FEATURE ARTICLE

Of Phylogenies and Tumors: Cancer as a Model System to Teach Evolution

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ABSTRACT

When students think of evolution, they might imagine T. rex, or perhaps an abiotic scene of sizzling electrical storms and harsh reducing atmospheres, an Earth that looks like a lunar landscape. Natural selection automatically elicits responses that include "survival of the fittest," and "descent with modification," and with these historical biological catch phrases, one conjures up images of large animals battling it out on the Mesozoic plane. Rarely do teachers or students apply these same ideas to cancer and the evolution of somatic cells, which have accrued mutations and epigenetic imprinting and relentlessly survive and proliferate. Our questions in this paper include the following: Can cancer become an important teaching model for students to explore fundamental hypotheses about evolutionary process? Can the multistep somatic cancer model encourage visualizations that enable students to revisit and reenter previous primary concepts in general biology such as the cell, mitosis, chromosomes, genetic diversity, ecological diversity, immune function, and of course evolution, continually integrating their biology knowledge into process and pattern knowledge? Can the somatic cancer model expose similar patterns and protagonists, linking Darwinian observations of the natural world to our body? And, can the cancer clone model excite critical thinking and student hypotheses about what cancer is as a biological process? Does this visually simple model assist students in recognizing patterns, connecting their biological curriculum dots into a more coherent learning experience? These biological dynamics and intercepting aptitudes of cells are amplified through the cancer model and can help shape the way biology students begin to appreciate the interrelatedness of all biological systems while they continue to explore pivotal points of biological fuzziness, such as the microbiome, limitations of models, and the complex coordination of genomic networks required for the function of even a single cell and the realization of phenotypes.

In this paper we use clonal evolution of cancer as a model experience for students to recreate how a single, non-germline cell appears to shadow the classic pattern of natural selection in body cells that have gone awry. With authentic STEAM activities students can easily crossover and revisit previous biological topics and the ubiquitous nature of natural selection as seen in the example of somatic cells that result in a metastasizing tumor, giving students insight into natural selection's accommodating and tractable patterns throughout the planet.

Key Words: *Cancer, Clones, Evolution, Somatic cells*

Background

Cancer will touch everyone at some point in their lifetime either personally or through a dear relationship.

By illustrating this simple model, students can compare and contrast cellular processes and mechanisms that may become derailed in the progression of cancer and come to appreciate that all living systems are complex, variable, and changing.

Despite advances in treatments and increased knowledge about cancer, cancer rates continue to rise globally. Childhood cancers have been steadily increasing (Zahm, 1995). Some cancers such as thyroid carcinomas have risen sharply over the last 30 years (Miranda-Filho, 2021). In 2022, a Harvard report revealed a dramatic increase in cancer in people under 50 with risk increasing in every generation (Brigham & Women's Hospital Communications, 2022). The progression and outcomes of this broad and often fatal disease are largely unknown with growth and metastasis becoming difficult barriers to a cure. One significant reason for cancer's tenacity is the variable, diverse nature of cells themselves, environments, and individual genomes and the cellular response to new mutations and epigenetic changes (Boland, 2005). Cancer as a topic in biology can offer students opportunities to explore the cell cycle in more detail, the effect of environment on cell dysregulation, all possible causes, and the effect of mutations on regulatory genes, and of course insight into evolutionary process. For

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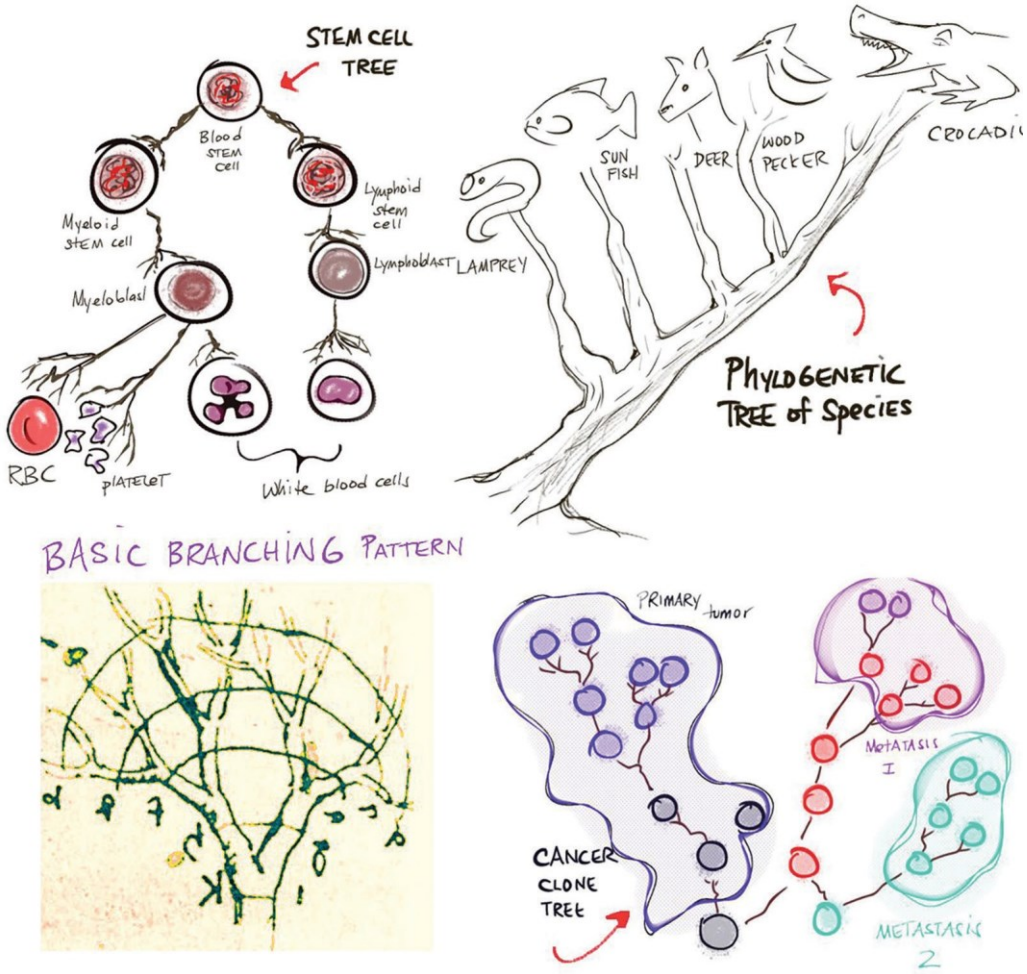

Figure 1. Comparison of different types of branching trees used for three different processes: stem cells, evolution of species, and cancer. To the farthest left, Leonardo DaVinci's sketch of branching patterns in trees.

students, cancer would be an example of somatic cell evolution as opposed to the germline evolution of sexually reproducing species, or stem cell differentiation. Students can see the differences in the evolution of single cells that make up tissue communities by comparing different simplified tree diagrams (see Figure 1). Somatic mutations in cancer models provide three very important teaching points: (a) a simplified example of eco-evolutionary relationships, one that students themselves can visualize at the cell level; (b) cancer as a sub-interdisciplinary activity, drawing in such topics as cell function, genetics, mitosis, evolution, ecology, and immune function; and (c) encouraging students to recognize similar biological patterns throughout the natural world (genetic diversity, community interactions, community diversity, selective pressures, convergent evolution, interdependency within all living systems, inter and intraspecific competition). Together these allow students to evaluate the model itself. Understanding the conceptual model of somatic cancer spread can act as a scaffold for other biological inputs to the process.

Somatic evolution plays out in everyone, making evolution visible and experienceable! This is unlike the tree of life in which the whole process has run once to produce the tapestry of life around us. The repeatability of cancer makes it possible to learn general evolutionary rules (Townsend and evolutionary tape is rerun all the time; https://www.yalescientific.org/2016/08/replaying-the-tape-of-cancer-development/).

Cancer across the Tree of Life

Almost everyone knows someone with cancer, but in biology we also know that some species seem almost impenetrable to the disease, and others seem more susceptible. We know that in somatic cells that do not typically divide, cancer is sparse or nonexistent, such as in striated muscles or neurons of our own bodies. We also marvel at species such as naked mole rats who never seem to develop cancer or rotifers who defy aging. Even water bears (Tardigrades) can teach us about evolutionary resiliency and resistance to cancer-causing agents such as radiation. Models that explore the cost-benefit ratio of tumor suppressor genes posit the drawbacks of dedicating significant genomic energy to staving off cancer such as reduced fertility. This is an opportunity to explore biological, cellular, and genomic diversity across the tree of life, introducing students to organisms such as the naked mole rat and maintaining the theme of diversity in living systems.

Here we can introduce students to the animals that are less susceptible to cancer such as elephants and bowhead whales, and we

can also explore animals such as clams that transmit cancer through the horizontal transmission of cancer cells. Again, even with bivalves, fatal leukemia that has appeared in marine bivalves across the world could be traced back to a clonal transmissible cell derived from a single original clam (Metzger, 2015). This is somewhat like the viral cancers of Tasmanian devils. And, still other animals such as Beluga whales have been experiencing extremely high rates of cancer while close relatives such as bowhead whales do not (Nair, 2022). The connection between cancer and environmental toxins cannot be denied, as a plethora of new synthetic chemicals and their unknown combinations have been and continue to be introduced to the environment. Many substances that never existed in the billions of years of cellular evolution have the potential to induce mutations leading to genomic instability, and this too can be introduced in the cancer discussion for students as they explore species. Searching across the tree of life for diverse organisms that can get cancer, finding those that do not can stir up some inquiry and hypothesizing by students in important dialogues that showcase what students perceive, know, and understand about the biology they have acquired. To add to discussions such as comparing cancer rates in one whale species with those rates in another, we suggest exploring the TimeTree: The Timescale of Life website (http://www.timetree.org/) for students to explore divergence times between cancer-resistant species and cancer-susceptible species.

O Biological Diversity and Cancer Clones

"*Cancer cells have defects in regulatory circuits that govern normal cell proliferation and homeostasis. There are more than 100 distinct types of cancer, and subtypes of tumors can be found within specific organs"* (Hanahan, 2000). Distinct cancer types are a mirror of the complexity of normal functioning cells and, therefore, offer an excellent contrast. But what about other kingdoms, they also have complex cellular systems. Students sometimes wonder whether plants get cancer, as they are multicellular. Saguaro cactuses have cancer-like protrusions on their surfaces as these cacti can develop mutations in their meristem cells leading to over proliferation (Nedelcu, 2022). And that cute goldfish with the lumps on its head (Oranda goldfish), those are an excess proliferation of cells from a genetic mutation that creates the morphological variation. In the case of the Oranda goldfish, the tumor on its head is benign and won't grow or spread, unlike metastasizing cells of cancer clones. The Saguaro cactus doesn't circulate cells within its vascular system, and if part of the cactus dies, it can grow another part elsewhere. What about other kingdoms such as fungi—could they also develop a type of cancer too? What limits the growth of some cancers and not of others? We can ask students, is a tree gall like a tumor, and what is unique about the animal kingdom regarding cancer? This is an opportunity to contrast benign versus metastatic, to take another look at the cell cycle, not only in animals but in plants and fungi as well, and to explore the idea of genomic repeats of regulatory regions that control cell proliferation in the genome. We might contrast what is different among these kingdoms.

Mutational fingerprints and variation are also focuses of cancer and tumors that contain inter and intra-heterogenicity, which in effect means that each tumor is made of unique, albeit uncontrolled, rogue cells. Studying cancer will help students conceptualize ideas such as convergent evolution, which would be happening within the human body such as the exchanges that happen between gut microbiota and their own cells and cell lines. In this classroom activity, with the genomic medicine perspective on cancer and tumorigenesis, we can reveal fundamental ideas about evolution and mutations, exploring multiple concepts simultaneously or focusing on just one while exploring questions about why cancer would evolve in the first place. Through the paradigm of cancer clones, students can simulate the process of evolution using paper and pencil tools, storyboarding, and flipbooks. We reexamine terms from biology such as a "clone," and we revisit the idea of why every cell is unique. Through a microscopic and histological backdrop, evolution is played out through familiar protagonists in the intimate geography of a human body.

O Cancer Genes across the Tree of Life

Our cells comprising the tissues of organs live in a complex ecological matrix, just as we do in our individual form, consisting of diverse cells even among the same cell types. It is this variation that aids in the trajectory upon which a tumor may or may not metastasize within its microenvironment. Experiences in cells vary, genomes vary, and that produces different outcomes for progeny. The location and type of mutation also play a pivotal role while the multistage carcinogenesis model suggests that "individual cells become cancerous after accumulating a specific number of mutational hits" (Mishra, 2013). "On the basis of this model, larger (and longer-living) animals are expected to have higher cancer incidence as they have more stem cell divisions overall, resulting in a higher likelihood of producing and propagating carcinogenic mutations" (Nair, 2022). A comparative genomics approach can demonstrate to students how potential cancer genes can be identified across vertebrate species to help illuminate which species are more cancer prone or cancer resistant and demonstrate how diversity (including diversity of pathways of resistance to cancer) spans the tree of life and may or may not be related to character traits such as size or lifespan.

This brings us back to the basics of the cell cycle of mitosis—genes associated with cancer resistance appear to be enriched in the cell cycle, DNA repair, immune response, and different metabolic pathways. Students can then make the connection between robust repair and immune response in some species versus others and the breakdown of these conserved biochemical pathways that may lead to cancer.

The cell cycle is often just illustrated as a flat pizza pie diagram, but its molecular dynamic is enhanced when the cancer model is integrated with it. Protein TP53 is a cancer suppressor gene that codes for the proteins pr53 that regulate cell division. P53 has been studied extensively and is considered a keystone protein as it appears to have many regulatory functions such as halting cell cycles, repairing DNA, and triggering apoptosis (Amaral, 2010). Diverse functions and concepts showcase the diversity of gene functionality and intensify the dimensionality of that pizza pie diagram into a three-dimensional, time-expansive landscape (see Figure 2). Some genes wear many hats and have principal roles, while others have supporting roles. Mutations in genes such as the BRCA gene can demonstrate to students where and why some people are more predisposed to certain cancers than others and demonstrate that gene's existence among diverse phyla. Simultaneously, with the many metabolic events and variables of evolution and development in cells, students can see that genome integrity and stability are evolutionarily very important

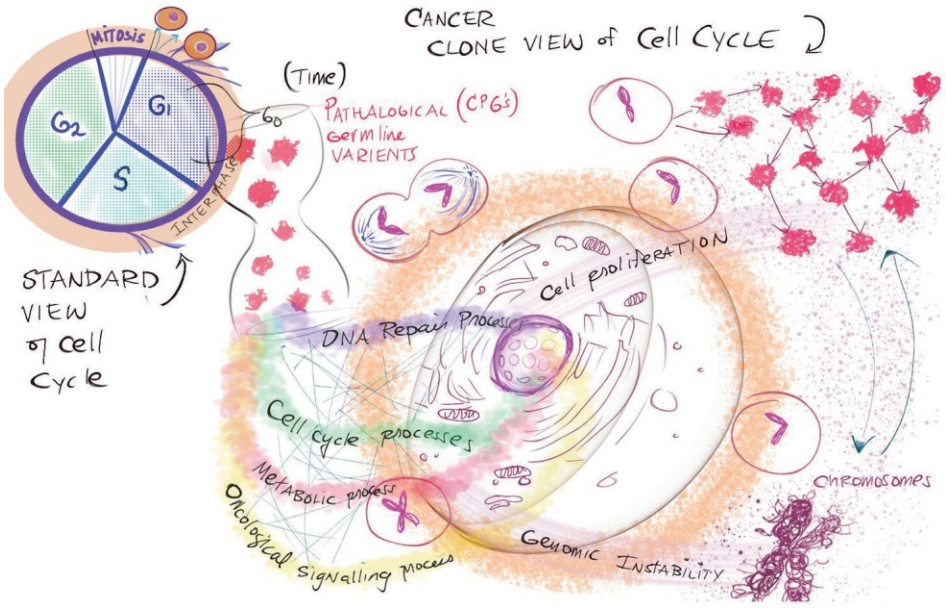

Figure 2. Comparison of the standard cell cycle diagram with a cell cycle that would include a cancer clone model. Students will get a greater sense of the complexity of a cell's life and its genome by using both kinds of visuals. In the cell cycle/cancer clone we see overlapping sub systems within the cell being affected by CpG variants, which further destabilize the cell's normal functions and repair mechanisms.

and evolved very early in animals, with an ancient creature such as the sea anemone having core genes such as TP53. This gene/protein perhaps conferred a survival advantage to early cells in times of strong UV radiation. Showing students a phylogeny of animals along with a discussion of cancer's origins in disrupted protective systems unites us across the tree of life and through evolutionary time with many of these regulatory systems evolving before multicellularity itself. The use of trees for both evolution and cancer assists in conveying multiple visual perspectives on biological processes. Teachers may want to briefly mention Peto's paradox to discuss body size and cancer; "*The evolution of multicellularity required the suppression of cancer. If every cell has some chance of becoming cancerous, large, long-lived organisms should have an increased risk of developing cancer compared to small, short-lived organisms. The lack of correlation between body size and cancer risk is known as Peto's Paradox"* (Caulin, 2011). Another research paper showed that elephants have multiple copies of P53 and are likely to avoid cancer! In another paper, cancer is correlated with a carnivorous lifestyle (Samraj, 2015).

○ Rethinking the "Clone"

Star Wars had its clones, and Dolly the sheep had hers. Clone is a word often used to describe a duplicate, which appears indistinguishable from the original, but we all know there is no such thing as an exact duplicate of anything, especially of anything living. What is surprising to most students of biology and people, in general, is that tumors are diverse populations of cells, not just all the rouge cells. If mutations and epigenetic changes are happening all the time, how is something identical possible? When we talk about cheek cells dividing and producing a new cheek cell in our mouth, we probably envision an identical cell being formed. This is true that the cells are the same cell line, perform the same functions, and are essentially equivalent in their phenotypes, but they are not the same, they are not identical. This is true of everything as it is impossible to replicate identical circumstances, and every single variable that happened along the road of mitosis to that new daughter cell has imparted a change. Every cell and the individual organism is unique as its past imprints on its present, continually. And so, a clone is not an identical cell. Along its short journey, stuff happens—a generation ago, 28 days ago, a minute ago—and is happening all the time. The more students appreciate this idea of continual change, the more evolutionary and biological processes will make sense and we can start to accept that biology will always be a little out of focus. So, for this activity, we will redefine a clone to be a similar cell with a similar genome and fate.

○ What Questions Cancer Can Raise about Evolution

No one wants cancer, just like no one wants to get sick with a cold, but we know that if we get swollen lymph nodes or sneeze or cough that our body is trying to destroy invading pathogens and expel them. The symptoms are a byproduct of a system actively protecting the whole organism. Could cancer be doing the same? The cancer puzzle is far from solved and a handful of hypotheses mingle in the literature, proffering perspectives on cancer and why it occurs. This is an important caveat to the cancer discussion for students. There are multiple models, new models, canceled old models, and revisited models, and students may start to appreciate what a model is by examining multiple templates and prototypes of scientific models. As an example, some have suggested that cancer could be an ancient pathway conservatively operating on a "safe mode," this model is called the "atavistic model." In this model,

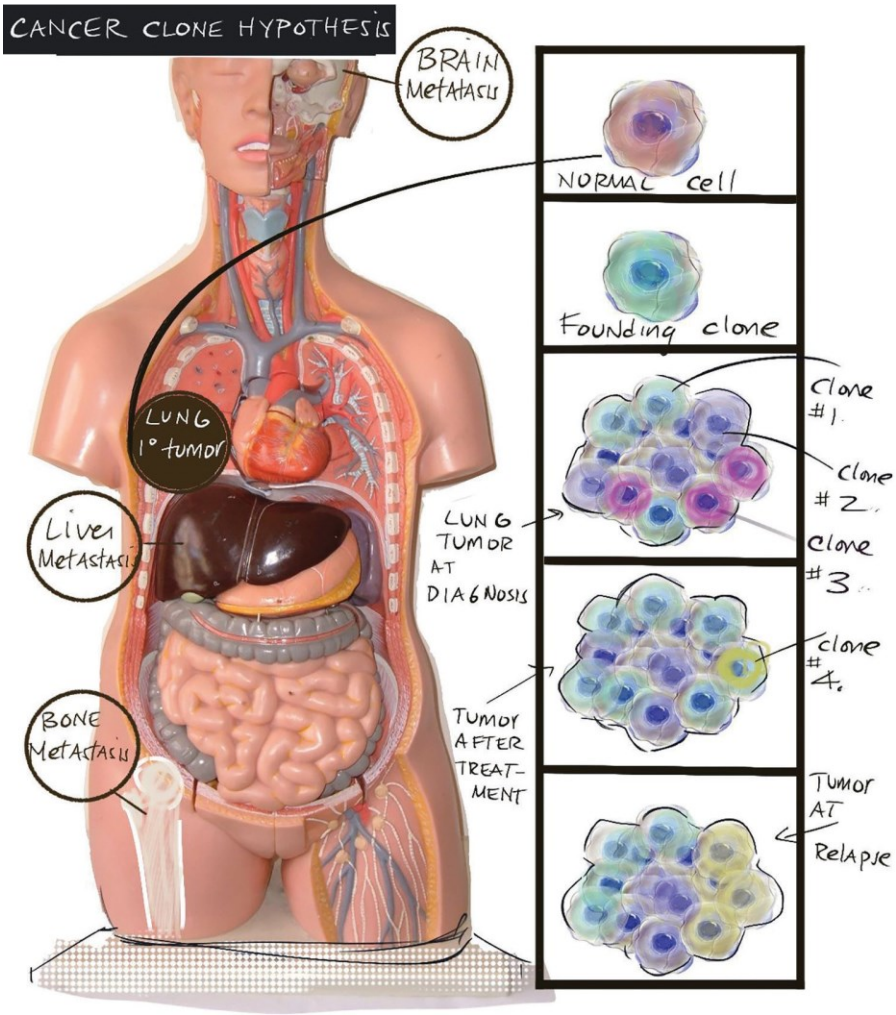

Figure 3. "Activity-in-figure" In this picture, teachers can develop an easy in-class experience using the cancer clone hypothesis, anatomical models, and storyboarding. Here we see the "founder cell," which has accrued mutations developing into metastasizing tumors. Students can cut out colored paper dots to represent the different clones and stick them to the anatomical model while they storyboard the hypothesis. Ask students to explain, in evolutionary terms what is going on, such as what is a founder cell? Or why are the cells changing into cancer clones? Build your discussion with groups around the anatomical model or draw the anatomy on the board.

the more primitive mitotic state becomes activated as genes for the more complex regulatory state become dormant. In other words, ancient genes become more active, and more evolved genes diminish their function (Lineweaver, 2021). This concept is an interesting one to explore with students as it takes students back to the primordial Earth and the first cells and propels them to take another perspective on the cell cycle and the disease itself from a grander evolutionary standpoint. From the more common perspective, with multicellular life we experience cooperation among cells and mechanisms that evolve cooperative biochemical pathways. Are cancer cells capable of cooperation? In a cellular civilization, cancer cells appear to be rule breakers. Do normal cells cooperate to curb cancerous cells from proliferating? This provides insight into the interplay and cooperative nature of the genome in health and disease. Abnormal cell growth has been around a long time simply because the proliferation of new cells is essential for the continuation and expansion of multicellularity—but why? This question is an interesting one to start with in our cancer introduction.

○ Drivers, Passengers, and Shape Shifting Mutations

Some of the most identifiable terms associated with somatic cancer cell models of increasing mutations are the terms "driver mutation" and "passenger mutation." It appears that all cancers are due to changes to the DNA sequences that constitute the genome. Genes that acquire mutations that facilitate tumor growth are called "driver genes." It is the accumulation of somatic mutations and various genetic alterations that impair the important conserved repair and immune functions in cell division/cell cycle check points. This leads to the formation of a tumor, and the mutations that promote and thrust a normal cell into a cancer cell are driving it to that state of instability. Drivers are under positive selection (see Figure 3). Cancer driver genes can be of two types: (a) proto-oncogenes or (b) tumor suppressor genes, such as TP53 (Salk, 2010). Driver mutations confer a proliferative advantage to the cancer cell by increasing the fitness of the cancer cell while passenger mutations are those which

are accumulated along the way through cell division, and just appear to ride along in and through the clonal expansion of cancer. This is the model of cancer that students will be illustrating a storyboard to flipbook activity later. It turns out, however, that identifying driver and passenger mutations is not that simple. In silico simulations and "virtual" tumors, environmental conditions can shift altering the fecundity and survivability of the cancer cell and altering whether a mutation remains a driver. In other words, just like any ecological state, our cells are in constant fluctuation and change, met with new variables and conditions continually, shifting outcomes one way or another (Wala, 2017). This alters the spatial variations and molecular properties of a developing tumor along with the accumulation of mutations and epigenetic imprints. This also confers an evolutionary "history" to the tumor and moves us to a discussion on ecology—the ecology or microenvironment of the tumor. Even with the complexities of driver and passenger mutations, with epigenetic imprinting students start to see a simplified evolutionarily process in multistage carcinogenesis. "Species evolve by mutation and selection acting on individuals in a population; tumors evolve by mutation and selection acting on cells in a tissue" (Muir, 2016). This demonstrates that cancer biology can be an across-the-board teaching tool for connecting the dots of fundamental biological concepts and the fuzziness of biology in general.

The Concept of the Niche

Each visceral space within a human body is a niche and biogeography is one of the major evidences of evolution. Tumors have been described as "evolutionary, biogeographic islands" (Chroni, 2021), complete with migrations, new colonization, and the same mathematical models as traditional biogeographical studies in evolution. We often find tumors growing into areas where there is space, such as the lumen of the intestine, the bladder, or the uterus (Li, 2006). Tumor cells may be sensing out new landscapes and niches where other cells are not occupying that space. This is an opportunity to discuss what an ecosystem is if it has not been encountered and that an ecosystem can be anywhere on this planet, in armpits, intestines, and oceans, but that some important differences exist even though the terminology is similar. The primeval nature of the cell is expansion, and tumor cells, as the atavistic model implied, may be reverting to a baseline function of proliferation without constraint into any area free of other cells. The niche a cell or tissue occupies is very similar to the ecological niche concept. For students, the two comparisons, that is, the ecological niche of the outside environment and the inside niche of the cell, may be beneficial to developing an understanding of the niche concept as applied to living systems. For cancer cells, there may be the realized niche and the real niche, the competition for resources, and the evolution of a specialized "role" within the system. Most people would ask, "Do cancer cells have a specialized role?" Cancer seems counterintuitive to an interdependent system. However, perhaps there is more to cancer's evolutionary function in evolving our immune systems, and this might get students thinking about how a niche functions in similar and different ways throughout living systems.

Competition for Resources

When cancer starts, the drive is to reproduce and often outstrip the environment by hoarding resources. Cancer cells do this very effectively, they break boundaries and they exploit the vascular system by siphoning nutrients into growing cancer cells through angiogenesis. Angiogenesis along with unlimited replicative adaptations and dysregulation of apoptotic mechanisms enhance cancer cell nutrient procurement (Allen, 2011). Cancer cells have an adaptive advantage and to achieve these advantages specific tumor suppressor proteins must be disrupted, but even when cells continue to divide uncontrollably the disruption is halted as the system enters a "crisis" state, which stops continued growth with massive cell death. Karyotypes of fibroblast cells reveal this intervention, which results in fused and deformed chromosomes, however, out of this massive die-off, an occasional variant emerges, one that has resisted the systems senescence shut down (Allen, 2011) and a reason why telomere maintenance is extremely important. Even one hundred years ago, messy-looking, tangled chromosomes were indicators of cancer or tumorigenesis (Holland, 2009). Again, this gross morphological view of the chromosome is a great teaching point and prelude to cancer clones. Students can contrast and compare tangled, distorted chromosomes against healthy-looking ones (see Figure 4) in a sort of chromosome "line up."

The ecological and evolutionary perspective views cancer as a sort of "species" that is operating outside of healthy ecological parameters, goes with the idea of the chromosome as an individual, and encourages the student to think about the dynamic ecological space of cell as it relates to competition among cancer and normal cell lines. The competition concept between cells ushers in all sorts of questions about the breakdown of regulatory systems in a cell and mutations in regulatory regions of the genome. Students see that ecosystems, where uncontrolled consumption have taken place (cancer) become "unhealthy" and if regulating proteins just like apex and meso-predators have been compromised then cooperation too becomes compromised. The comparison of ecological niches and cell niches can evoke an understanding of how populations in systems run astray if the dynamics of the system change. The Zion National Park study where predators were eliminated caused overgrowth of herbivores and collapse of the forest ecosystem. This is a great example to use and compare alongside rouge cancer cells. The outcomes in both the cellular and the forest systems share many similarities, and this creates a great comparison for the idea of competition for resources.

Modes of Selection

"Evolution by natural selection is the conceptual foundation for nearly every branch of biology and increasingly also for biomedicine and medical research. In cancer biology, evolution explains how populations of cells in tumors change over time (Fortuno, 2017)." While the prime directive of cancer cells is quite unlike healthy cells, they still follow the patterns of natural selection. This creates cell competition in the tissue and the selection for the most robust of the cancer clones to survive and proliferate. Cell competition boosts clonal evolution with certain micro and macro environments selecting for greater survivability of the cancer cell. In other words, fitness between cells of a tissue or within an organ leads to the elimination of less competent fellow cells (Greaves, 2012). Students can easily model this and draw this, embodying an understanding of natural selection through the somatic cancer model. Stem cells, and all cells for that matter, are going through natural selection all the time so mitosis is not just a replacement of cells but an evolutionary fixture of mitosis, which can also be compared to the cancer clone hypothesis. From this perceptive we can see that

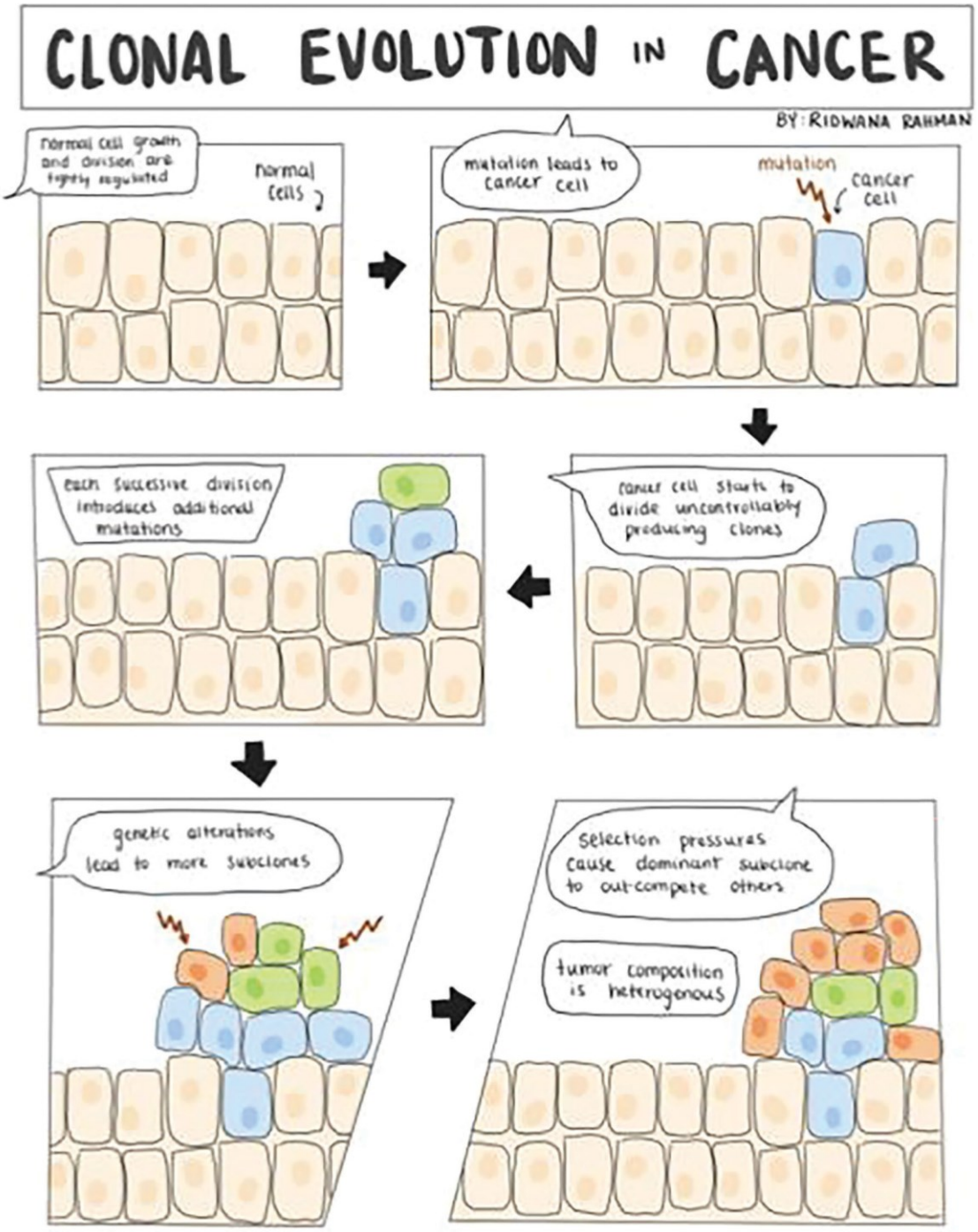

Figure 4. A student's storyboard of the cancer clone hypothesis.

no two cells are ever alike as conditions fix or imprint biochemical signatures on each cell with a plethora of one-time variables and variable interactions, translating the experience of the cell and the genome into unique phenotypes. This binds an understanding of mitosis and evolution together and presents a cross sub-disciplinary teaching point. Like antibiotic resistance, persistent cancer clones become resistant to treatments and students can gain appreciation of the processes of nature, where pushing against something sometimes makes it "stronger."

○ Founder Cells, Cancer, and Cellular Fitness

Tumor growth is an evolutionary process (Boland, 2005), so tethering students' first major conceptual topic, the cell back to and through mitosis and into evolution through the cancer clone hypothesis, is a great way for students to keep the theme of the cell contiguous. It also maintains the cell as a salient feature of their biology course. Using a pertinent, personal health topic helps to

bridge and retain the beginning concept in general biology of the cell with the ending topic of a course, which is typically evolution. In between the cell and evolution are ecological archetypes of change governed by somatic mutations, clonal selection, and random genetic drift. Together, these concepts also link sequential genetic events that pop up through processes, further connecting a student's genetics unit to evolutionary process and fitness. The genome is the conduit by which genes interpret the nuanced experiences of the cell's life including selective pressures, which can be the main takeaway message from the cancer clone model as general cellular fitness is reduced as cells age, as mitochondrial dysfunction grows or cell exposure to radiation and carcinogens increases. Aging, carcinogens, and changes in the histological niche all impart varied selective pressures on cells. Giving students an example of lung cancer and talking about the ciliated endothelial niches of the lung helps students visualize that space. Students can think about changes in that specific microenvironment from toxic intrusions or disruptions such as pollution and smoking where cells are destroyed, as in emphysema. This leaves new niches to be filled by potentially cancerous cells (Satcher, 2022). To make ecological comparisons, the term "landscape" of the lungs or the respiratory membrane can be used to help students visualize this smaller ecosystem evolving inside their own lungs and the lungs as an ecosystem in direct contact with the planet's atmosphere. If the instructor has time, photosynthesis and climate regulation through forests can also be factored into the discussion. This multilayered dynamic can be easily illustrated on the board or through composite images in PowerPoint. Instructors can also cut out different colored dots and place them on anatomical models to demonstrate the metastasis of cancer clones.

o Activities

There are many ways to visualize multistep processes such as cancer. Most students could watch an animation of cells becoming cancer, and admittedly this would be beneficial, but it is always more engaging and more advantageous for students to create something that demonstrates to themselves that they have mastered the terms and the concepts in a personal and unique way. For this experience, the cancer clone simulation can be provided to help students gain more visual insight into the process by showing healthy chromosomes next to unstable ones and healthy histology next to pathological images. We suggest students do this through the flip book. Students work in pairs and one student creates a storyboard (to layout the flip book) for healthy or normal mitosis and the other student creates the cancer clone storyboard and flip book. Students can draw these structures easily as most of them are just circles and oblong shapes or they can use crafting paper and materials to represent variations of the cell throughout the process.

o Materials

- Somatic cancer clone model to teach the concept
- Construction paper of different colors/scrapbooking materials
- Example of a phylogenetic tree
- The human body with organs map (to show spread)
- Sample photographs of actual cancer cells, chromosomes, and histology slides
- Regular card stock paper from storyboards and flip books

o Conclusion

The somatic cancer clone model provides many inputs and reconnections for basic biology concepts that can associate back and forth with each other and to the cancer model. Students can achieve a bigger-picture perspective on cells and the genome through this model and become acquainted with the crossover of ecological terms into a cellular and evolutionary vocabulary. By illustrating this simple model, students can compare and contrast cellular processes and mechanisms that may become derailed in the progression of cancer and come to appreciate that all living systems are complex, variable, and changing. Many interesting questions can continue to be posed regarding the cancer clone model, events such as HGT and regulatory roles of cancer genes and switches, transposons, the role of epigenetics and the microbiome in cancer, and cancer gene behavior are all expandable topics. With arts and crafts, storyboarding, and flipbooks, students can delve into complex topics and enjoy constructing their own models.

References

Allen, T., Allen, T. D., & Cowling, G. (2011). *The cell: A very short introduction*. Oxford University Press.

Amaral, J. D., Xavier, J. M, Steer, C. J, & Rodrigues, C. M. (2010). "The role of p53 in apoptosis." *Discovery medicine, 9* (45), 145–152.

Boland, C. R., & Goel, A. (2005). "Somatic evolution of cancer cells." *Seminars in Cancer Biology*, *15*(6), 436–450.

Brigham and Women's Hospital Communications. (2022). Dramatic rise in cancer in people under, 50. *The Harvard Gazzette*. https://news.harvard.edu/gazette/story/2022/09/researchers-report-dramatic-rise-in-early-onset-cancers/

Caulin, A. F. *Peto's paradox and the evolution of cancer suppression*. University of Pennsylvania, 2014.

Chroni, A., & Kumar, S. (2021). "Tumors are evolutionary island-like ecosystems." *Genome Biology and Evolution*, *13*(12), evab276.

Fortunato, A., Boddy, A., Mallo, D., Aktipis, A., Maley, C. C., & Pepper, J. W. (2017). "Natural selection in cancer biology: From molecular snowflakes to trait hallmarks." *Cold Spring Harbor Perspectives in Medicine*, *7*(2), a029652.

Greaves, M., & Maley, C. C. (2012). "Clonal evolution in cancer." *Nature*, *481*(7381), 306–313.

Hanahan, D., & Weinberg, R. A. (2000). "The hallmarks of cancer." *Cell*, *100*(1), 57–70.

Holland, A. J., & Cleveland, D. W. (2009). "Boveri revisited: chromosomal instability, aneuploidy and tumorigenesis." *Nature Reviews Molecular Cell Biology*, *10*(7), 478–487.

Li, L., & Neaves, W. B. (2006). "Normal stem cells and cancer stem cells: The niche matters." *Cancer Research, 66*(9), 4553–4557.

Lineweaver, C. H., Bussey, K. J., Blackburn, A. C., & Davies, P. C. W. (2021). "Cancer progression as a sequence of atavistic reversions." *BioEssays*, *43*(7), 2000305.

Metzger, M. J., Reinisch, C., Sherry, J., and Goff, S. P. (2015). "Horizontal transmission of clonal cancer cells causes leukemia in soft-shell clams." *Cell 161(2),* 255–263.

Miranda-Filho, A., Lortet-Tieulent, J., Bray, F., Cao, B., Franceschi, S., Vaccarella, S., & Dal Maso, L. (2021). "Thyroid cancer incidence trends by histology in 25 countries: a population-based study." *The Lancet Diabetes & Endocrinology*, *9*(4), 225–234.

Mishra, P. A., Chaudhari, H. R., Desai, J. S., and Khan, U. N. A. (2013). "p53: An overview." *International Journal of Pharmacy & Pharmaceutical Sciences* 5, 59–65.

Muir, B. M. (2016). *Peto's paradox and the evolution of cancer suppression: Lessons from flies, humans, and elephants*. University of California.

Nair, N. U., Cheng, K., Naddaf, L., Sharon, E., Pal, L. R., Rajagopal, P. S., Unterman, I., Aldape, K., Hannenhalli, S., Day, C. P., Tabach, Y., & Ruppin, E. (2022). "Cross-species identification of cancer resistance–associated genes that may mediate human cancer risk." *Science Advances*, *8*(31), eabj7176.

Nedelcu, A. M. (2022). "Evo-devo perspectives on cancer." *Essays in Biochemistry*, *66*(6), 797–815.

Salk, J. J., & Horwitz, M. S. (2010). "Passenger mutations as a marker of clonal cell lineages in emerging neoplasia." *Seminars in Cancer Biology*, *20*(5), 294–303.

Samraj, A. N., Pearce, O. M. T., Läubli, H., Crittenden, A. N., Bergfeld, A. K., Banda, K., Gregg, C. J., Bingman, A. E., Secrest, P., Diaz, S. L., Varki, N. M., & Varki, A. (2015). "A red meat-derived glycan promotes inflammation and cancer progression." *Proceedings of the National Academy of Sciences*, *112*(2), 542–547.

Satcher, R. L., & Zhang, X. H. F. (2022). "Evolving cancer–niche interactions and therapeutic targets during bone metastasis." *Nature Reviews Cancer*, *22*(2), 85–101.

Wala, J. A. "Genome-wide detection of structural variants and signatures of their selection in cancer." PhD diss., Harvard University, 2017.

Zahm, S. H., & Devesa, S. S. (1995). "Childhood cancer: Overview of incidence trends and environmental carcinogens." *Environmental Health Perspectives*, *103*(Suppl 6), 177–184.

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