RESEARCH ARTICLE

Finding Normality in Abnormality: On the Ascription of Normal Functions to Cancer

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Abstract

Cancer biology features ascriptions of normal function to cancer. Normal functions are activities that parts of systems, in some minimal sense, should perform. Cancer biologists' ascriptions pose difficulties for two main approaches to normal function, leaving a gap in the literature. One approach claims that normal functions are activities that parts are selected for. However, some parts of cancers have normal functions but aren't selected to perform them. The other approach claims that normal functions are part-activities that are typical for the system and contribute to survival/reproduction. However, cancers are too heterogeneous to establish what's typical across a type.

Word Count: 4996

1. Introduction

Cancer biology features the ascription of normal functions to parts of cancers. Normal functions are activities that parts of biological systems are, in some minimal sense, supposed to perform. In this paper, I argue that the ascription of normal functions to parts of cancers poses difficulties for the two main approaches to normal function in the philosophy of biology. One approach claims that normal functions are activities that the function-bearing part of a system is selected to perform. I identify these with selected effects accounts. The problem with selected effects accounts is that at least some parts of cancers that have normal functions aren't selected to perform those functions. The other approach claims that normal functions are activities by which the function-bearing part (typically) contributes to the survival or reproduction of the system. Following Garson ([2016](#)), I call these "fitness-contribution accounts." The problem with fitness-contribution accounts is that cancers aren't uniform in the way required to establish what (typically) contributes to their progression. The failure of both approaches leaves open a gap in the literature on function in the philosophy of biology. Though I don't attempt to close the gap in this paper, I claim that the ascription of normal functions to parts of cancers is legitimate on the grounds that ascribing normal functions to cancers provides therapeutic benefits in so far as it allows cancer biologists to identify standard activities, dispositions, and structure of parts of cancers that can be undermined by clinical intervention. I claim that one countervailing intuition, namely, that normal functions

should be reserved for the activities of healthy tissue, is the result of conflating what is normal with what is healthy.

In §2, I briefly discuss different types of function and introduce function pluralism. In §3, I present a representative example of cancer biologists ascribing a normal function to a part of a cancer. In §4, I briefly consider two philosophical approaches to normal function and raise difficulties for them in explicating the ascription of normal functions to parts of cancers. I conclude in §5 by considering an objection to the claim that cancer biologists ascribe normal functions to parts of cancers.

2. Normal Function and Function Pluralism

Function ascription is pervasive in biology. To a first approximation, functions are activities[1] that parts[2] of biological systems perform and that, by being performed, contribute in some way to those systems (*cf.* Weber, 2017). Consider the philosopher's favorite example: the function of the heart is to pump blood. This ascription tells us, first, that hearts (should) pump blood and, second, that pumping blood contributes in some way to biological systems with hearts, for instance, by transporting nutrients and waste to and from various tissues in the body. Ascribing a function explains by drawing our attention to the dispositions and structural features of systems that are or are supposed to be causally relevant for system-level phenomena of interest. Biologists are keen to understand how and why biological systems persist and propagate. Functions are indicative of how those systems do so and, often, why they have those dispositions and features which, in the good case at least, allow them to do so.

Different types of function are ascribed in different subdisciplines of biology. Take cladistic systematics, the branch of biology that studies common descent and changes in phenotype as a function of descent. When studying a phenotypic trait, systematists ascribe a function to the trait either to mark continuity in the activity performed by that trait with that of traits in ancestral systems or as evidence of innovation in that trait or its activity (Griffiths, 2006). For instance, a systematist might ascribe to the tail of *Crocodilus* the function of propelling the animal through its aquatic habitat in recognition of the fact that its ancestor, *Mystriosuchus*, made the same adaptive use of its archosaur tail (Griffiths, 1994, 218-219). Or the systematist might ascribe to the carapace of *Proganochelys* (a genus of proto-turtle) the function of protection in recognition of its novelty as a trait. In this case, functions are activities that traits perform. Their ascription does not necessarily tell us what a trait is supposed to do, only what it does or did or the causal role it plays or played.

By contrast, take physiology, the branch of biology which is said to study the normal functions of parts of organisms (Roux, 2014, 2245). When physiologists say of the heart that its function is to pump blood, they do so in full awareness that not all hearts pump blood. In this case, the functions referred to as normal are normative in the minimal sense that they embody a standard for trait activity (Roux, 2014, 2248; Garson, 2016, 5-6, 36, 48). Their ascription tells us not what a trait does but what it's supposed to do and, in turn, what it's supposed to be disposed to do and the features it's supposed

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[1]I use 'activity' for both processes and continuous states, e.g., presence of the ventricular septum.

[2]I use 'part' and 'trait' interchangeably to cover system-level and subsystem traits, parts, components, phenotypes, characters, items, and genotypes except in contexts where using one of the other terms provides greater clarity.

to have so that it can perform its function. Standards for trait activity, disposition, and structure guide identification of instances of traits as being of the same type despite variation between individuals, system types, and environments. A deformed or diseased heart that cannot pump is still recognized as an instance of the type 'heart' at least in part by appeal to its function to pump blood (*cf.* Amundson and Lauder, 1994). Ditto for radically morphologically distinct hearts across species and environments.

The takeaway is, in line with function pluralism, that different types of function are ascribed in different subdisciplines biology for different explanatory purposes.[3] However, I'll be concerned primarily with normal functions throughout the rest of the paper, especially as ascribed to parts of cancers by cancer biologists.

3. The Normal Functions of Cancer

3.1. Cancer Biology: Finding Exploitable Sameness in Aberrant Variation

A consistent challenge for those working in cancer biology is dealing with treatment relevant variation among cancers. Here is a non-exhaustive list of dimensions of treatment relevant differences that individual cancers can exhibit: anatomical site and tissue type of origin, genome, mutation rate, growth rate, tumor formation, incidence and rate of metastasis, cancer microenvironment, and initiation, e.g., environmental carcinogens, pathogens, etc. Like inquiry in any domain, a central task in cancer biology is finding within all of this variation sameness that's of causal and explanatory relevance. For instance, cancers have historically been classified by anatomical site, tissue type, stage, and grade (Plutynski, 2018, Ch.1 and Appendix). A stage I, grade 1 lung adenocarcinoma is a cancer originating in glands (tissue) in the lung (site) that has yet to form a tumor (stage) and whose cells still resemble healthy, somatic cells (grade).

The standard classificatory scheme is effective at grouping cancers together and bears explanatory fruit. For instance, other properties relevant for treatment often cluster around tissue type, stage, and grade. Only some types of tissue form solid tumors, viz., clumps of cancer-associated cells. Size is a property of solid tumors that's predictive of disease progression. And the degree of apparent similarity between cancer cells and healthy cells is predictive of growth rate and metastatic potential—grade 4 cancers with cells very unlike their healthy kin are likely to grow and metastasize more quickly and aggressively.

However, the standard classificatory scheme isn't perfect (Plutynski, 2018, 2019). For instance, cancers originating in the same organ can be genetically more similar to those originating in a different organ than to each other. Precision oncology depends on targeting specific mutated genes and proteins. So, sameness in anatomical site of origin isn't always explanatory or helpful for guiding treatment. Luckily, this scheme represents only one of many tools for finding treatment relevant sameness among cancers. One tool that cancer research shares with several subdisciplines of biology is normal function, or so I will now argue by example.

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[3]A reader who is convinced that there is only one type of function ascribed in biology and that it is not normal function can still humor the following counterfactual claims as motivation: if normal functions were ascribed in biology then cancer biology is a subdiscipline in which they would be ascribed to parts of cancers. In which case, this would pose a problem for accounts of normal function.

3.2. Case Study: The Normal Function of Melanoma-Derived sEV

A widely cited paper, Peinado et al. (2012), claims to have "explored the function of melanoma-derived [small extracellular vesicles (sEV)] in the formation of primary tumors and metastases" (883). And Zhang and Yu (2019), reporting their results, say "[Peinado et al. (2012)] have advanced our understanding of the novel function of [sEV] in pre-metastatic niches" (458). The (novel) function explored and of which our understanding is advanced is the delivery of a signaling protein to cells in bone marrow via small membrane-bound packages produced mostly by late-stage melanomas (Figure 1).

Through a series of experiments, Peinado et al. identify an activity that melanoma-derived sEV perform and which results in greater primary tumor growth and more aggressive metastasis. Melanomas produce sEV carrying mesenchymal-epithelial transition factor (Met), an oncoprotein that can trigger several signaling pathways in cells (Organ and Tsao, 2011). Melanoma-derived sEV carrying Met travel through the blood to cells deep in bone marrow that have yet to differentiate. Receiving Met sets off a cascade of signaling in those cells that mobilize them to inflame distant organs, cause them to exhibit vascular leakiness, and produce vascular tissue. The result is pre-metastatic niche formation, which facilitates greater primary tumor growth and metastasis(Quail and Joyce, 2013; Mashouri et al., 2019; Gonzalez et al., 2020).

Peinado et al. (2012) features the ascription of a normal function. Beyond use of the definite article, both Peinado et al.'s and Zhang and Yu's talk of the (novel) function of melanoma-derived sEV generalizes over them without distinguishing between later stages of melanoma, sEV that successfully deliver Met, sEV that are deformed or fail to carry Met, or melanomas that fail to produce any sEV at all. Generalizing over these divergences is no accident.

In the process of identifying the function, Peinado et al. examined sEV production and Met delivery across early- and late-stage melanoma patients as well as low and highly metastatic melanoma mouse models. They also examined sEV production in melanoma mouse models designed to produce sEV lacking Met, fewer sEV, or no sEV. The point was to home in on the mechanism(s) responsible for sEV mediated pre-metastatic niche formation. This in turn required Peinado et al. to re-identify sEV or mark their absence and to identify and relate in a systematic way the effects of their presence or absence on niche formation. Some of this was accomplished by tracking sEV-related proteins in blood. However, at least some of it was accomplished by hypothesizing the activity melanoma-derived sEV are supposed to perform, positing the dispositions and structure that in the good case (for the cancer) allow them to perform it. Their hypothesis drew Peinado et al. to look for sEV and Met in bone marrow and potential sites of metastasis in patients and mouse models. It also drew Peinado et al. to infer from a lack of sEV, a lack of Met, reduced tumor growth, and reduced metastasis that they had successfully disrupted the functional dispositions and/or structure of melanoma-derived sEV in mouse models designed to produce sEV lacking Met, fewer sEV, or no sEV.

In confirming their hypothesis, Peinado et al. show that deformed sEV and sEV that don't carry Met are, in some minimal sense, supposed to deliver Met to bone marrow and are, in some minimal sense, supposed to have the dispositions and structure that allow them to do so. I will discuss the sense in which they're supposed to have these dispositions and that structure in §5. For now, the generalization over both defective
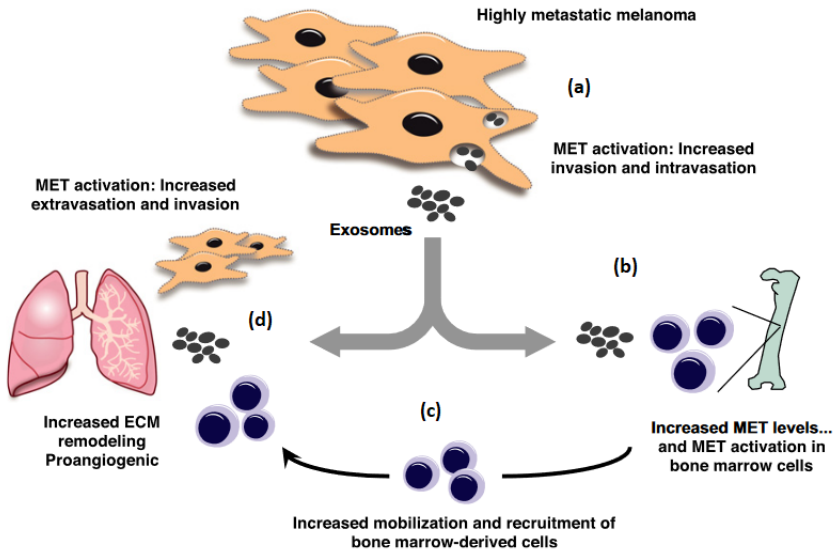
Figure 1. (a) Melanoma-derived small extracellular vesicles (sEV) (here labeled "exosomes") carry mesenchymal-epithelial transition factor (here labeled "MET") to bone marrow progenitor cells (b) as well as sites of metastasis (here represented by the lungs) (d). The function ascribed to melanoma-derived sEV in Peinado et al. (2012) is the delivery of Met to bone marrow progenitor cells (b), which mobilizes those cells (c) to inflame sites of metastasis, induce vascular leakiness (here labeled "extravasation"), and promote vascular growth (here labeled "proangiogenic") altogether facilitating tumor growth and metastasis (d). Adapted from Matsumoto et al. (2017).

and non-defective sEV in the process of discovering their function and possible clinical interventions suggests that the ascription identifies a norm for part activity, disposition, and structure. In which case, delivering Met to bone marrow is a normal function of melanoma-derived sEV.

4. Difficulties for Current Accounts of Normal Function

Cancer biologists ascribe normal functions to parts of cancers. This poses difficulties for the two main approaches to explicating the ascription of normal function in the philosophy of biology.[4] These approaches roughly divide on whether normal functions are i) activities whose performance by the function-bearing part results in that part being selected for (by natural selection) or ii) activities that confer a benefit to (inclusive) fitness. The first approach is often identified with selected effects accounts (e.g. Neander, 1991; Godfrey-Smith, 1993; Buller, 1998; Garson, 2011, 2017b). The second can be identified with a number of accounts that, following Garson (2016), I group

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[4]There is another approach in the philosophy of biology that aims to give accounts of how normal function ought to be ascribed, e.g., Millikan (1984, 1989). Addressing Millikan's technical notion of Normality and other, similarly prescriptivist accounts of normal function is beyond the scope of this paper.

under the heading "fitness-contribution accounts" (e.g. Boorse, 1977, 2002; Bigelow and Pargetter, 1987; Piccinini and Garson, 2014). I consider each in turn.[5]

4.1. Selected Effects Accounts

Selected effects accounts claim that an activity of a part is a normal functions if and only if that part is selected for performing that activity. Thus, the heart has the normal function of pumping blood because hearts are selected for pumping blood, in this case, by natural selection (*cf.* Garson, 2017*b*). However, at least some functional parts of cancers aren't selected for.

For a trait to be subject to selection, the system(s) in which that trait is present has to meet at least the three following conditions. First, the system(s) has to exhibit heritable variants of the trait or trait-type. Second, the fit between system(s) and environment has to favor some traits over others. Finally, the selected trait has to be retained over variants.

Satisfying these conditions (and others) is a matter of degree (Godfrey-Smith, 2009). The more paradigmatically Darwinian a population is—the better it satisfies these conditions—the more likely the functional traits are present in that population as a product of selection. The less paradigmatically Darwinian a population is, the more likely at least some functional traits are present in that population as a product of some other evolutionary process. For instance, only barely meeting the second or third conditions on selection can result in traits that are the product of genetic drift or genetic hitchhiking.

Unfortunately, several cancers fail to meet these conditions except minimally (Germain, 2012; Germain and Laplane, 2017; *cf.* Lean and Plutynski, 2016). At the cellular level, parts of cancers that are ascribed normal functions are often the product of drift or genetic hitchhiking without necessarily being fully coopted (Germain, 2012, 806). And at the tumor level, these parts are often neither heritable or recapitulated in metastases nor the product of competition between tumors (Germain and Laplane, 2017). In which case, at least some parts of cancers have normal functions despite not being subject to selection (*cf.* Greaves and Maley, 2012; Plutynski, 2017, 2018; Bozic and Wu, 2020; Hausser and Alon, 2020). But, on selected effects accounts, a necessary condition on a part's having a normal function is that part's being selected to perform the relevant activity. The ascription of normal function to parts of cancers therefore poses a difficulty for selected effects accounts that may prove intractable (*cf.* Garson, 2017*a*, 1100; Neander, 2017, 21).

4.2. Fitness-Contribution Accounts

Fitness-contribution accounts claim that an activity of a part of a system is a normal function only if performance of that activity by that part increases the (inclusive) fitness of the system. Thus, the heart has the normal function of pumping blood because its

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[5]The division between selected effects and fitness-contribution accounts cuts across many more nuanced distinctions. Some selected effects accounts are historical while others aren't; some require that functional parts be reproduced while others don't; and some require natural selection while others allow for more liberal selection mechanisms. On the other hand, some fitness contribution accounts are ahistorical or forward looking and some ground normality in terms of a propensity of a part to contribute to fitness while others don't. Discussing how each account might approach the ascription of normal function in cancer biology is well beyond the scope of this paper (for thorough overviews of the function literature, see Wouters 2005; Garson 2016).

doing so increases the (inclusive) fitness of the vertebrate. Unfortunately, bare appeal to contributions to fitness fails to establish a standard for the activities, dispositions, or structural features of parts. Moreover, attempting to establish a standard in a way that fits with fitness-contribution accounts proves difficult by threatening to undermine the point of ascribing normal functions, at least in the case of cancer.

Bare appeal to contributions to fitness cut across instances in which performance of an activity by a part is of fortuitous benefit and those in which it contributes to fitness in the normal way. For instance, a belt buckle might at some point deflect a bullet from hitting the soldier wearing it (Boorse, 1976). The belt's deflecting the bullet increases the soldier's (inclusive) fitness by protecting her from a potentially fatal wound. However, in contrast to the heart's pumping blood, we wouldn't want to say that it's a normal function of belt buckles to protect their wearers from being fatally wounded. This is because we think of normal functions as setting standards for the activities, dispositions, and structural features of parts.[6] Even granting that belt buckles can form part of a biological system, they aren't designed to deflect bullets nor do they tend to deflect them. Thus, it's very unlikely that they're supposed to do so or have the disposition and/or structural features that would allow them to do so.

If fitness-contribution accounts reject appealing to the normalizing force of natural selection to set a standard, they will need to appeal to something else. Another type of normality that's thought to be scientifically respectable is conditional statistical typicality (Boorse, 1977, 2002; Piccinini and Garson, 2014). The normal function of a part then becomes what that part does to contribute to the (inclusive) fitness of an individual system which, conditional on that part's so contributing, is typical for systems of the type. Thus, the normal function of the heart is pumping blood because, given the heart does something to contribute to the (inclusive) fitness of some vertebrate, that's how it typically contributes to vertebrates. By contrast, belt buckles don't typically contribute to their wearers by deflecting bullets.

The move to conditional statistical typicality does not work in the case of cancers. Establishing what is statistically typical for a type of system requires specifying a reference class for the systems the type comprises. But it's not clear that reference classes can be specified for cancers without significant overlap between them. Given their rank variability, no one classificatory scheme has proven effective at unifying cancers into types without overlap or remainder (Plutynski, 2018, 2019). This leaves reference classes for cancers severely underdetermined.

Without appeal to the standard classificatory scheme, one could try to stipulate a reference class for a type of cancer *ad hoc*. But doing so threatens to undermine the normal function (pun intended) of ascribing normal functions, namely, identifying standards of the activities, dispositions, and structural features of parts which allow us, in turn, to identify deviations from those standards. *Ad hoc* stipulation of a reference class threatens to make those standards arbitrary or otherwise interest-relative. In which case, differences between parts of members of the class may not reflect any genuine deviation, deformity, or failure. And differences that are of genuine casual relevance between members may go unnoticed. The explanatory payoff of finding genuine standards among

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[6]Distinguishing activities of fortuitous benefit from normal functions is often glossed as a basic desideratum on theories of function under the heading of 'the function-accident distinction' (Wright, 1973; Garson, 2016).

a type of system and figuring out how deviations from those standards impair those systems is figuring out how that type of system works. This is the point of ascribing normal functions. We threaten to lose sight of that payoff if we elect to stipulate reference classes *ad hoc*. If this is right then the ascription of normal function to parts of cancers poses a difficulty for function-contribution accounts that may prove intractable (*cf.* Hausman, 2012, 538-540).

5.   The Objection From Loose Talk

There is at least one objection to the claim that cancer biologists ascribe normal functions to parts of cancers. The objection amounts to this: there is no reason to think that the ascription of 'the function' or 'the novel function' to a part of cancer identifies a norm for its activity, dispositions, or structural features. That these phrases show up in cancer biology is likely loose talk. These functions are no more than the actual or typical causes of disease progression, e.g., metastasis. Talk of function signals only that these activities are functions of the kind ascribed in, e.g., cladistic systematics. Moreover, cancer biologists appear to reserve talk of 'normal function' for the activities, dispositions, and structure of healthy tissue when contrasting them with the activities, dispositions, or structure of aberrant tissue.

In response, there is at least one reason to try to identify standards for part activity, dispositions, and structural features among types of cancers. Namely, doing so successfully provides viable avenues for treatment. The ultimate aim of cancer biology is the development of effective clinical interventions. This aim is problematized by the variability that cancers exhibit (§3.1). And it's further problematized by cancers effectively exploiting that variability. In particular, cancers that escape immune response and resist treatment are more likely to effectively maintain themselves (at least until the patient's death). The more thoroughly a cancer establishes itself in its host the more specialized the knowledge required to root it out becomes.

At the same time, the variability that a cancer can exhibit and exploit is constrained by the evolutionary history of the organism, the mutations driving it, the rate at which it mutates, the organism's environment, etc. (*cf.* Neander, 2017, 62-63). These limits on variability can guide cancer biologists to commonalities across cancers. Hence the use of a plurality of classificatory schemes. I submit that knowledge how to undermine particular traits or mechanisms of types of cancer is often gained by identifying the normal functions of their parts. Identifying these activities as standard cuts across instances in which the relevant traits or mechanisms fail to behave as predicted. Idiosyncratic failures may not be a focus of cancer biology because clinicians may not want to rectify those failures. Nonetheless, in seeking to undermine the disease, cancer biologists identify standards for the activities, dispositions, and structural features of parts of cancers that many cancers do embody. That is, in seeking to undermine the disease, cancer biologists try to figure out how those cancers work.

I want to stress that giving up on normal functions here threatens to deprive us of an extremely useful tool in the cancer biologist's toolbox. I also want to grant that cancer biologists might sometimes speak in confused ways, running together normality with health. Even if their ascription is a dispensable part of cancer biology, the case presented by Peinado et al. (2012) shows us that normal functions serve as an effective guide to at least some commonalities of clinical significance among cancers. The resistance to

allowing normal functions to be ascribed to parts of cancers, rests, I suspect, in the conflation of what is normal with what is healthy. This conflation is exacerbated by the fact that cancer biologists will often refer to the activities of healthy variants as their normal functions, reserving 'the function', 'the novel function', 'the function of *X* in cancer', or 'the normal function of *X in cancer*' for the ascription of normal functions to parts of cancers. Despite appearances, I believe all are tracking normal functions.

To back up this up, I need to disambiguate normality from health. Health is a state that's good to be in. And what is healthy is conducive to being in that state. The heart's pumping blood (efficiently) is healthy. But health isn't synonymous with normality where normality merely sets a standard for a type of system (*cf.* Boorse, 1977). Consider an Olympic sprinter whose leg muscles are quickly atrophying. The state of her leg muscles is unhealthy despite crossing into what is normal for the species on a number of dimensions, e.g., volume or mass, as they wither. By contrast, an Olympic sprinter in their prime will have leg muscles that differ from what is normal on those dimensions and many besides.[7] Normality and health can come apart.

To conclude, normality sets a standard and some parts of cancers have standard activities, dispositions, and structural features. That cancers are pathological and that cancer biologists will often talk of normal functioning when they mean (or should say) healthy functioning in no way undermine the legitimacy of ascribing normal functions to their parts. In which case, we need an account of normal function that explicates their ascription in cancer biology.

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[7]It is partly for this reason that Boorse restricts focus to a negative or minimal conception of health. Olympians are paradigms of positive health. Yet, in being as much, they're literally extraordinary.

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