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Cancer Community Ecology

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Abstract

Here we advocate *Cancer Community Ecology* as a valuable focus of study in *Cancer Biology*. We hypothesize that the heterogeneity and characteristics of cancer cells within tumors should vary systematically in space and time and that cancer cells form local ecological communities within tumors. These communities possess limited numbers of species determined by local conditions, with each species in a community possessing predictable traits that enable them to cope with their particular environment and coexist with each other. We start with a discussion of concepts and assumptions that ecologists use to study closely related species. We then discuss the competitive exclusion principle as a means for knowing when two species should not coexist, and as an opening towards understanding how they can. We present the five major categories of mechanisms of coexistence that operate in nature and suggest that the same mechanisms apply towards understanding the diversification and coexistence of cancer cell species. They are: Food-Safety Tradeoffs, Diet Choice, Habitat Selection, Variance Partitioning, and Competition-Colonization Tradeoffs. For each mechanism, we discuss how it works in nature, how it might work in cancers, and its implications for therapy.

Keywords

cancer community ecology, tumor heterogeneity, mechanisms of species coexistence, environmental heterogeneity, niche axis, evolutionary tradeoffs, tumor heterogeneity, cancer cell types, tumor microenvironment

Introduction

Cancerous tumors are strikingly heterogeneous. What was previously thought to be a homogeneous collection of cells is remarkably diverse. We now know that tumors comprise many types of tumor microenvironments, tissues, and cells, including cancer cells, various lymphocytes, macrophages, neutrophils, and other immune cells, fibroblasts, stroma, vasculature, and more.[1-4] Up to 50% of the cells comprising a tumor may be noncancerous. Those that are also exhibit considerable genetic, morphological, metabolic, and phenotypic variation[5,6]

The various microenvironments of a tumor are themselves diverse and heterogeneous. Microenvironments near the tumor's edge or close to blood vessels will be rich in nutrients, but more exposed to immune cells.[7-9] Those located deep within the tumor or far from vasculature will see acidity, hypoxia, and low nutrients.

The corresponding cancer cells may vary within these microenvironments or between them, and their characteristics should vary systematically in space and time. We hypothesize that cancer cells form local ecological communities within tumors. The cancer cells will group into a limited number of distinct cancer species each with their own ecological niche determined by local conditions and the types and diversity of ecological opportunities and hazards. Thus, each cancer species in a community will possess predictable phenotypic traits that enable them to cope with their environment and coexist with each other. What is the significance of this diversity? By what mechanisms is it maintained? Can we take advantage of these mechanisms to guide our approach to disease treatment? Recognizing tumors as comprised of communities of diverse, co-evolving and coexisting types may suggest

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therapies for favoring more benign, manageable cancer cells, or suggest ways to strategically engineer the extinction of all of the cancer species either collectively or one at a time.

Ecologists have asked questions similar to these. Community ecology studies how species in nature interact and coexist by partitioning space, resources, and hazards such as predation risk. Ecological communities and why species diversify can be studied through mechanisms of coexistence. Here we advocate *Cancer Community Ecology* as a valuable focus of study in *Cancer Biology*.

Useful Concepts and Assumptions

In this essay, we take the following perspectives for applying ecological and evolutionary concepts to cancer. Ecology can be understood as the interaction of species within a biotic and abiotic context. Similarly, cancer cells inhabit their tumor ecosystem. Populations of related cancer cells from the same lineage and with similar traits can be thought of as an oncospecies (hereafter, "cancer cell species," or simply "species"), distinct from other cancer species possessing different traits.[10-13] If different species of cancer cells coexist within the same tumor microenvironment or region of a tumor then they form an ecological community of interacting species that experience similar "predators" (lethal immune and/or fibroblasts cells) and compete for the same set of resources. Normal cells are highly regulated within their tissues, and cooperate to achieve a group optimum for the whole organism—in this case the patient. They occur within the context of a multicellular diploid organism, and act to support that organism's survival and reproduction. In contrast, a cancer cell is effectively a single celled protist living in a universe comprised of its host's body. It is free of homeostatic and tissue controls by its host (i.e., the patient), and like all protists, it reproduces by binary fission. Its descendants acquire new heritable traits by genetic mutations and epigenetic alterations, favoring traits that promote cell line proliferation.

As tumors grow and become more complex, competition within the original cancer species intensifies, and there is selection for diversification of cancer species through greater specialization.[14,15] What emerges is a tumor in which there is temporal and spatial variability in food and nutrient availability, oxygen availability, acidity, exposure to the immune system, and so forth. These provide niche axes along which opportunities for specialization and speciation can take place, leading to a diversity of cancer species, each excelling at coping with different sets of conditions and exploiting different sets of resources. As in nature, these different cancer species fill different ecological niches.[16-18] In this regards, the niche of a cancer species is the set of environmental conditions within a tumor under which it can proliferate and successfully persist.

The result is that some lineages of cancer cells adapt to the conditions of the tumor center, some to its leading edge,[19] some to conditions closer to vascularization, some far away.[20,21] Thus, a diversity of cancer cell species interact in time and space and coexist by partitioning space and various resources. Only by understanding the salient features of the tumor environment and the salient features of the cancer cell species can we understand the diversity of cancer cells, and only by understanding the diversity of cancer cells can we best treat these diseases.[22,23]

Cancer Community Ecology is the Study of Closely Related Competitors

A striking feature of cancer is that although each case in each patient represents newly evolved species, what emerges time and again is so repeatable from patient to patient that we actually recognize particular types of cancer (e.g., there are 10 different types of breast cancer including tubular carcinoma and 5 different types of prostate cancer including adenocarcinoma). This suggests that the conditions of the human body are sufficiently predictable and the problems that cancer cells have to solve so repeatable that cancers hit on the same set of traits to solve those problems from patient to patient again and again.[10,24] Thus cancers represent remarkable examples of convergent evolution.[25,26] In nature, competition can occur between closely related species as well as between distantly related ones. Typically, competition is more intense and its consequences more striking in more closely related species.[27-29] This is because closely related species resemble each other more and share more traits and requirements than more distantly related ones. Thus they are more likely to have similar aptitudes and abilities and similar deficiencies, including how they exploit resources and how they avoid predators. Cancer cells within a patient are especially closely related. They likely derive from a single lineage of cells that initiated the cancer, and the subsequent diversity of cancer species can all trace their phylogeny (ancestry) back to this single clade of cells. Hence, insights from the ecology of closely related species should provide us with the most relevant analogies for understanding cancers.

To illustrate the mechanisms of coexistence that may be relevant to cancer, we can draw from the seed-eating, sand-dune dwelling desert rodents from North America and from the Negev Desert of Israel.[30-32] The rodent communities in each region are comprised of independent sets of closely related species from the same genus or family. Middle Eastern and North American assemblages show strong ecological and evolutionary convergence to each other.[33,34] That is, the species from the two different regions have evolved to resemble each other in appearance and foraging aptitudes, and the communities are similar in the types and numbers of resources, competitors, and predators. In both regions, species compete with each other for scarce seed resources while facing threats from diverse types of predators.[35-38] In these respects, they provide a compelling analogy for communities of cancer cells within (= same desert) and between patients (= different continents).

Competitive Exclusion Principle

Ecological communities may comprise several consumer species exploiting several resources while at risk from several predators. A consequence of this is that some consumers may

be better at obtaining certain types of resources, while some excel at others. For example, in desert rodent communities in the Sonoran Desert of Arizona, wood rats eat plants and are able to detoxify a wide range of plant poisons including oxalates, alkaloids, and phenolics found in the cacti, creosote bushes, and mesquites that comprise their diets.[39] Kangaroo rats instead eat seeds. They have especially sensitive olfaction for discovering buried seeds and cheek pouches to facilitate carrying them home to store. No matter how numerous wood rats may be, they have little impact on the seeds and therefore little impact on the kangaroo rats, and vice versa. Competition between these species is weak, and wood rats and kangaroo rats often co-occur.[40] Among the kangaroo rats, Merriam's kangaroo rat and Ord's kangaroo rat are very similar to each other in appearance and body size and eat nearly identical diets. These two species compete intensely for seeds and rarely co-occur.[40] These examples illustrate how species that differ greatly from each other can more easily coexist because they use the same resources in very different ways or they use very different resources. For similar species, though, coexistence is less likely. This is summed up in the competitive exclusion principle, which states that species that compete for the same resources in the same ways cannot coexist.[41] For two or more similar species, there is a limiting similarity beyond which coexistence is impossible.[42] For coexistence, competition among members of one's own species must be stronger than competition from the members of other species,[43] that is, an individual must have stronger negative effects on its own kind than on its competitors.

Mechanistically, species coexistence requires: 1) heterogeneity in the environment that interacting organisms experience in time or space, i.e. an axis of environmental heterogeneity or niche axis. Otherwise, in completely uniform conditions, one species will always be superior to the others. 2) The aptitudes of the interacting species must be such that being better at one set of conditions necessarily means being worse at others[44] (jack-of-all trades principle). For desert rodent species of different sizes, the evolutionary tradeoffs associated with coexistence involve finding, harvesting, and then handling seeds of different sizes and characteristics.[45,46] Coexistence occurs when each species has a part of the niche axis at which it profits more than any of its competitors. In this manner, mechanisms of species coexistence explain and give rise to niche partitioning.

What sorts of species might coexist? In the following sections, we discuss five different mechanisms of coexistence found in nature, and how these have parallels in the context of cancer. We then consider potential ways to therapeutically target each of these mechanisms for better patient outcomes.

Food-Safety Tradeoffs

In Nature

The tradeoff of food and safety is among the most fundamental tradeoffs that organisms face and arises for three reasons. First, most organisms have an activity that they can engage in that is relatively safe. This can range from retreating to a refuge to being vigilant for predators to staying stationary to investing in defensive compounds. All these come at the expense of the ability to capture resources, and create a choice between being safer and being better able to obtain resources. Second, all other things being equal, organisms prefer to exploit resources where it is safer and so deplete resources there, leaving behind the most resources where it is riskiest. Third, organisms tend to aggregate where there are plentiful resources, which in turn draws predators. This creates ecological and evolutionary opportunities involving predation risk and competitive abilities affecting traits involving vigilance, foraging efficiency, and mobility.

Communities in nature frequently see the coexistence of a species that is a superior competitor, but that is more vulnerable to predators, and one that is better able to avoid predators at the expense of being able to compete successfully for resources. The former excels in safer places where they can thoroughly deplete resources. The latter excels in risky habitats that either contain more predators or are places where predators can hunt more effectively. In a number of North American Desert systems, bipedal kangaroo rats coexist with quadrupedal pocket mice. Kangaroo rats are better at detecting and avoiding predators, possessing large ear cavities that allow them to hear the wingbeats of owls and using erratic hopping to confuse and flee foxes. Pocket mice lack these advantages, but through their smaller size and simple quadrupedal locomotion they have an energetic advantage when foraging for seeds under shrubs.[35] In a field experiment, adding additional protective shrub cover resulted in the loss of kangaroo rats whereas removing shrub cover resulted in the loss of pocket mice.[47]

In Cancer

Such a mechanism of coexistence is likely to occur when there are tradeoffs in immune evasion and efficient resource uptake. Successful immune evasion can include the production of PD-L1 ligands or the down regulation of surface antigens.[48-52] The production of ligands may be costly, and presumably the surface antigens that otherwise would be present aid the cancer cells in resource detection and uptake. Other forms of safety can involve signaling cancer associated fibroblasts that then serve to protect cancer cells from T-cells or from detection.[53] These are equivalent to anti-predator morphology, defensive chemical compounds, and the ability to effectively use vigilance. Such anti-predator measures would be most valuable where immune cells are at their greatest abundance. Coexistence of cancer cell types may happen because if all other cells are immune-suppressive at a cost, then a cancer cell that forgoes these traits will be favored as a free-rider. Alternatively, if all other cancer cells forgo any immune evasion traits, then one that does will be favored. In tumors exposed to immune surveillance, we might expect to see two types coexisting within the same region: one that is immune-suppressive at a metabolic cost and the other more efficient at nutrient acquisition at an immune cost.[54,55]

Furthermore, the immune-suppressive types would be in greater relative abundance in the risky environment near vasculature or the tumor's edge, and the type most efficient at nutrient uptake in locations farther away from immune infiltration.

Implications for Therapy

The goal of most therapies is to successfully treat all of the cancer cells regardless of type. Once there are several coexisting types of cancer cells, some therapies may be effective for some types, but not others. With regard to the coexistence of an immune-evasion specialist and a resource acquisition specialist, some favored drug combinations may already target both types of cancer cells. For instance, when two immune-therapies are given together, each with a different mode of action, one may serve as a checkpoint inhibitor (e.g, anti-PD-1 nivolumab) thus unmasking the immune-evasion specialist, while the other may stimulate a direct immune response (e.g., anti-CTLA-4 ipilimumab)[56] that is effective against the resource specialists, though combinations create toxicity risks.[57] Or, it may suggest the application of a chemotherapy that targets rapidly proliferating cells after having used a checkpoint inhibitor to suppress the immune-evasion specialists. The first drug creates competitive release of the resource specialists, thus promoting enhanced cell proliferation. In this case, it may be better to give the immune-therapy and chemotherapy in fairly rapid succession as a first and second strike[58,59] rather than together.

The philosophy behind adaptive therapy recognizes that continuous high dose therapy will eliminate sensitive cells and permit the proliferation of resistant cells.[59] If there is a cost to resistance then there is a kind of food-safety tradeoff between the sensitive and resistant cancer cell types. By strategically withdrawing therapy before all of the sensitive cells have been eliminated, the sensitive cells can rebound in a manner that competitively suppresses and slows the increase in resistant cells. Once the tumor burden rebounds, therapy can be reapplied to suppress the now resurgent sensitive cells. This cycling of therapy in response to nadirs and peaks in tumor burden effectively promotes the coexistence of these two cancer cell types, but in a manner that prevents or stalls either from reaching unacceptably high tumor burdens.[60]

Diet Choice

In Nature

Diet choice provides the most basic mechanism of species coexistence.[61,62] The environment offers different types of foods or resources. The foods may have different energetic content, require different amounts of time or different techniques to handle, differ in nutrient content, have different types and amounts of toxins, and so forth. The tradeoff necessary for coexistence is that to be more efficient on one type of food, an organism sacrifices efficiency on another type of food. Coexistence is possible if foragers each have a food type on which they are more efficient than their competitors.[63]

The classic example of resource partitioning via diet choice comes from the Galapagos Islands.[64] There, different species of ground foraging Darwin's finches (*Geospiza spp.*) partition seeds according to the size of the seed and the size of the bird's beak. Those birds with deep, broad beaks can crack open large seeds, but are slow and clumsy in handling small seeds to the point where they spend more energy opening the seed than they can recover from digestion. Those birds with small, slender beaks can handle smaller seeds quickly and profitably, but are unable to open larger seeds. In this manner, each finch species has a range of seeds that profits it more than its competitors.[65,66]

Another example concerns Bailey's pocket mouse, a notable specialist among desert rodents. It eats jojoba seeds.[67] These seeds are so rich in lipids that their oil is widely used in cosmetics. But, the jojoba seeds are protected from most rodents and insects by cardioglycosides.[68] Bailey's pocket mouse has evolved the ability to detoxify these defensive compounds. This gives the pocket mouse a supply of unusually rich food that none of its competitors can touch.[69] But such specialization comes at a cost. The more specialized a species becomes at one resource, the worse it is at others. In the case of the pocket mouse, its geographic range is almost entirely limited to where jojoba grows.[70] With jojoba, the Bailey's pocket mouse has nearly exclusive access to a valuable resource and can coexist with other rodents. Elsewhere, it is outcompeted by other species of pocket mice.

In Cancer

Sugars, lipids, amino acids, nucleic acids, trace nutrients provided through the blood, and the molecules secreted by cells within a tumor (sometimes in the form of cancer associated fibroblasts and macrophages co-feeding cancer cells) and detritus (macromolecules from dead cells) provide the diverse and heterogeneous pool of foods that could promote coexistence of different cancer cell types that specialize on subsets of these. The resource acquisition tradeoffs among cancer cells that could promote coexistence have not been well studied. Tradeoffs likely take the form of investment in specialized types of nutrient transporters and nutrient specific membrane permeabilities (perhaps pertaining to hydrophobic lipids and hydrophilic amino acids). There may also be tradeoffs in the capacities for micro- and macropinocytosis and the associated metabolic pathways associated with extracting useful materials from lysosomes.[71,72]

Thus far, cancer biologists have identified the coexistence of different cancer cell types in terms of the obligate need for or independence from certain growth factors such as estrogen (breast cancer), testosterone (prostate cancer), EGFR (lung cancers and others), or HER2 (breast cancer). Essentially all breast cancers possess both ER+ and ER- cancer cells (cells with or without estrogen receptors that either depend on estrogen or progesterone to grow). It is their frequency that determines how the cancer is classified. Lloyd et al.[20] found that the

degree of vascularity was positively correlated with the frequency of ER+ relative to ER- cells.

Implications for Therapy

Therapies already target those cancer cells that require growth factors as an essential resource, and it is known that such therapies often favor cancer cells that become independent of the growth factors, thus reducing therapeutic options (e.g, progression following anti-EGFR therapies in lung cancer[73]) For instance, triple negative breast cancer (cancer cells independent of a triplet of growth factors) has a poor prognosis and a more limited and effective range of therapies. Therapies can also include targeting nutrient transporters such as GLUT-1, but these seem to favor cancer cells that specialize on other resources. If there are coexisting cancer cell types including some that are targetable and others that are not, then a close sequencing of a targeted therapy with a chemotherapy may be more effective than giving them in combination. The targeted therapy will reduce the cell types specialized on the resource, allowing the follow-up chemotherapy to be more effective against the other cell types experiencing a fleeting competitive release.

An adaptive therapy trial with abiraterone more than doubled progression free survival of men with castrate resistant metastatic prostate cancer.[64] At this stage of the disease there appear to be three cancer cell types, each with different nutrient needs: T+ cells that require exogenous testosterone; TP cells (CYP17 mutation[74]) that produce their own testosterone and leak it into the environment as a public good; T- cells that are independent of testosterone, but at a very high metabolic cost.[75] Androgen deprivation therapy (Lupron) effectively limits T+ cells, and Abiraterone targets the androgen receptor and eliminates TP cells. But together, continuous lupron and continuous abiraterone will eventually select for lethal tumor burdens of T- cells. Instead, to prevent the competitive release of the T- cells, the adaptive therapy called for abiraterone to be administered only until PSA levels dropped to below 50% of initial. At this point, abiraterone administration was halted until the PSA levels of the patient climbed back to the initial value, at which point it was again resumed. In this way, cycling abiraterone greatly prolonged progression free survival by maintaining communities of T+ and TP cell types.

Habitat Selection

In Nature

Ecosystems offer spatial heterogeneity in predation risk, physical features, and resource availabilities. As such, habitat selection is one of the largest sources of biodiversity.[76] At the largest scale of biomes, climatic patterns of temperature, precipitation, and seasonality promote entirely different communities of plant species ranging from tropical rainforests to deserts and tundra.[27] At smaller scales, physical conditions can dictate the habitat-specific communities. The deeper water of a pond supports floating aquatic vegetation such as lily pads, the shallow water supports emergent vegetation such as reeds and cattails, the edge of the pond supports shrubs and smaller trees that can tolerate shallow, water-logged soils, and finally upslope from the pond there may be large hardwood trees.

Fox squirrels and grey squirrels of North America exhibit habitat selection via a food-safety tradeoff.[77] Grey squirrels, as the better competitor for resources, dominate in the deep woods where predators such as hawks and coyotes have obstructed access. Fox squirrels succeed on the wood margins where predators have unobstructed access. Continuing with squirrels, North America has tree squirrels (like the grey and fox squirrels) as well as ground squirrels inhabiting meadows, grasslands, and pastures. Each of these groups of squirrel species exhibit habitat specific adaptations that make them suitable for one, but not the other habitat.[21,78]

In Cancer

Habitat heterogeneities in cancers likely promote the diversification and coexistence of specialized cancer cells. At the smallest scale, there is the gradient of conditions from near to far from vasculature.[79,80] This gradient may be only 5-10 cell diameters long. At the scale of whole tumors there can be necrotic zones, vascularized regions within the tumor, and regions on the edge of the tumor.[81] At the largest scale there can be disseminated metastatic tumors in various tissue types.

Proximity to vasculature likely selects for different cancer cell types. Those near the vessels experience crowding as well as greater access to nutrients, physiologic pH, and normoxia. Those farther away experience lower densities of competitors, but less resource replenishment, buildups of toxic metabolites, hypoxia, and acidic pH. Like the tree and ground squirrels, different suites of adaptations are required to succeed near and away from vessels. For example ER+ breast cancer cells occur closer to blood vessels with a supply of estrogen than ER- cancer cells.[20]

Lloyd et al.[19] found that the majority of cancer cells inhabiting the tumor edges of breast cancer patients had upregulation of CAIX and a variety of other characters suggesting adaptations for a resource rich, but risky habitat. Those inhabiting the interior of the tumor upregulated CAXII and had other adaptations associated with a resource poor, but safe habitat. Like the fox squirrels and grey squirrels, respectively, the edge cancer cells experienced greater immune infiltration while those on the interior experienced greater resource competition. Different cancer cell types on the edges and interiors of tumors may be the norm though characteristics may be both cancer and patient specific. Whether the necrotic zones are uninhabited, or like deserts, occupied by sparse populations of cancer cells with specialized adaptations remains an open question. We suspect that like extreme habitats in nature, there will be a few specialized cancer types that would best be described as "extremophiles."[82]

Metastases, particularly in tissues different from the primary tumor, exhibit cancer cells that are different genetically and

phenotypically.[83] Like plant biomes, this would be expected as different tissues offer different hazards, opportunities, and cellular structure.[84] For instance melanomas metastasizing to the brain are going from a stiff, relatively resource poor and immune cell rich environment to one that is quite the opposite.[85] In fact, when a colorectal cancer metastasizes to the liver one might expect that the cancer cells will begin to evolve and converge on types that are increasingly similar to primary liver cancer cells.

Implications for Therapy

A number of therapeutic regimes recognize the gradient effects of near and away from vasculature, implicitly recognizing that the cancer cells themselves may be of different types. For example, anti-angiogenics aim to starve subsets of cancer cells, but the frequent failure of this therapy points to cancer cell types capable of surviving under the resulting extreme conditions. More recently, it has been suggested to apply a sequence of therapies: the first strike is aimed at eliminating the cancer cells near the vessels, and then a second strike of therapies that then more successfully diffuse into areas farther from vasculature.[86-88] Combinations of therapies have been proposed that either reduce (bevacizumab) or encourage vasculature (vascular normalization therapies).[22] Expanded vasculature may favor the rich-habitat cancer cell types as well as increased proliferation, possibly enhancing the effects of chemotherapies. Reduced vascularity will favor the poor-habitat types and may possibly enhance the application of drugs intended to disrupt habitats further by destroying the extra-cellular matrices.

The presence of acid-adapted, immune-evasive cancer cells on the edges of tumors versus more resource efficient cancer cell types in the interior invite therapies that target the most aggressive or target one and then the other. For example, in a laboratory trial, a chemotherapy proved far more effective in targeting CAIX expressing cells when the mice were also given bicarbonate in the drinking water. This neutralized acidic conditions around the tumor, changed the community of cancer cells towards a less aggressive phenotype, and altered the habitat characteristics of the tumor in a manner that favored normal cells.[89,90]

Current therapies for disseminated cancers generally use the drugs that are considered appropriate for the primary tumor. In some cases, it might be better to have separate therapeutic regimens for the different metastatic sites. For instance, drugs typical of primary liver cancers might have value for other cancers that have metastasized to the liver. By seeing the metastatic sites as distinct communities of cancer cells, it might be useful to collectively or serially target each of these communities.[91]

Variance Partitioning

In Nature

Cyclic or stochastic variation in resource availability can provide environmental heterogeneity that can promote the coexistence of different species. Two tradeoffs can allow for this: travel speed versus foraging efficiency, and foraging speed versus foraging efficiency. There is an additional mechanism of species coexistence under temporal variability known as the storage effect; this interesting mechanism is treated in detail in another contribution to this special issue.[92]

If resource heterogeneity occurs in space, coexistence can occur between a species that travels easily and quickly between patches, seeking out the richest patches or concentrations of nutrients from which it "skims the cream," and an efficient species that can deplete patches thoroughly, "crumb picking" from patches previously exploited by its competitor. Each species tailors a distribution of resources better suited to its competitor, the "cream skimmer" by revisiting patches frequently to reduce variance among patches while leaving a high mean, and the "crumb picker" by allowing long renewal and resource accumulation in rare rich patches.[93] Harris's antelope ground squirrels (cream skimmer) and Merriam's kangaroo rat (crumb picker) are known to coexist via this mechanism in the Sonoran Desert of Arizona. The kangaroo rat's smaller body size and lower metabolic costs give it a foraging efficiency advantage as it depletes resources more thoroughly. The ground squirrel uses its greater speed and mobility to seek out the richest patches and exploit those patches quickly to obtain the lion's share.[37]

Temporal or seasonal variability can create pulses of productivity and subsequent depletion by foragers. This creates alternating times of plenty and times of scarcity. Coexistence can occur between a species that can harvest abundant resources quickly during times of plenty and one with low foraging costs that can deplete resource patches more thoroughly when resources are scarce.[36] In popular imagination, sand dunes almost define the essence of deserts. These dunes are populated by diverse assemblages of seed-eating rodents that depend on temporal variation. Each day, the wind blows the sand and carries with it seeds of desert plants. These seeds accumulate in small depressions and wind shadows and provide resource patches that renew daily. Each night, the rodents emerge from the safety of their burrows to harvest those resources. On Negev Desert sand dunes, two species of gerbils nearly identical in every way save body size coexist on these pulses of seeds. The larger species (greater Egyptian sand gerbil) emerges first, using its greater speed to avoid predators and seek out and deplete rich seed patches first. It also uses its large size to aggressively fend off the smaller species (Allenby's gerbil). But its large size requires more food, and soon the depletion of food patches forces its retreat to its burrow. Then, the smaller species, freed of interference and needing a far lower density of seeds to make a profit, can continue to exploit the seed patches until dawn.[36,94-96]

In Cancer

Tumor micro-environments show regular or stochastic variation in blood flow, inter-cellular matrices, crowding, and the frequencies of various normal cells that may promote or suppress the cancer cells. In particular, occlusion of existing blood vessels or redirecting of others guarantees fluctuating availabilities of glucose, amino acids, oxygen, pH, growth factors, trace

nutrients, and metabolites.[97] It is recognized that cancer cells moving in this environment can show varying degrees of motility, and that this motility may be metabolically expensive. Like for the ground squirrel, greater motility allows the more mobile species of cancer cells to travel towards favorable spots and away from less favorable ones. Conversely, the less motile cancer cell species may be able to maintain proliferation and survival when a location is less favorable. The epithelial (efficient yet less motile) mesenchymal (less efficient but mobile) transition (EMT) of cancer cells may demonstrate such as tradeoff.[98]

Variance partitioning in such an environment may be predicated from contrasting metabolic adaptations. Pseudohypoxia or the Warburg effect may favor cream skimming.[99,100] The high rates of glycolysis may fuel membrane transporters that allow for an inefficient, but otherwise high rate of nutrient uptake, particularly when nutrient availabilities are high. The ability to go dormant or quiescent[101] would add a further advantage for avoiding bad periods. Conversely a cancer cell species that emphasizes oxidative phosphorylation may be a slower, but much more efficient forager. While not accruing resources as quickly during times of plenty, it would be able to continue foraging profitably at lower resource availabilities. Cancer cells certainly exhibit phenotypes that match the tradeoffs of speed versus efficiency (in time or space), and it remains an open question whether this acts to diversify cancer cells into distinct species exhibiting different foraging speeds and efficiencies.

Implications for Therapy

The implications for therapy resemble those for habitat selection discussed above. Anti-angiogenics should be effective against the fast foragers, the cream skimmers adapted to exploiting pulses of productivity or seeking out the richest patches. Therapies intended to disrupt conditions in the tumor microenvironment that favor efficiency, then, should be effective against the cancer cells adapted to forage efficiently on depleted resources. This may include pro-angiogenics that normalize vasculature. These can be used either in the framework of first and second strikes or in an alternating fashion as part of an adaptive therapy program.

Competition-Colonization Tradeoffs

In Nature

This mechanism of species coexistence is an extreme case of spatial and temporal variability that influences whole subpopulations within a location. If local catastrophes are sufficiently severe then whole subpopulations may be eliminated. Some individuals must then disperse both to avoid extirpation at their current location, and to colonize empty and now favorable locations. Dispersal between subpopulations versus the ability to compete within an extant subpopulation provides the tradeoff for species coexistence. Within a subpopulation the better competitor will eventually exclude the better disperser. The better disperser will be able to colonize more rapidly recently extirpated subpopulations and enjoy a period of competition free growth.[102,103]

In one example, on the Pacific coast of North America, the mussel *Mytilus californianus* dominates the intertidal zone and can crowd out all of its competitors. In exposed areas, wave action periodically sweeps away the mussels and creates open patches on the rocks. These are rapidly colonized by the sea palm *Postelsia palmaeformis*, and there they remain until they are eventually displaced by the slow-colonizing mussels.[103]

In Cancer

This mechanism of coexistence has been proposed for promoting a diversity of cancer cell types.[104] Under the guise of "go or grow" models, cancer cells are viewed as experiencing a tradeoff between proliferative capacity (competitive ability) and migratory capacity (colonizers).[105-107] If there are new spaces to be colonized at the boundary of the tumor's growing edge, then one species of cancer cells (growers) predominates in the interior, and the other (goers) at the edge. Just as likely are catastrophic events within the tumor itself. Necrotic and favorable areas within a tumor are not necessarily static. As locations switch between the two,[108-111] both types of cancer cells can now be favored and coexist. Conventional wisdom sees colonizer species as having more metastatic potential. Indeed, the capacity to colonize unoccupied space may include additional adaptations for tolerating the immune system and novel conditions. This may be seen in the characteristics of the highly glycolytic and motile MDA-231 breast cancer cell line that metastasizes easily in mouse models, versus the MCF-7 breast cancer cell line that exhibits strong cell-cell adhesion, less motility, and less glycolysis. This latter cell line will grow in mouse models as a single, non-metastatic tumor.

Implications for Therapy

Existing therapies that aim to prevent metastases and target the EMT make sense within the context of colonization-competition tradeoffs.[112-114] Targeting the more motile, colonizing species of cancer cell should be a high priority. As an unintended consequence, their colonizing strategies are likely to produce metastases. But, success at treating the colonizers may provide competitive release for the more competitive species resulting in the progression of existing tumors. The competitive species should proliferate rapidly. Thus, alternating chemotherapy with kinase inhibitors that target the motile species may show more success than combination therapies that may speed the evolution of co-resistance. A recurrent theme is that drug sequences should change relatively frequently before resistance has had a substantial chance to evolve. Radiation therapy and surgery (particularly for glioblastomas) create space that may encourage the motile, colonizer species. Hence, neoadjuvant therapies may want to be directed towards the colonizer species and then adjuvant therapies could in

combination be aimed at both species of cancer cells. Therapies for glioblastomas already consider the presence of two or more coexisting cancer cell types that may require different regimens.[115-117]

Concluding Remarks

We feel it is likely that some of the genetic and epigenetic heterogeneity seen among cancer cells in a patient represent distinct cancer species that occupy different ecological niches. If so, then when we apply therapies we are treating heterogeneous and well-structured communities of coexisting cancer cell types. Many contemporary therapies comprise administering one to several drugs simultaneously to patients repeatedly at maximum tolerated doses until remission or until issues arise with tolerance or the cancer cells evolve resistance and the cancer progresses. This approach can and often does succeed so long as the drugs are well chosen and the cancer cells strongly resemble each other. But for tumors comprised of highly diverse cancer cells, therapy applied blindly may instead lead to competitive release of certain classes of cells especially if resistance is involved. However, we should be able to take advantage of knowledge of the structure of cancer cell communities in tumors to successfully manage or even eliminate the cancer. To do so requires an understanding of the mechanisms of coexistence of the different cancer cell species in question. For example, therapies with immune-modulators affect issues of food and safety and will favor cancer species that excel at evading immune cells and mechanisms of coexistence involving habitat selection at various scales; hormone therapy will affect issues of diet selection and mechanisms of coexistence based on them. We hope that knowledge of the communities of cancer cells and the mechanisms that promote the diversity of coexisting cancer species can guide the therapy to more favorable outcomes.

Authors' Note

An ethics statement is not applicable to this essay since it does not involve the use of animals or human subjects.

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