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PERSPECTIVES

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Cell Fate: What's Evolution Got to Do With It?

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Theoretical frameworks concerning cell fate typically center on proximate causes to explain how cells know what type they are meant to become. While major advances in cell fate theory have been achieved by these mechanism-focused frameworks, there are some aspects of cell decision-making that require an evolutionary interpretation. While mechanistic biologists sometimes turn to evolutionary theory to gain insights about cell fate (cancer is a good example), it is not entirely clear in cell fate theory what insights evolutionary theory can add, and why in some cases it is required for understanding cell fate. In this perspective we draw on our work on cellular mortality to illustrate how evolutionary theory provides an explanation for death being selected as one of the potential cell fates. Using our hypothesis for why some microbes in a community choose death as their fate, we suggest that some insights in cell fate theory are inaccessible to a theoretical framework that focuses solely on proximate causes.

INTRODUCTION

Cell fate theory aims to explain the "choices" cells make and their subsequent trajectories to becoming a specific cell type. Early in the life of a totipotent cell, it has four possible cell-type outcomes: self-renewal (replication), differentiation, programmed cell death (PCD), and quiescence [1]. The cell type is typically inherited by its progenitors (except, of course, where PCD is selected), although the reversal of cells to totipotency sometimes occurs and is an area of keen interest in stem cell biology and oncology [2].

Cell fate theory has achieved its accomplishments primarily through studying cell mechanisms, and this will presumably remain the case. This allows us to see how cells make their choices to become one kind of cell or another. In Mayr's terminology, an investigation of the mechanisms provides a *proximate explanation* of cell fate [3]. Evolutionary theory reveals what Mayr called *ultimate causes*, which (in the case of cell fate theory) are causes that explain *why* cells become one type or another rather than *how* they achieve this. (While its discussion goes beyond the scope of this article, we acknowledge challenges to a clean proximate-ultimate cause distinction. See [4].)

Evolutionary theory is frequently used in the mechanistic life sciences to introduce testable hypotheses by framing biological problems in new and interesting ways. In this perspective, we begin by using the example of cancer to show how thinking about proximate and ultimate causes can complement each other. We then draw on our work on programmed cell death, to show that evolutionary theory can explain why some cells in a microbial community choose death as their fate even when this cell type seems nonadaptive. This example illustrates how some insights in cell fate theory are accessible only by

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Abbreviations: PCD, programmed cell death; BQH, Black Queen Hypothesis; BQs, Black Queens.

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asking evolution-based questions.

The Complementarity of Asking Proximate and Ultimate Questions in Cancer Biology

Cell fate is key to understanding cancer progression and metastasis because the type that a cell chooses to become impacts overall tumor survivability and spread. How cancer cells make choices is, of course, uncovered through experimentation and mathematical models. Evolutionary theory complements these advances by placing mechanistic questions in an evolutionary context leading to a deeper understanding of cancer biology. When "cancer research meets evolutionary biology" [5 p.62], new insights are gained, some of which yield practical applications in clinical oncology. As advocated by Aktipis [6] in her monograph, *The Cheating Cell: How Evolution Helps Us Understand and Treat Cancer*, there are many cases—such as disease progression, which we discuss below—that demonstrate the value of this complementarity.

Cancer progression is characterized by several stages, one of which is when the tumor bulk has outgrown its blood supply and cells are faced with the dilemma of remaining replicative (and potentially facing necrotic death because of a depletion of resources) or selecting alternate cell types like acquiescence or differentiation. To remain replicative, which for most cells in the population remains optimal in the short term, a fresh blood supply is required. By asking how this is achieved, it was discovered that tumor cells release angiogenic factors that direct some cells to switch their cell fate trajectories from replication to differentiation. The result is the emergence of specialized cells like vascular endothelial cells. When enough cells make this switch, a new vasculature emerges that delivers oxygen and nutrients to the cells, thus facilitating cancer progression by allowing cells to again become replicative, which advances tumor growth and metastasis.

A key feature of neovascularization was uncovered by asking questions about ultimate causality. Angiogenic factors seemed to have no effect on the cells producing them or on others in the vicinity. It was not clear, therefore, why cells were producing them. What was discovered by asking questions about ultimate causes is that the formation of new blood vessels is a population-level property. No single cell is capable of producing a sufficient quantity or diversity of angiogenic factors to cause itself or others to differentiate into vascular tissue. Instead, angiogenesis is best understood by multilevel selection in that it is a population-level response to quorum-sensing molecules (a case of supra-organismal selection). Angiogenic factors explain how neovascularization occurred, while multilevel selection theory explains why it was selected for by growing populations of cancer cells [7]. The complementarity of proximate and ultimate causal questions provided an explanation for disease progression by showing that cells change their fate in response to hypoxic and nutrient depleted conditions.

Ultimate Causes of PCD in the Unicellular World: The Black Queen Hypothesis

In the cancer biology example above, proximate and ultimate explanations are complementary and together they provide a synthetic account of the observed changes in cell fate trajectories. In the case of PCD, evolutionary thinking is not merely helpful, but is necessary to answer some questions about cell fate.

In the last two decades, evolutionary biology has driven some of the major advances in our understanding of PCD across the tree of life [8,9]. One of the areas currently being pursued is the evolutionary ecology of PCD in microbial communities, which has emerged as a major issue in a wide range of cell fate contexts [1]. In communities comprising mixed taxa, it is common for only some species to exhibit PCD, even if some form of PCD is ancestral to all species [10]. If we focus solely on proximate mechanisms, we may be able to determine the environmental stressors—such as nutrient deprivation (eg, nitrogen or iron depletion) and physicochemical fluctuations (eg, temperature or oxidative potential)—that trigger cellular pathways that lead to a PCD cell type in some of the species (for a review, see [11]). However, what seems inaccessible to accounts centered on proximate mechanisms are questions like these: *Why is PCD selected as a cell type in unicellular organisms? Why in mixed species microbial communities do only some species typically exhibit PCD?* Such questions require an account of the evolutionary pressures driving cell fate choice in mixed communities. An exclusive focus on proximate mechanisms fails to provide satisfactory answers.

In microbial ecology, costly traits that benefit others have generally been a challenge to explain. This is because cells that express them risk being exploited by others. In the case of taxa that exhibit PCD, the cost of the trait is death, and one would expect that these species are readily driven to extinction. Morris et al. [12] suggested a general evolutionary ecology framework—the Black Queen Hypothesis (BQH)—to address the evolution of costly traits in microbial communities. Black Queens (BQs) are costly traits that are essential for the survival of the community. (The name comes from the card game Hearts, in which players get stuck with the costly black queen—the queen of spades). In these communities, some taxa must necessarily bear the cost of exhibiting the BQ, since without them all members of the community perish.

Exhibiting the BQ can, in some cases, serve as a benefit, not just a cost. One way of leveraging a BQ trait

is to become a keystone species, that is, a species indispensable to the community. This provides some protection since its extinction means the extinction of the entire community. Morris et al. [12] used the production of catalase-peroxidase (katG)—a costly enzyme necessary for detoxifying oxygen free radicals in the community—in conceptualizing the BQH. Some species in the community lost the ability to produce katG because they exploited the capacity of others to do so. In doing so, however, species that do produce katG became indispensable to the community, since without them the entire community dies.

In a similar way, we previously suggested that PCD fulfills the criteria for being a BQ [13]. In conditions of environmental stress like nutrient scarcity, some taxa typically undergo PCD (eg, [14]). As the cells die by PCD, they detoxify harmful intracellular materials and release beneficial nutrients into the environment [15]. Other community members survive periods of scarcity by using the released materials as a nutrient resource. It was discovered that in some cases, the released nutrients appear to be specifically targeted at relatives [16], while in other cases they are also available to unrelated taxa [17]. The ecological dynamics of the microbial community will, of course, depend upon the taxa in the community, but what is clear is that some individuals choose PCD as their fate. By dying in an organized way, they are able to provide essential resources to relatives who are not undergoing PCD (PCD is phenotypically plastic [18]), as well as to others. Taxa that select PCD as their fate allow others to endure periods of resource limitation and are key to the survival of the community, thus ensuring their own survival.

With this evolutionary framework in hand, let's revisit the two questions posed above. First, why does PCD thrive as a cell type in unicellular organisms despite its obvious cost? The answer is that in times of scarcity, communities face the dilemma of either being completely wiped out, or having some individuals preemptively sacrifice themselves, preserving others. Second, why does PCD in mixed species communities exhibit a mosaic pattern, in which some species appear to have given up their ability to undergo PCD? The BQ framework predicts that if a species can gain the benefit of the BQ without bearing its cost, then it will. The species that lose the ability to undergo PCD have thus won the game of chicken—they dropped their ability to perform a costly task before the other species did so. At the same time, however, the taxon that expresses the costly trait of PCD may become a keystone species, thereby helping to protect it against extinction. This example of PCD in microbial communities shows that in some instances an explanation for why cells choose to become a specific type requires going beyond understanding the proximate mechanisms underlying their ability to do so. Instead, we must draw on the evolutionary history of the species to account for the patterns of cell type expression.

CONCLUSIONS AND OUTLOOK

There are two key sources for understanding cell fate: proximate mechanisms and evolutionary histories. In this perspectives piece we illustrate the value of including evolutionary histories. In some instances, such as the example of neoplastic progression, the mechanistic studies are complemented by evolutionary explanations that, together, have transformed our approach to cancer and its treatment. In other instances, such as the case of the BQH and PCD, we have argued that there are some insights that are accessible only from an evolutionary perspective.

Cell fate theorists have highlighted cell decision-making as one of the major challenges in the field [19]. The aim is to develop a comprehensive framework that includes all cells across the tree of life and in all possible environments. As Casey et al. [1] suggest, this will involve a cross-disciplinary effort that goes beyond experimentation. They argue for greater use of mathematical approaches like dynamic systems theory to formulate the inherent complexity and nonlinearity in cell fate decisions. We suggest that, in addition to the mechanistic discoveries and the mathematical models, a complete theory of cell fate will also require an understanding of the evolutionary ecology of cells. Furthermore, incorporating cell death theory into the cell fate literature will be essential if the question of PCD as a microbial cell type is to be fully appreciated.

If we consider Mayr's [3] classic proximate-ultimate distinction, the mechanistic sciences uncover how cells make choices via their (proximate) molecular pathways. Why they do so, however, depends on the (ultimate) evolutionary pressures that direct their choices in different environments. Following an integration of the mechanistic and evolutionary insights, subsequent mathematical formulations of the data will capture the complexity of cellular systems and lead to further hypotheses that can be tested empirically.

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