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17 Patchwork narratives for tumour heterogeneity

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Abstract. Molecular biology, in particular post-genomics, is determining the proximal and the distal future of both biomedical research and clinical practice. Thanks to the advancements in understanding the molecular bases of diseases, we are drastically changing our approach to prevention, diagnosis and therapy. In particular, through recently available sequencing techniques, we have realised that each instance of cancer affecting a particular individual is actually composed of a set of different cancer subpopulations. This phenomenon, called *tumour heterogeneity*, is posing a tremendous challenge to biomedicine but also to philosophy. In this paper the notion of *patchwork narrative* is introduced in order to offer a philosophical framework for the description and the explanation of the many different events and processes ascribable to tumour heterogeneity and to its complexity.

Keywords: tumour heterogeneity, patchwork narrative, complexity, explanation, description.

1 Introduction

Molecular biology, in particular post-genomics, is an important game-changer that is determining the proximal and the distal future of both biomedical research and clinical

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practice.[1] Thanks to the advances in understanding the molecular bases of diseases –which makes individuals' genetic makeup, their life styles and the environments in which they live, amenable to systematic scrutiny– we have the promise to drastically change our approach to prevention, diagnosis and therapy.

These achievements, especially in the oncological field on which this paper is focused, have suggested to some that we are in the age of *personalized medicine*.[2] Nevertheless, despite its importance and novelty, personalized medicine seems to attract more researchers and clinicians, rather than patients. Indeed, understandably, the latter have shown much more interest in the "care" side of the matter, starting from the consideration that healthcare delivery should not be limited to disease treatment in a strict technical sense, but in the act of taking care of a human being as a whole (van Heist, 2011; Cornetta & Brown, 2013; Boniolo & Sanchini, 2016).

However, the passage from *personalized medicine* to *personalized care*, especially in the oncological field, is made more intricate by an aspect, that is, *tumour heterogeneity*, which so far has not been discussed sufficiently from an epistemological perspective (see Bertolaso, 2011; Germain, 2012; Plutynski, 2017; Fagan, 2017).

Tumour heterogeneity means not only that each cancer has to be individualised in a specific patient, but, more importantly, that each individual cancer affecting an individual is actually composed of a set of different cancer subpopulations. That is, cells belonging to the same cancer show distinct genetic and phenotypic characteristics (such as gene expression, metabolism, motility, and angiogenic, proliferative, immunogenic, and metastatic potential).

This fact, which emerged from recently available sequencing technologies and which is at the centre of an intensive biomedical research program[3], is posing a huge challenge to personalized medicine and thus to personalized care.

Needless to say, if we were able to provide a good epistemological analysis of this issue, we would be able to understand the core of contemporary biomedicine and its epistemic role in the fabric of knowledge. It is a task that we should undertake, if we want to comprehend the current status of biomedical research and clinical practice and

[1] Of course, these new ways of seeing disease and health should be at the core of the philosophers' attention (see Boniolo & Nathan, 2017). By *post-genomics* we usually refer to a research field that extends the domain of genomics (characterised, in particular, by genome sequencing, functional genomics, gene architecture) to include transcriptomics (the study of patterns of gene transcription), proteomics (the study of patterns of protein expression), metabolomics (the study of patterns of chemicals influencing our cellular biochemistry and metabolism), and, above all, epigenomics (the study of gene expression due to micro and macro-environmental inputs particularly affecting DNA methylation and histone modifications).

[2] It can be broadly defined as the tailoring of medical treatment to the individual patient's (especially genetic and epigenetic) characteristics, needs and preferences during all stages of care, including prevention, diagnosis, treatment and follow-up. See the *Report on Personalized Medicine* by European Science Foundation and the report *Paving the way for personalized medicine* by Food and Drug Administration and Golubnitschaja et al. (2016, 23).

[3] See the recent issue of *Nature* devoted to it (Vv.Aa., 2013).

if we want to be more aware of the vagaries that life could present whenever we are in the unfortunate role of patient or patient's relative.

In order to philosophically set the question, after a first survey on what tumour heterogeneity is and on what its clinical consequences are, I introduce the notion of *patchwork narrative*. This concept allows me to indicate how molecular oncologists describe and explain the extremely complex set of events and processes ascribable to tumour heterogeneity by resorting to conceptual terms belonging to other biological fields (in particular, evolutionary biology, developmental biology, ecology and stem cells biology). Then I present the main accounts of tumour heterogeneity in order to make clear their patchwork narrative structure. I conclude by discussing the reasons why speaking in terms of evolutionary, developmental, or ecological models is not satisfactory and why a patchwork account could be ideal to cope with the epistemological complexity of this biomedical field.

2 Tumour heterogeneity

Any multicellular organism shows cellular heterogeneity in its several compounding tissues. For example, in humans there are about 200 different types of cells. Nevertheless, such heterogeneity is guided by an ordered developmental program starting from the zygote's single initial genome and governed by a proper coordination of dynamic signal transduction and then by long-term maintenance of gene expression patterns due to epigenetic mechanisms. These processes ensure a balance between cells capable of continuous self-renewal or remaining in stem-cell-like states and their progenies committed to tissue lineages and differentiation. The same processes occur, more or less, in a neoplastic tissue but in that case, we do not have the initial developmental program starting from the genome and resulting in ordered structures. Instead, the neoplastic process results in a complex situation—*tumour heterogeneity*—that is difficult to describe and to explain and even more difficult to clinically treat.

It is important to recall that since the advent of cancer nosology, an organ based classification system has been used with good success in clinical practice and research. Thus, for a long time we have spoken about breast cancer, lung cancer, prostate cancer, liver cancer, etc. With the development of molecular technologies, both genetic (e.g., KRAS mutation for colon and lung cancer; EGFR mutation for lung cancer; BRAF mutation for colon cancer and melanoma) and epigenetic (e.g., DNA methylation alterations) biomarkers have began playing a major role both in the diagnostic phase and in the drug discovery process that could lead to new therapies (see Febbo et al., 2011; Baylin & Jones, 2011; Boem, Pavelka, & Boniolo, 2015). But the introduction of extensive sequencing technology has revealed the genetic and epigenetic heterogeneity among tumours and, thus, not only that there are no two identical tumours, but that not even two samples from the same patient's cancer are exactly the same. So, step-by-step, we have understood that cancer is not a single disease, rather that any cancer is a "different disease", and that in the same cancer actually we have

"many cancers", each with its own histopathological and biological features.

In a slogan, as any individual human being is unique (Boniolo & Testa, 2012; Boniolo, 2013a), so any tumour is unique, or, rather, any tumour cell population in an individual tumour is unique.

Such uniqueness has two facets: the *intertumour heterogeneity* (the variability occurring between tumours arising in the same organ) and the *intratumour heterogeneity* (the variability occurring in the same individual tumour) (see Burrell, McGranahan, Bartek, & Swanton, 2013).

In what follows, I will focus my analysis particularly on intratumour heterogeneity, since it is the more relevant from a research and clinical point of view and the one which necessitates a more accurate epistemological investigation.

Before beginning, it is worth recalling two pairs of notions that will help understanding what follows. The first pair is the *cell-of-origin* and the *cancer stem cell* (CSC). By the former we intend a normal cell that acquires the first cancer driven mutation. The latter is a cell that possesses the characteristics usually associated with normal stem cells, that is, self-renewal (which, in our case, produces daughter cancer stem cells) and potentiality (which, in our case, begets sub-type cancer cells).

The second pair has to do with *spatial heterogeneity*, indicating that different regions of a tumour present different series of genetic aberrations, and *temporal heterogeneity*, referring to the course of disease progression (see Geyer et al., 2010; Torres et al., 2006; Martelotto, Ng, Piscuoglio, Weigelt, & Reis-Filho, 2014). Concerning this latter aspect, one should note that heterogeneity within primary tumours is only one of the many aspects of cancer heterogeneity. Cancer is a systemic disease: over time, malignant cancers shed a large number of cells into the blood stream and lymph vessels; some of these cells find a place in distant sites and develop into metastases. Therefore, to have a really complete understanding of cancer heterogeneity we should also understand metastatic tumours, which, as is known, are the most fearsome aspects, since they are responsible for the majority of cancer-related deaths.

3 Clinical relevance

Needless to say, spatial and temporal heterogeneity –that is, inter and intratumour heterogeneity and heterogeneity between primary and metastatic lesions– have profound implications for patient care (Bedard, Hansen, Ratain, & Siu, 2013, see).

Concerning the diagnostic aspect, heterogeneity poses a challenge to personalized cancer medicine because a single needle biopsy, or a single surgical excision, almost never accurately captures the complete genomic landscape of a patient's cancer. One might think that serial tumour sampling, at crucial times, may help to monitor the temporal heterogeneity. In many cases, however, this multiple sampling is not clinically feasible. On the other hand, heterogeneity also involves clinically relevant

biomarkers. This means that, due to genetic differences within and between tumours, biomarkers that may predict treatment responses or prognoses vary from situation to situation.

Concerning therapies, the extent of heterogeneity observed in various cancer types suggests we need a new paradigm for thinking about how they should be delivered. Heterogenic tumours may exhibit different sensitivities to cytotoxic drugs among different clonal populations (see Yap, Gerlinger, Futreal, Pusztai, & Swanton, 2012). This is attributed to clonal interactions that can inhibit or alter therapeutic efficacy. Thus, drug administration in heterogenic tumours, even if it results in initial tumour shrinkage, seldom kills all tumour cells. The initial tumour population can bottleneck, such that few drug resistant cells can survive.[4] This allows resistant tumour populations to replicate and grow a new tumour, which is resistant to the initial drug therapy and sometimes even more aggressive (see Sequist et al., 2011; Turner & Reis-Filho, 2012; Landau et al., 2013) (see **Figure 1**, from Kleppe and Levine, 2014).

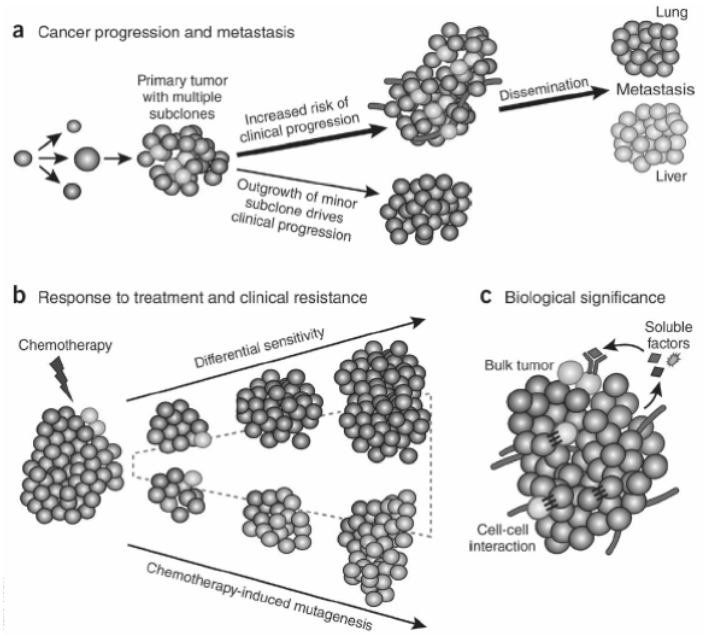

Figure 1.

[4]For example, *temozolamide*, the standard first-line therapy for glioblastoma multiforme, induces mutations in tumour DNA. Some are deleterious for the cells and result in death, others neutral and act as passenger mutations, but others such as mutations in mismatch repair genes are potentially advantageous for tumour cells (see Johnson et al., 2014). *Imatinib mesylate* is the gold standard of treatment of chronic myeloid leukaemia. Although response rates to imatinib are high at 5 years, approximately 6% of patients progress to the accelerated phase and 3% have a haematological relapse (see Druker et al., 2006).

4 The patchwork narrative

Given this brief introduction on tumour heterogeneity, let us move on to the philosophical tool I wish to introduce.

In order to describe and explain scientific events and processes, we need a particular kind of *narrative*, which, depending on the specific field, takes different forms. Here by 'narrative' I mean a form of human discourse that, more or less coherently, communicates something about something. Thus, a 'scientific narrative' communicates something, which should be epistemologically valid, about a given piece of nature, also by offering a representation of it. Different scientific fields allow for different kinds of scientific narratives. Just as there is the research field of gravitation, there is also the research field of tumour heterogeneity. But while a narrative concerning gravitation has the form of a theory (i.e., the theory of gravitation), it seems that this is not true of tumour heterogeneity: we do not have any theory of tumor heterogeneity. Maybe here 'theory' could be used in a very loose and non-technical manner, but without any strong epistemological commitment concerning its logical structure and its predictive power. On the other hand, we know that the question of whether there are theories in biology and medicine has a long and controversial history, recently revamped (Pigliucci, Sterelny, & Callebaut, 2013).

Nevertheless, even if we do not have a theory of tumor heterogeneity, we need some kind of narrative in this field, since we have to describe and explain why there is such a genotypic and phenotypic diversity among the neoplastic cells of a single tumour, or among those of a primary tumour and those of its metastatic products. In order to do this we have to consider a matter of great great complexity, both from a spatial and a temporal point of view, involving both differences among cellular populations and intricate intersecting probabilistic causal pathways where genes, proteins, chemicals, intrinsic and extrinsic cellular properties[5], etc. have a role. It is not important here to address the problem of whether this extreme ontological complexity has to be considered in a metaphysical way –that is, as something pertaining to the real nature of tumors, or just epistemically –that is, as something concerning our level of knowledge of what tumors are and of how they develop. What is at stake is the fact that we have to describe and explain such a complexity in the most accurate and reliable possible manner. This is not merely of philosophical interest, and not even a sheer matter of scientific curiosity, but a practical need since we want to cure actual, and to take care of potential, patients affected by cancer pathologies.

[5]By *cell intrinsic properties* we mean the properties related both to the genetic mutations driving the primary tumour formation (for example, HER2, or BRCA1 and 2 mutations for breast cancer), and to the alterations of the epigenetic landscape (disruption of DNA methylation, histone modification, and chromatin compartments). Instead the *cell extrinsic properties* concern the usual interactions between cells (in this case cancer cells) and the surrounding microenvironment, connected with the recruitment of both endothelial cells to generate the blood supply for the developing tumour and other stromal cells (inflammatory cells, fibroblasts, pluripotent mesenchymal stem cells, etc.).

We could think pluralistically that in the field of tumour heterogeneity we have a narrative realised by a set of different phenomenological models, each of which is able to grasp a particular aspect.[6] This may resemble what happens in population genetics or nuclear physics. We know that there is no theory of population genetics as a whole and (for totally different reasons) that there is no theory of nuclear physics as a whole. Instead, we have a set of (more or less mathematized) phenomenological models able to describe and explain events and processes belonging to the field of population genetics (see Hartl & Clark, 2007; Ewens, 2004) and, similarly, we have a set of (mathematized) models able to describe and explain events and processes belonging to the field of nuclear physics (see Boniolo, Petrovich, & Pisent, 2002). Nevertheless, the narratives concerning both population genetics and nuclear physics have their own language, with their own conceptual terms on (or by means of) which the (more or less mathematized) phenomenological models are constructed. But this does not happen with tumour heterogeneity. As I will show in the next sections, in order to describe and explain events and processes, each researcher constructs a peculiar narrative borrowing concepts from other biological fields, mainly evolutionary biology, developmental biology, ecology, and stem cell biology.

Certainly, as could be easily observed by reading the literature, there are molecular oncologists constructing narratives in terms of an 'evolutionary/Darwinian model of tumour heterogeneity', 'cancer stem cells model for tumour heterogeneity', 'ecological model for tumour heterogeneity', etc. Actually, they are using the term 'model' in a very loose way. As far as I know, in none of their papers is there an analysis of what a model is, or an indication on what they mean by 'model'. On the other hand, the fact that they use a philosophically (epistemologically) loaded term like 'model' implies neither that they use it in a technical sense, nor that they recognize the need to clarify in which sense they are adopting it. They simply use it in an "epistemologically relaxed" way, as has happened with terms like 'information', in the field of coding DNA, or 'mechanism', especially in molecular biology (see Boniolo, 2003, 2013b). And, I think, nothing should hinder this way of proceeding. They are not philosophers of science and they are not publishing in philosophical journals.

The same problem attaches to their narratives: molecular oncologists claim that the latter are evolutionary/Darwinian, or developmental, or ecological. Certainly, what they are providing could have a certain *Familienähnlichkeit* with an evolutionary/Darwinian account, or with a stem cell account, or with an ecological account. But, as we will see, it is just a *Familienähnlichkeit*.

This points have induced me to introduce the idea of *patchwork narrative*. By this

[6]There is an extremely long (and well-known) story about what a model is and about what are (if there are) the differences between a theory and a model. There is also a long story about different taxonomies of models in different scientific fields. Of course, it is not worth entering now such a topic (see Boniolo, 2007). For the sake of what I am discussing here, it suffices to speak in terms of 'phenomenological models', intended as those models constructed by the researchers in order to *save the phenomena* in a given domain in which there is no theory available.

concept I mean a scientific narrative which is not a theory (in any technical sense), not even a model (in any technical sense) or a set of models, but a descriptive and explanatory discourse which, by borrowing conceptual terms (the "pieces of the patchwork") belonging to evolutionary biology, developmental biology, stem cells biology, ecology, etc., offers a logically coherent and epistemically valid view of a given aspect of tumour heterogeneity.

Let us see if and how this philosophical idea really works. In order to accomplish this, I will review the main narratives adopted to describe and explain events and processes concerning (intra)tumour heterogeneity. Then, I will return to philosophy.

5 Describing and explaining intratumour heterogeneity

As mentioned, by *intratumour heterogeneity* we mean the complex coexistence of subpopulations of cancer cells that differ in their genetic and phenotypic characteristics within a given primary tumour, and between a given primary tumour and its metastases. In order to describe and explain it, four main narratives have been offered: (i) *the clonal evolution narrative*; (ii) *the cancer stem cell narrative*; (iii) *the cell plasticity narrative*; (iv) *the ecological narrative*.

5.1 The clonal evolution narrative

The clonal evolution narrative was brought to wide attention in the Seventies (see Cairns, 1975; Nowell, 1976; Attolini & Michor, 2009; Polyak, 2014). It is based on the idea that cancer cells evolve progressively during multistep tumourigenesis and heterogeneity is caused by heritable genetic and epigenetic changes, which form the material for the selection and the clonal development of novel cell populations.

Tumours arise from a single mutated cell (the cell-of-origin) and accumulate additional mutations as they progress. Such mutations give rise to additional subpopulations, each of which has a different ability to divide and mutate further. As a consequence, there could be subclones possessing an evolutionary advantage over the others within the tumour microenvironment, and these subclones may also become dominant in the tumour over time. It is important to note, however, that the generation of variants can occur more rapidly than the elimination of less-fit clones, resulting in an increase of heterogeneity.

Already from this, it is evident that such a narrative borrows its jargon mainly from evolutionary biology: the evolution concerns cancer cells and the selection pressure is given by the tumour microenvironment.

For the sake of simplicity, tumour evolution is often described as a *linear succession of clonal expansion rounds*, where every new step is driven by the acquisition of an

additional mutational event, which leads to a new selective situation (**Figure 2a**, from Marusyk and Polyak, 2010).

However, this linear representation does not reflect the dynamics of any tumour evolution, even if it has been observed in multiple myeloma and in acute myeloid leukaemia. More common appears to be a so-called *branched-evolution*, found in many tumours (breast, ovarian, prostate, pancreatic, and bladder cancers, as well as in chronic lymphocytic leukaemia, multiple myeloma, acute myeloid leukaemia, glioma and clear cell renal cell carcinoma) (**Figure 2b**, from Marusyk and Polyak, 2010). Here, random mutations are constantly produced as a result of both proliferation and increased genomic instability and then tested by selection. Concerning these mutations, only a minority of them is selectively advantageous, while the majority is discarded by selection. Nevertheless, there are many neutral or even slightly disadvantageous mutations that can be retained and even undergo some expansion due to genetic drift. These are the so-called *passenger mutations*, which are acquired as incidental by-products of the cancer cells' high mutability (they are the *hitchhiker mutations* of the evolutionary account; see Greaves and Maley, 2012).

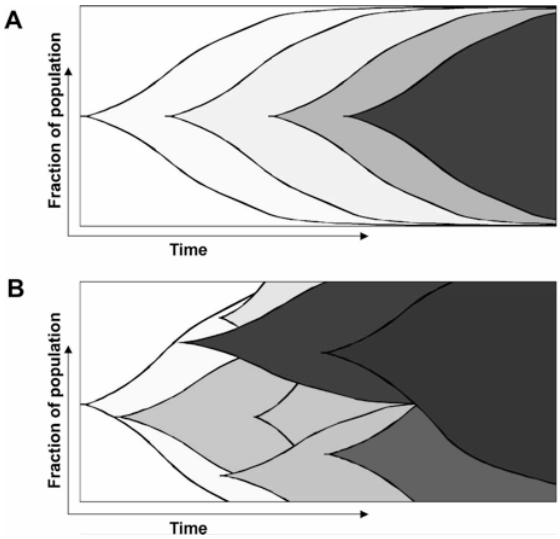

Figure 2.

As the selective pressure changes, for instance, between the microenvironment of the primary and metastatic site or due to the administration of systemic therapies, a different set of mutations may become advantageous. The presence of differential selective pressures can, therefore, cause subclones to diverge, generating additional intratumour heterogeneity. Moreover, since selection is context-specific and blind to the future, some of the mutations that are selectively advantageous at certain stages of tumour progression may lead to evolutionary dead ends and, therefore, cannot be present at a successive time.

It should also be noted that in addition to genetic alterations, epigenetic events could be heritable and subject to selection. But the complexity of tumour evolution is further influenced by the continuous variation of the tumour microenvironment, which alters the selective pressures on tumour cells.[7]

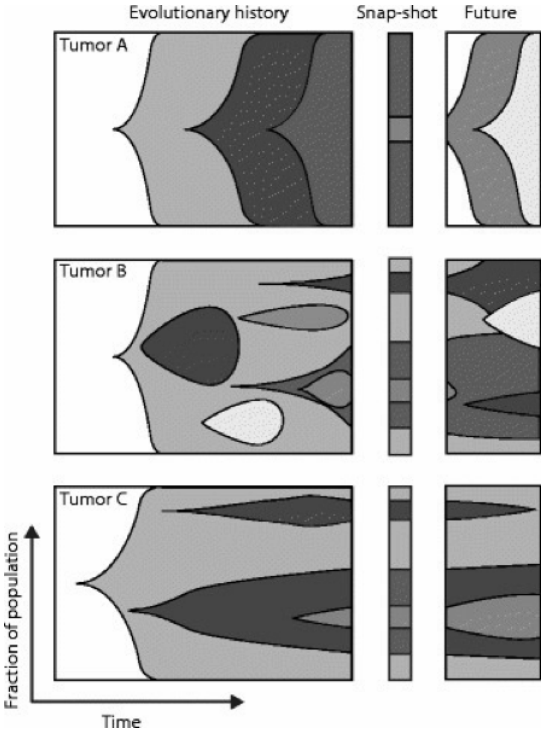

Figure 3. *The left panel shows the evolutionary history of a tumour; the central panel represents a snapshot of the tumour at a given time; the right panel shows the potential future development. Tumour A shows a linear evolution pattern; tumours B and C show a branched pattern. Single snapshots of tumours B and C could suggest that they have identical evolutionary processes, but their past and future evolution actually follow different patterns.*

Note that the subclonal diversity within a tumour if viewed as a snapshot, rather than longitudinally, provides little information about the future evolution paths that the tumor and its cellular populations might take. On the other hand, as already noted above, the acquisition of mutations is a stochastic process, and it is blind to the future.

[7] In addition, there could a change of tumour cell populations over time due to the *epistatic relationships* that there are among the effects of driver mutations (see Weigelt & Reis-Filho, 2014). Generally speaking, in genetics by *epistasis* we mean that the effect of more genes together is different from the effect of each one considered individually (see Cordell, 2002; Phillips, 2008).

All of this implies a lot of difficulties for clinicians in prognosticating what will happen to that particular patient in the near and more distant future. (**Figure 3**, from Hiley, de Bruin, McGranahan, and Swanton, 2014).

5.2 The cancer stem cell narrative

The concept of *cancer stem cell* (CSC) was proposed to describe and explain heterogeneity of cancer cells more than three decades ago (see Dick, 2008). However, it emerged as a mainstream idea only recently, initially for hematopoietic neoplastic phenomena (Lapidot et al., 1994). Then, it was expanded to solid tumours, such as breast cancer (see Al-Hajj, Wicha, Benito-Hernandez, Morrison, & Clarke, 2003; Visvader & Lindeman, 2008).

The CSCs narrative proposes that, within a given tumour, a phenotypic hierarchy exists, with a minor subset of the CSCs at the apex and highly proliferating, lineage-committed progenitors and terminally differentiated cells at the base. This means that tumour growth, disease progression and heterogeneity generation are driven by a small population of tumor cells, while the vast majority do not contribute and would be unable to regenerate a tumour after a successful therapeutic intervention. In principle, CSCs could self-renew indefinitely, drive growth and differentiate into virtually all cancer cell types, thereby producing heterogeneity. On the other hand, progenitors and terminally differentiated cells should be highly proliferative, display lineage commitment, have limited proliferative potential[8] and very poor capacity to contribute to disease progression.

However, the existence of CSCs is under debate. One reason is that is not easy to reproduce markers for CSCs across multiple tumours. Moreover, in order to determine tumourigenic potential, we utilize xenograft models. Unfortunately, these methods suffer from limitations such as the need to control immune response in the transplant animal, and the significant difference in environmental conditions between the primary tumour site and the xenograft site (see Quintana et al., 2008; Anderson et al., 2011; Meacham & Morrison, 2013). This has raised some doubts about the accuracy and the relevance of the results concerning CSCs. Further, the CSCs hypothesis is disputed given the evidence showing the existence of a dynamic equilibrium between differentiated cells and CSCs (Gupta et al., 2011). It seems not only that CSCs can differentiate into terminally differentiated cells, but terminally differentiated cells can also de-differentiate into a CSCs state. This means that, in some contexts, the CSCs phenotype may represent a state that cancer cells within a tumour can acquire rather than an isolated population of cancer cells that constantly exhibit those properties. Moreover, the difficulty in replicating solid-CSCs markers, the variability from patient to patient, and the dissimilarity in results from different xenograft models have

[8]The cellular division is linked to the so-called *Hayflick's limit* (see Hayflick, 1965).

made it even more unclear which cancers can be positively grasped with this approach (Magee, Piskounova, & Morrison, 2012).

5.3 The cell plasticity narrative

The two approaches above might not be mutually exclusive. For example, a driver mutation could occur in a cell with stem cell properties. Or a mutation might promote cancer stemness by reprogramming a cell that lacked this potential before (see Visvader, 2011). The *cell plasticity narrative* develops this idea.

It is an approach, mixing the evolutionary jargon and the stem cells jargon, according to which cancer heterogeneity is due to a series of processes concerning different cell populations in which committed, non-stem cells and non-CSCs can undergo a de-differentiation program and re-enter the cancer stem state (**Figure 4**, from Marjanovic, Weinberg, and Chaffer, 2013).

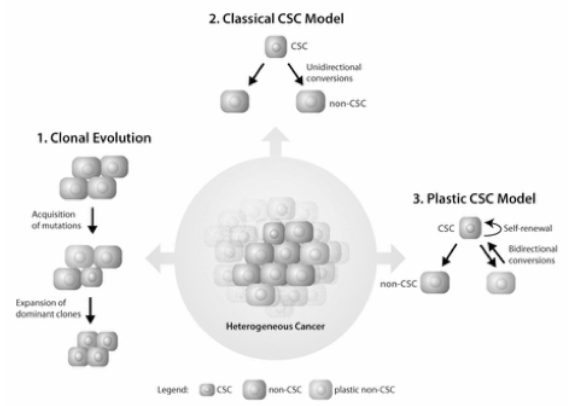

Figure 4.

Note that epigenetic variation might be one of the changes contributing to cellular plasticity. On the other hand, this would be an additional factor in countering the strictly hierarchical hypothesis of the existence of CSCs as a stable and isolated population (see Easwaran, Tsai, & Baylin, 2014).

5.4 The ecological narrative

We know that the tumour microenvironment is a highly heterogeneous mix of cellular and non-cellular components, consisting of the extracellular matrix, vasculature, fibroblasts, smooth muscle cells, immune cells, nerves, and proteins in the immediate extracellular environment. As briefly described, it plays a major role in heterogeneity, since it is the selective agent.

There is not only a one-way direction: from the microenvironment to the tumour; but the reverse pathway also occurs: from the tumour to the microenvironment. Any tumour creates its own particular microenvironment, and since any tumour is unique, due to its heterogeneity, each microenvironment is unique. On the other hand, any microenvironment selectively acts differently on tumour cells, and since any microenvironment is unique, any selective action is unique (see **Figure 5**, from Ungefroren, Sebens, Seidl, Lehnert, and Hass, 2011, 1). Moreover, the tumor microenvironment is modified by drug therapies, but different microenvironments allow for a different efficacy of drug therapies (Junttila & de Sauvage, 2013). Starting from these considerations, there are many molecular oncologists who have elaborated narratives, by borrowing concepts from ecology and by emphasising the idea of *niche construction*, based on a strong mutual causal relation between tumour heterogeneity and tumour microenvironment (see Odling-Smee, Laland, & Feldman, 2003; Merlo, Pepper, Reid, & Maley, 2006; van Dijk, Göransson, & Strömblad, 2013; Barcellos-Hoff, Lyden, & Wang, 2013; Yang et al., 2014; Chen et al., 2015; Kareva, 2015; Amend & Pienta, 2015).

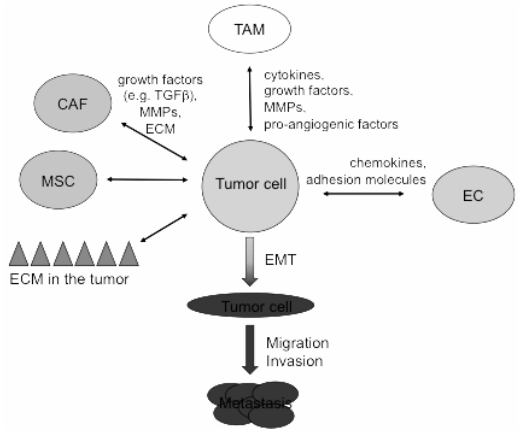

Figure 5. *Mutual interactions between tumour cells and the extracellular matrix (ECM), tumour-associated macrophages (TAM), carcinoma-associated fibroblasts (CAF), mesenchymal stem cells (MSC), endothelial cells (EC).*

6 The patchwork narrative and its competitors

As seen, many scientists working on tumour heterogeneity speak of an evolutionary, or developmental, or ecological model. Unfortunately, there is no indication of the criteria to be satisfied in order that those accounts could be really considered as such. This mission has been taken by some (not so many) philosophers who have exercised their analytical expertise exactly on this point.

One of the first (if not the first) works facing tumour heterogeneity from a philosophical perspective was a paper in which the author argued that the 'Darwinian (or evolutionary) model' is not Darwinian (or evolutionary) in a paradigmatic sense (Germain, 2012).

Germain first recalled the characteristics which should be satisfied in order for a population to be considered "Darwinian". Then he showed that among the events and processes ascribable to tumour heterogeneity, there were some that could not exactly satisfy those criteria. Note that Germain had many possibilities of identifying the set of characteristics considered as individuating a real Darwinian population, and therefore a real Darwinian model. Instead of choosing among the evolutionary biologists' proposals (for example, that one suggested by Mayr, 2002 or by Ridley, 2007), he decided for a philosopher's account, that is, the one indicated by Godfrey-Smith (2009). According to Godfrey-Smith, a population in order to be Darwinian should be characterised by (i) fidelity of heredity; (ii) abundance of variation; (iii) continuity, or smoothness, of the fitness landscape; (iv) dependence of reproductive differences on intrinsic characters; (v) reproductive specialization; (vi) integration, or the extent of mutual dependence. Germain showed, by resorting to the scientific literature, that although cancer population meets these requirements to some degree, and can therefore be considered minimal Darwinian populations, they do not quite qualify as paradigmatic Darwinian populations:

> Let us now summarize our evaluation of cancer cells. Cancer cells have sufficient variation for evolutionary change, and although their relatively low fidelity of heredity might threaten the possibility of complex adaptation, it is generally in the range compatible with minimal Darwinian processes. However, cancer cells display a level of integration reminiscent of organs, and share reproductive fate to an important extent. Much of the fitness differences between cells does not depend on their intrinsic features, which strongly suggests that these differences cannot be the basis for paradigmatic Darwinian processes. Perhaps the most crucial dimension, the degree of reproductive specialization will vary from case to case, depending on the extent to which a given cancer follows a CSC model. When it does, long-term proliferation will be restricted to a tiny subpopulation of the tumour, rendering most cancer cells unable to accumulate evolutionary changes [. . . Therefore c]ancer cells are at least minimal Darwinian populations [that is, there are heritable variations in fitness], but not paradigmatic ones. (Germain, 2012.)

This perspective has recently been challenged by Lean and Plutynski (2016). They claim that Germain is not wrong but that his view is too narrow since he does not take into account a "multilevel evolutionary perspective" (see Sober & Wilson, 1998; Okasha, 2006), especially in the formulation offered by Damuth and Heisler (1988). Here there are some points to be noted. First, this perspective is not totally shared both among the scientists and among the philosophers, even if, honestly, this fact is

not so important for what is here on the stage.[9] Second, Lean and Plutynski do not show that each of Germain's counter-examples to the evolutionary model of tumour heterogeneity is really graspable by the multilevel evolutionary perspective. Third, they assert that "this multi-level perspective provides a representation of cancer progression that is both predictive and explanatory. The accumulation of mutations (and epigenetic changes) in neoplastic progression involves heritable variation in fitness of cancer cells and lineages, e.g., timing and acquisition of particular mutation types, chromosomal instability, hypoxia, acid resistance, transition to mesenchymal phenotype. Cancer progression involves several transitions in individuality and levels of selection, and, is a unique case of multi-level selection: it evolves at the level of populations of cells, competition among cell lineages, via cooption, a kind of cross-level exaptation, and as a group, or higher level individual" (Lean & Plutynski, 2016, p. 52). In reality, they show that some events and processes ascribable to tumour heterogeneity can be coopted by a multilevel evolutionary account. Nevertheless, as we know, this does not mean that such an account is epistemologically useful in general, but only that it is epistemologically useful in grasping those particular items. Moreover, I have some doubts about "predictability". If they were right, the difficulties indicated towards the end of section 5.1 above (and depicted in Fig. 3) would not exist and the clinical prognosis of any tumour would be easy and sure. Unfortunately for the patients, this is not so.

Certainly, and I could agree with Plutynski (2017), there are no "devastating objections to the evolutionary perspective on cancer", even if she herself concedes that cancer cells do not have the same heritable variation in fitness and the same level of adaptation of other living beings. Nevertheless these objections exist and they weaken the claim that we have an evolutionary model for cancer heterogeneity.

There is another point that is worth mentioning. Speaking in favour of an evolutionary model, it has been said that even if the cancer cells have a short life (due to the death of the host, or to their –fortunate for the host— total elimination due to a working therapy), there is the case of the canine transmissible venereal tumour and of the *in vitro* cancer cells, like the famous HELA cells.[10] These should be examples of immortal, or at least long living, cancer populations. Actually the canine transmissible venereal tumour is one of the very few examples of non-viral transmissible cancer, that is, cancer transmissible but not by oncoviruses or cancer bacteria (others are the Tasmanian devils' facial tumour disease; the Syrian hamsters' contagious reticulum cell sarcoma; the soft-shell clams' neoplasm of the hemolymphatic system). It is important to note that they are transmitted from non-humans to non-humans and that they happen very rarely in humans and in a totally different way.[11] Given their rarity and particularity, instead of being considered as a good proof of the long life of cancer cells and thus

[9] For a first hint on the debate, see http://edge.org/conversation/the-false-allure-of-group-selection.

[10] These are immortalised cancer cells derived from a cervical cancer of a woman, Henrietta Lacks, who died of her tumor in 1951 (see Skloot, 2010).

[11] In the literature, very few cases between humans are reported, for example, Gärtner et al. (1996).

as an argument in favour of an evolutionary model, I would consider them as one of many aspects of the complexity of the phenomenon 'cancer', especially considering the fact that species with different genotypes do have or do not have (as it happens in naked mole rats) peculiar cancerogenous manifestations. Concerning the immortalized *in vitro* cancer cells, there is a misunderstanding. The *in vitro* cancer cells (and we have dozens of different varieties of these cancer lines, which are now commercialised for the benefits of the researchers) have almost nothing to do with the real *in situ* cancer cells or with the primary tumour cancer cells, as I discussed elsewhere (Boniolo, 2017).

As seen above, beyond the evolutionary account, there is also the CSCs account. This could be a problem for those who think that the evolutionary model is enough. Nevertheless, Plutynski (2017) claims that there is no reason to consider the CSCs as a counterexample, since instead of considering one single evolving lineage starting from a cell-of-origin, one should think in terms of many evolving cell lineages. She grounds this observation on a paper by Sprouffske and colleagues (2012). Actually, as we know from the Popperian debate on this topic in the Seventies, every counterexample can be inserted in any theory by *ad hoc* modifications. But we know, from that old classical debate, that such a modified account should be empirically more powerful than the unmodified account and it seems to me that neither Sprouffske and colleagues nor Plutynski have provided such a proof.

This mention to stemness and tumours allows me to move to the CTCs "model". As far as I know, among philosophers only Laplane (2014) and Fagan (2017) have offered a view on this issue. I focus on Fagan, since, on the one hand, her conclusions are more or less similar to Laplane's and, on the other hand, her account is more interesting for my aim to show how weak an account can be in terms of CSCs and 'model'.

First of all, while the approach above interpreted tumour progression as an evolutionary process, this reads it as a developmental process starting from an initial cell characterized by stemness. Fagan, honestly, admits that it is not so clear what a 'CSCs model' is. She is not thinking about the 'model' part of that locution (as said, no one tells us in which sense he/she is using the term 'model'). Instead she wants to show the ambiguity of that locution as a whole. She says that, in reality, there is a "minimal model" characterised by two features: "(i) cells comprising a tumour are heterogeneous in phenotype and function; and (ii) these patterns of variation map onto a hierarchical lineage structure, with more tumourigenic cells giving rise to less tumourigenic, more differentiated, progeny". Actually, these two features work well also for a possible evolutionary model, as seen above, since they describe two of the main aspects of tumour heterogeneity in general. Moreover, surprisingly enough, the two usual features of stemness (self-renewal and potency) are not mentioned for this minimal model! But let us move on. Fagan proceeds to schow that different authors add different features to the minimal set above. In particular, it could be added that CSCs (iii) are rare within tumours; (iv) are more likely to survive cancer therapy than other tumour cells; (v) either acquire or inherited that molecular characteristic of stemness that protect them from anti-cancer drugs; (vi) divide at a low rate; (vii) exhibit gene expression

patterns associated with pluripotency and long-term self-renewal; (viii) derive from a cell-of-origin which is a normal stem cell.

Of course, this means that we do not have just one "model" but many "models", each one characterised by a different set of assumptions added to the "minimal" two. This implies that each one should be articulated differently and therefore be capable of describing and explaining different ensembles of events and processes ascribable to tumour heterogeneity.

There are, however, two other aspects highlighted by Fagan that deserve attention. The first is that some of the assumptions just mentioned do not have adequate empirical support. The second is that any CSCs "model" underestimates events or processes which can be grasped only evolutionarily or by emphasising the role of the tumour microenvironment. That is, none seems to be completely empirically adequate and epistemologically powerful.

With reference to tumour microenvironment and its correlated concepts, while we have (even if very few) philosophical analyses of the evolutionary approach and of the CSCs approach, we do not have, as far as I know, any philosophical analysis of the ecological approach and of its use of the niche construction concept.

Summing up, we have, on the one hand, scientists who speak loosely about evolutionary models, CSCs models, ecological models and, on the other hand, philosophers who argue for the epistemological relevance of the evolutionary "model", or for the CSCs "model" (but not for the ecological "model"), without telling us why it should be a model and without being able to argue for their epistemological capability to exhaustively describe and explain all the facts belonging to tumour heterogeneity. But, more importantly, we have a field, i.e. tumour heterogeneity, whose complexity, maybe due to lack of knowledge maybe due to intrinsic features, is so great that no account alone seems to be able to describe and explain comprehensively. Instead we have molecular oncologists who use terms like heritable genetic and epigenetic changes, selective pressure, evolutionary advantage, less-fit clone, driver mutation, passenger mutation, random mutation, genomic instability, neutral mutation, disadvantageous mutation, genetic drift, developmental program, linear and branched evolution, cellular phenotypic hierarchy, cellular differentiation and cellular de-differentiation, lineage commitment, niche construction, etc. By means of these concepts, borrowed from evolutionary biology, developmental biology, CSCs biology and ecology, they construct what I have called *patchwork narratives*, which allow them to describe and explain a certain set of events and processes in a logically coherent and epistemologically valid way.

More precisely, each paper contains a phenomenological patchwork narrative on a particular aspect of tumour heterogeneity. Such a patchwork narrative can be more evolutionary, or more developmental, or more ecological, depending on the particular situation to be coped with and depending on the particular researcher's perspective. But none is exhaustive; none is able to cover all the aspects of the complexity of tumour heterogeneity. On the other hand, if we really wanted something fully compre-

hensive, we should collect all the narratives contained in all the papers. In such a way we would have a sort of big patchwork narrative which is able to grasp all the known aspects of tumour heterogeneity and where the compounding narratives frequently intersect or superpose, sometimes using the same jargon sometimes using a jargon borrowed from different biological fields. Nevertheless, while each single patchwork narrative contained in a paper is logically coherent and epistemically valid, this big patchwork narrative as a whole is epistemically complex, superabundant and sometimes also logically incoherent. However, it is surely phenomenologically extremely useful, if only because it is what we have now!

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