17] Recently, however, empirical data show that despite the presence of mutations in common cancer-associated genes (e.g., TP53, NOTCH), indicating that clones are incorporated into tissues, these do not show signs of cancer growth.[18,19] Therefore, the emergence of the cancer phenotype cannot be reduced to endogenous genetic modification only, challenging the paradigm of genetic mutations as the sole determinants of the cancer phenotype.[20,21] Alternatively, an emerging paradigm highlights

the role of the external physicochemical environment studied at the scale of the organism,[22] and also at the small scale of the cellular biotic environment as a driving force of cancer dynamics.[20,23–28] In particular, the cell's external physicochemical environment (e.g., pH, nutrient) shapes its internal environment. That interaction can modulate the emergence[25,26,29,30] and progression[31] of the cancer phenotype, as well as its biotic interactions with other cellular elements (e.g., immune cells and fibroblasts), which play a key role in shaping stem cell differentiation[32,33] and the evolutionary trajectory of this unique ecosystem.[34] Henceforth, we consider the external environment in its dual nature as the physicochemical environment wherein the cell is embedded (extracellular matrix), but also as the network of interactions among different cell type that could modulate cancer emergence and local establishment.

Besides the somatic mutation model, another evolutionary hypothesis was proposed to explain oncogenesis considering cancer behaviour as a cellular atavism (both reviewed in[35]). We propose that these two hypotheses are complementary in the light of ecological theory and in particular of how a cell, considered as an information processing system, makes sense and reacts to (i.e., computes) the external environment as we will explain. Here, we use the term computation to refer to the capability of the system (a cell or a collective of cells) to interpret, create and modify its external environment.[36,37] It raises the question of whether the external cellular environment contains the elements that cells transduce and interpret as symbols (physical patterns),[24] and whether such representations of the cell's outside world lead to a cellular behaviour of a particular kind. That framework includes the system's capability of interpreting external signals and adjusting its internal environment (Ashby's homeostat[38]). Hence, these concepts consider the notion that biological systems can modify, and be modified by, their external environment, a process that is integrated through the dialectic co-emergence, of both the "self," or cellular individuality, and the enacted extracellular environment. The mechanisms of this dialectic co-emergence are natural selection,[39] niche construction[40] and self-organisation.[41–43] The ability of cancer cells to modify their immediate external environment and change as a consequence of these alterations (niche construction) are essential characteristics that contribute to explaining their success in invading an organ either in the form of primary tumours or as distant metastases.[44] However, this raises the question of what elicits the appearance of such innovations in cancer cells such that they can proliferate and sustain a local population despite the prevailing social contract of cells wherein they are embedded. In this essay, under the idea of cellular computation, we propose that the cancer strategy co-emerges with its external environment (at the cellular scale) as a consequence of dynamic cell/environment interactions; linking ageing with the ensuing rupture of the spatial and functional architecture of the multicellular organisation (Figure 1). Finally, it is worth making a point about the efficiency of the computation of the external variables, which might be facilitated by collective computation and the flux of information between individual systems.[45] Cells, beyond being single-isolated entities, modify their behaviour and environment as a collective system, and the emergence of cancer strategies and their evolution is mediated by the collective, heterogeneous, and enacted environment.

ONCOGENESIS AND THE CELL/ENVIRONMENT AS A CASE OF CO-DETERMINATION

Before addressing the evolutionary dynamics leading to the neoplastic phenotype shift, it is necessary to introduce some simple notation. Let us first define a cell as the focal system, wherein we can discern observables, such as phenotypic strategies $\omega_i(t) \in \Omega$, where Ω represents the space of possible strategies or cellular phenotypes (Figure 1). A phenotype is the realisation of a set of continuous life-history traits at a given point in space-time; in other words, the expression of the internal environment, a representation of the fluxes with the external environment. The internal environment is a multilayered network constituting the co-expression of genes to produce metabolic reaction paths that maintain and repair the cell over time, as well as producing secondary metabolism that distinguishes cell types. Now, let us define a process P: $\omega_i \rightarrow \omega_{o'}$ as the shift from a given cellular strategy to another one, in the case of cancer, the process P is called oncogenesis. This transition between cellular strategies might be related to a rewiring of the internal environment represented by a shift in the gene co-expression network,[11,12,46,47] which can be modulated by the environment.[24,28] From an evolutionary point of view, this shift and the resulting appearance of an ecological novelty within the population of non-cancer cells represents the invasion of a mutant phenotype into a "stable" structured community of cellular strategies, where the fate of this novel phenotype depends on its interaction with the biological and physicochemical environment.[48–50] Notice that we denote the cancer strategy as $\omega_{o'}$ to emphasise that it resembles a cellular strategy with a lower degree of spatial and functional structure (Fig. 1), an ancestral strategy that existed before multicellularity (atavistic hypothesis), but without neglecting the onset of a new local social contract that gives rise to the tumour ecosystem or microenvironment.

To gain an understanding of the mechanisms associated with the emergence of cancer, a new theoretical framework is needed whereby cells are envisioned as open autonomous systems that co-emerge with their external -biophysical- environment (enactivism *sensu* Francisco Varela[51,52]). The enactive principle implies a dialectic co-constructed individual environment, where any deformation or perturbation in the external environment is sensed and integrated by the cell (e.g., through a point mutation, DNA methylation), which in turn affects the external environment and how the cell enacts it. In this context, cells emerge as autonomous self-organising "selves" thanks to their organisational closure,[53] whereby they become autonomous entities in an environment with which they are in a continuous co-transformation.[51,52] This mutual specification or co-determination between a living entity and its environment is the result of a history of coupling that involves the exchange of matter, energy, and information within a multilayered network of interactions involving genes and their products.[51] This flux determines the state of the focal system (i.e., the cell's strategy), the associated population-level effects,[54] and the transformation of the

cell's immediate environment.[26,40,44,51,52] This dialectic view of cell-environment co-transformation, we argue, is essential to understanding the phenotypic transition of cells from a healthy to a cancerous phenotype (oncogenesis), and the evolutionary trajectory of that phenotype. Here, co-determination arises because the environment and the entity specify each other through selection, drift, epi-mutation, and niche construction,[1,40,51,55,56] which occur in physicochemical as well as biological components of the focal cell's environment.

AGEING: THE EROSION OF THE MULTICELLULAR ECOSYSTEM, AND THE FORMATION OF A PERMISSIVE LANDSCAPE FOR CANCER

So far, we have revisited the somatic mutation and atavistic hypotheses in the light of cellular environmental effects. Then it is natural to link such environmental dynamics to the inexorable process of ageing.[27,57] In the context defined by our model, ageing enables the cell transition to the atavistic phenotype through changes in the structural components of the extracellular matrix[58] and the biological elements of the stroma.[59] Ageing erodes the external information computed by a cell, and from which it reproduces a given strategy in a multicellular cooperative context, triggering the transition between the condensed and functionally-coupled collective (metazoan) and the non-condensed cellular collectives (pre-metazoan or pseudo-multicellular state); hence, increasing the likelihood of oncogenesis (i.e., the enaction of the pre-metazoan strategy), and invasion of the surrounding tissue as a result of individual selection based on the proliferation rate of cellular strategies.[60] In evolutionary terms, this transition implies a shift in the level of selection from the persistence of the collective[61] to one where the differential proliferation of the individual becomes more important, in agreement with the diachronic view of the level of selection,[62] at least at the beginning of the oncogenetic process. Further persistence is sustained by enacting a new local social contract with fibroblasts and immune cells that facilitates immune evasion[13] among other crosstalks with the cellular components of the stroma.[13,56,63] These behaviours create a unique ecosystem of different cell types called the tumour microenvironment.

The cancer phenotype is an amalgam between the cellular life-history traits and the environment where it is expressed. The environment, in its dual representation as physicochemical signals and biological entities, is dynamic. The dynamism raises the question about what exactly happens during ageing that favor the emergence of the cancer cellular phenotype; or in a more general sense what makes ageing the most substantial risk factor for most human malignancies.[64] We argue that with ageing those changes in the physicochemical and/or biological environments destabilize the multicellular organisational architecture. On one side, the extracellular matrix exhibits well defined and consistent changes in its components,[65] for example, the fibrous protein concentration[66] or the reactive oxygen and nitrogen species, which may be caused by ischaemia, inadequate vascularisation, and an activated or damaged stroma.[58] Pathological conditions (e.g., hypertension) associated with a changing extracellular matrix also have been associated with cancer (e.g.,[67–69]). On the other side, the cellular components of the stroma also change with ageing, and immune senescence lessens the control against cellular strategies threatening the multicellular organization.[70] These changes have been previously considered separately as promoters of carcinogenesis; here, we integrate them under the idea of environmental co-determination with the human cellular ecosystem. Ageing is not, however, the only promoter of changes in the extracellular matrix, and some of the hallmarks of the ageing processes on the extracellular matrix (e.g., increased stiffness due to an increase in collagen concentration) are also associated to pathological conditions (see [71] and [72], such as hypertension) as well, which—though more prevalent in older people—are not necessarily restricted to old age. Moreover, change in the ECM stiffness can modify the differentiation of stem cells[32,33] and produce pathologies that have been associated with cancer (e.g.,[67–69]). Thus, we hypothesise that this association is related to the fact that some pathological conditions, as is the case with ageing, promote extracellular matrix modification in a way that makes possible the emergence of the cancer phenotype and the reorganisation of the multicellular ecosystem.[73]

Looking at the internal cellular environment, which includes gene and metabolic networks, it contributes to the expression of a given phenotype in different ways, the molecular pathways of which are beyond the scope of this article. However, a particular gene that has contributed to the understanding of tumour suppression is the tumour suppressor phosphatase and tensin homolog (PTEN), the loss of function of which is frequent in both heritable and sporadic cancers.[74,75] PTEN is involved in the modulation of varied and vital cellular processes including survival, proliferation, energy metabolism and cellular architecture.[74,75] For example, PTEN promotes oxidative phosphorylation and decreases glycolysis; thus, hindering the metabolic reprogramming characteristic of cancer cells.[76] Interestingly, as has been shown in human and mouse tissues, the increase in the stiffness in the ECM reduces levels of PTEN.[28] Therefore, the link between ageing, cellular environment and cancer is unavoidable where the modulation of gene expression by the environment is crucial governing the cellular phenotype.[24,28]

MOVING FARTHER INTO THE ECO-ONCOLOGY OF CANCER EMERGENCE

Further evaluation of the ideas presented here may be conducted along at least two main paths. First, an in-depth analysis of the human body's ecosystem, starting by characterising the metabolomics, at the levels of single-cell and adjacent extracellular matrix,[77] of different normal tissues and their evolution in time. This "natural history" of tissues or organ could provide crucial evidence regarding the pre-tumoural niche and how much it changes as the organism ages. In this context, it is crucial to develop experimental approaches to characterise the metabolic niche sustaining multicellular life. A similar analysis should be undertaken for cancer cells during neoplastic progression in different tissues[78] in order to understand better the environmental conditions that foster the emergence of the cancer phenotype. A key point

here is the relationship between chronological age and biological age, which reflects how the organism interacts with the external environment, and how that interaction—which is dynamic in time with an unknown behaviour—is transduced to the cellular environment orchestrating cancer risk.[22] This interaction may mediate the latency of a tumour becoming clinically relevant—a concept that is decisively reminiscent of bottlenecks. Such points of extreme selection are most likely involved in reaching a minimum diversity and/or achieving a functional tumour microenvironment (a process that has been invoked in the colonisation of different organs during metastasis, see[79]). Second, the metabolic characterisation of the pseudo-multicellular tumour ecosystem holds promise for applications in the clinic: for example, by targeting cytokines, growth factors, or nutrients, it may be possible to control the short and long-distance spread of cancer propagules.[25,80]

Here, our focus is on the initial breach of the multicellular organisation leading to the emergence of the cancer phenotype. However, we think that it is essential to include some considerations of the diversity of clones in terms of their interaction with the environment and how they can be linked to ecological and evolutionary dynamics.[16,23,60,81–85] We mentioned how recent evidence suggests the conspicuousness of mutants in tissues without signs of clinically-relevant cancer,[18,19] suggesting that despite the fact that clones might be under positive selection, they are incorporated into the tissue without breaking its structure or functionality. This observation could be explained by the property of latency, where the diversity of clones is a necessary feature for the building of a tumour environment;[34] and particular thresholds, bottlenecks or trade-offs operating on clonal diversity may constrain further tumour growth.[34,86] Even though Darwinian trajectories are widely assumed to explain clone diversity, it remains a matter of longstanding debate whether selectionism or neutralism can be applied to the evolution of tumours.[87,88] If we combine this with the eventuality that multi-sampling of the same tumor might reveal internal ecology, we think that the discussion might yield clues on how the local community of cells interacts with its surrounding as an open system under unpredictable, fate-determining environmental and internal fluctuations.

CONCLUSIONS AND OUTLOOK

The current understanding of cancer is shifting from the traditional reductionist and closed system view towards a view where the configurations of the biophysical, cellular environment have a fundamental role shaping cancer's fitness landscape, and hence its evolution. Here, we discussed the idea of cancer as the result of a dialectic cell-environment interaction. For the sake of simplicity, we restricted ourselves to analysing the impact of environmental changes in the cellular environment associated with ageing. Notwithstanding this limitation, the cellular environment also changes in response to the environment that is experienced at the organismal scale, a factor that affects cancer risk.[22] Further research will expound the interaction between the organismal and cellular environments and how it may shape the cell's behaviour and modulate between maintaining or destabilising multicellular cooperative architecture.

Cancer emergence can be understood in an integrative way by combining ecological and evolutionary concepts and tools, because, as we have discussed here, cancer cells are not isolated entities, and the multicellular ecosystem is not merely a collection of independent cells.[89] On the contrary, cell-environment and cell-cell interaction in the context of a microbiome, a biofilm or a functional multicellular organism are crucial in determining function and behaviour: no living entity exists in isolation. Ecology and evolution are quintessential to tackle the complexity of the human body ecosystem, understanding the emergence of the cancer phenotype within it, and in using this knowledge to reach a robust and multidisciplinary understanding of cancer onset and evolution.[85]

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CONFLICT OF INTEREST

All authors declare no conflict of interest. We are very thankful for the comments and suggestions made by the Editor in Chief Dr Andrew Moore and two anonymous reviewers.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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