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Of cancer and cavefish

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Abstract

We propose that the drivers of carcinogenesis lie more in the adaptive changes enabled by local or systemic alterations of tissue architecture than the genetic changes observed in cancer cells. A full understanding of cancer biology and therapy through a cataloguing of the cancer genome is unlikely unless it is integrated into an evolutionary and ecological context.

Essay

Prevailing medical dogma holds that cancer is a “disease of the genes.” High-throughput molecular techniques have identified tens of thousands of genetic and epigenetic alterations in malignant cells. There is optimism that continued characterization of the cancer genome and epigenome will lead to a full understanding of cancer biology and definitive therapies. But, before ”betting the house” that cancer can be understood simply through more and more molecular analyses, it is important to consider cautionary lessons from evolution in nature. None of these is more compelling than that of the cave fish.

As the name implies, cave fish inhabit the perpetually dark waters of caves, wells and subterranean streams. Found throughout the world, cave fish exhibit remarkably common phenotypic adaptations - they are small, blind, eyeless, unpigmented, and possess exaggerated tactile organs[1–3] (Fig 1). Despite their uniformly similar morphology, cave-adapted fish represent 86 species in 19 different Teleost families. Darwin himself puzzled over the evolutionary dynamics leading to their loss of eyes “As it is difficult to imagine that eyes, though useless, could in any way be injurious to animals living in darkness.” We now know that the loss of vision is a driven adaptation that literally closes a window for infection, saves energy and reallocates the nervous system from sight to tactile senses[4].

Cave fish represent both convergent (different lineages developing similar biological traits) and regressive evolution (loss of unused traits over time). The teleost, *Astyanax mexicanus*, with both cave and surface dwelling forms, provides an experimental model for understanding the molecular and genetic dynamics associated with cave-adaptations. In northeastern Mexico, 30 caves harboring *Astyanax* populations have been investigated leading to two important generalizations[5–8]. First, the *Astyanax mexicanus* found in multiple caves, despite being virtually identical phenotypically, are not a single population. In some cases the founder group was an established population from an adjacent cave. More typically one or more new populations of surface fish independently evolved cave adaptations as each cave became available. Second, each cave-adapted population followed a different genetic evolutionary trajectory. Despite their morphological similarity, the

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molecular and genetic characteristics of populations in different caves are widely divergent. For example, the pathway by which sightlessness evolved is highly variable in different cave populations and even among the same population within a cave. In fact, when two closely related, but geographically-separated blind cavefish populations were cross bred, up to 90% of their hybrid offspring had vision indicating multiple genetic alterations[6].

Thus, *Astyanax mexicanus* has adapted to caves multiple times in multiple locations by evolving remarkably similar (although not identical) phenotypes. However, every evolutionary emergence of a cave-adapted phenotype followed a different genetic trajectory and even populations within a single cave exhibit evidence of several populations with divergent genetic lineages. Clearly, molecular analysis of surface and cave populations has great value in identifying the genomic changes that produced the necessary adaptations in different populations. However, genetic investigation alone leads to incomplete or misleading conclusions in two ways. First, isolated cataloguing of the genetic changes of multiple fish in multiple caves, while characterizing the diversity of the populations and the differences between them, understates the striking similarity of their adapted and functioning phenotypes. Second, genetic analysis can mix cause and effect. For example, one might conclude that the genetic changes in cave fish *caused* them to occupy the caves when, in fact, the genetic changes occurred only as a result of an ecological opportunity provided by a newly formed and opened cave. In other words, it might appear that normal surface dwelling *Astyanax*, because of accumulating mutations, had developed populations that invaded and colonized caves when, in fact, entry into the evolutionary opportunity provided by the cave preceded the emergence of the adaptive morphologies and associated molecular changes.

We use the example of cavefish as an analogy for cancer development to propose two caveats to the conventional paradigm of cancer as a disease of the genes. First, cancer is most generally a disease of ecological and evolutionary opportunity. The difference between a disease of the genes and a disease of evolutionary and ecological opportunity is subtle but impacts significantly on the biology of carcinogenesis and clinical strategies for prevention. Cave fish evolved from surface phenotypes only because of a new ecological opportunity (i.e. a cave) presented itself. The observed genetic changes provided the colonizers with the heritable variation from which adaptations to the novel cave environment could evolve. Normal epithelial tissue represents a distinctive and generally stable habitat in which cancer is ordinarily an unlikely event[9]. This restriction appears to break down with loss of tissue control due to aging, environmental insults or chronic inflammation. Thus, tissue niches emerge that permit and promote evolution of a cancer population. In other words, the origin of cancer may lie not in mutations within epithelial cells but within acquired or somatic changes in the mesenchymal cells that control tissue structure including proliferation of stem cells and differentiation of their daughters. It is interesting that Rubin and others have reported changes in skin fibroblasts prior to the onset of visceral cancers[9]. This suggests that a systemic development of evolutionary opportunity for cancer may in some cases provide the first step of carcinogenesis. These changes open tissue niches that permit colonization and subsequent adaptation that occurs through distinctive and predictable sets of phenotypic changes. These will be the result of a wide range of genetic alterations in the cancer cells but the driver of these changes is phenotypic adaptation of proliferating epithelial cancer cells within a tissue niche. Furthermore, that niche may result not from the local effects of the transformed cells (i.e. ecological engineering) but an entirely separate local or systemic “disease” that alters normal tissue dynamics.

Second, cataloguing the cancer genome may yield limited information about the underlying biology because the phenotypic products of natural selection supervene the molecular and genetic changes. The observations in *Astyanax mexicanus* illustrate a principle proposed by

Mitchell and Valone[10] — that an evolutionary adaptation or strategy is supervenient to the underlying genotype. As described by Rosenberg[11,12], supervenience is a common feature of linked sets of items, particularly when one set comprises functional properties and the other set comprises the physical or structural properties that result in the functional property. Set 1 supervenes set 2 if each item in set 2 corresponds to an item in set 1, but each item in set 1 maps to a subclass of items in set 2. Hourglasses, sundials, quartz crystal and atomic clocks all serve a similar function. The measurement of time supervenes the device used. In cavefish and cancers, the strategy or function of a cell can be generated by a large number of diverse genetic changes. Like cavefish, cancers in different patients exhibit convergent evolution. Despite arising from various cell types in multiple organs and following numerous different mutations, cancer cells eventually and invariably exhibit a small set of phenotypic hallmarks. Also like cavefish, cancer populations typically exhibit regressive evolution. A characteristic of virtually all cancers is de-differentiation as the cells lose the ability to carry out the specialized functions of the epithelial or mesenchymal populations from which they arose. Thus, like cavefish, the phenotypic similarity of the adaptations and the environmental selection forces that govern these changes become lost in the large number of genetic pathways that yield comparable adaptive strategies.

In summary, the current conceptual model of cancer as a disease of the genes assumes that transformed cells, through a sequence of mutations, produce a tumor more or less independent of the ecology of normal tissue. We point out that alternatively, analogous to underwater caves, regional or systemic alterations in normal tissue due to germ line mutations, chronic inflammation or senescence could provide an evolutionary opportunity that permits and promotes cellular evolution. As in cavefish, each evolutionary opportunity results in stochastic events that may produce convergent phenotypes but through multiple genetic lineages. Cancer cells may share significant phenotypic similarities but the genetic path to this morphology is likely to have been unique so that, at a genetic scale, each tumor is effectively a disease never before encountered in the clinic[14]. Thus, the search for cancer prevention strategies may need to focus less on cancer cell mutations and more on maintaining the integrity of normal tissue and in particular the functioning of the underlying mesenchyma. In the rush to identify prognostic gene signatures and attack mutant gene products, enthusiasm and optimism must be tempered by the cold reality that the Darwinian dynamics of adaptive evolution supervene the genomic changes.

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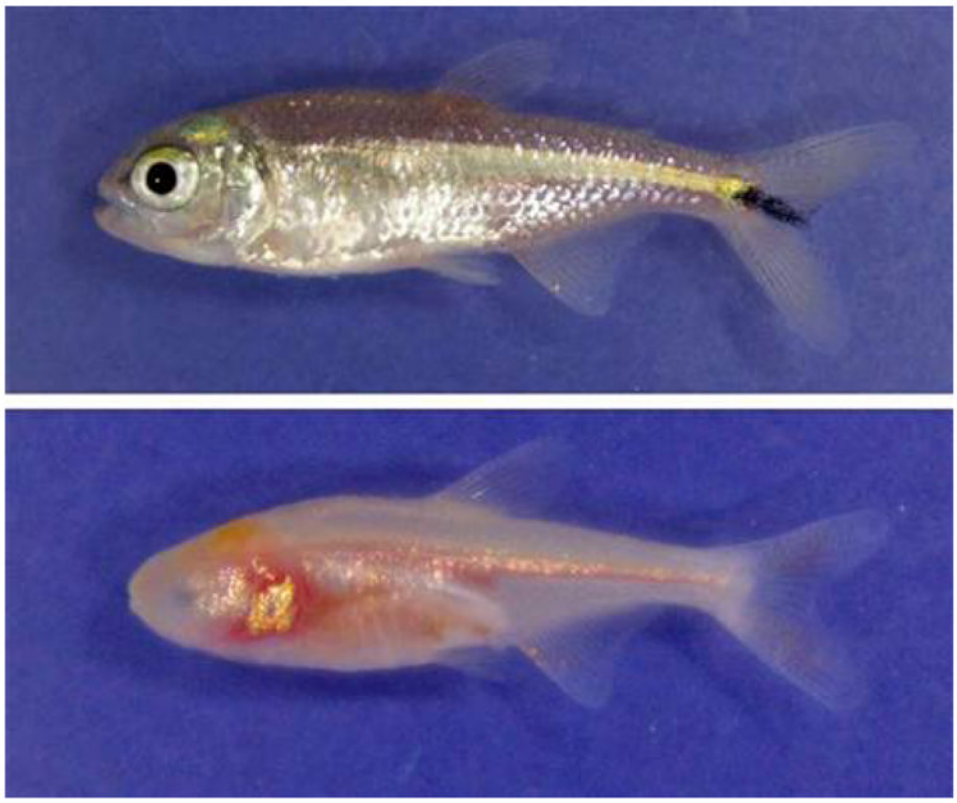

Figure 1.
Examples of *Astyranax Mexicanus* showing surface morphology (upper) and cave-adapted morph (lower) (Courtesy of Masato Yoshizawa/Univ. of Maryland)