EvMedEd

Evolution cancer guide

By Daniel Grunspan

1. Cancer and multi-cellularity

Multicellular species have proven to be extremely successful, with humans no exception. While the benefits of multicellularity include larger size and great complexity, a major obstacle in the way of evolved multicellularity is how to maintain continued "cooperation" among somatic cells that otherwise might just replicate themselves as fast as possible. Five major adaptations have been important to control replication. Cancers occur when mutations disrupt mechanisms that enforce cooperation:

i. Proliferation inhibition

Multicellular species evolved from a unicellular ancestor. In unicellular species, cell division is synonymous with reproduction. However, multicellular organisms must regulate cell proliferation to prevent cancer. Checkpoints on the cell cycle that prevent this proliferation represent an important adaptation in multicellular evolution that prevents cancer.

ii. Controlled cell death (apoptosis)

Controlled cell death is a process essential for multicellular organisms to manage development, fight infection, or prevent cancer. When a cell can no long be triggered for self-destruction, it loses an important cancer preventing mechanism.

iii. Division of labor

A major advantage of multicellularity is division of labor. As opposed to unicellular species, where one cell has to perform all metabolic functions necessary, cells can become specialized. This specialization required evolved mechanisms to differentiate stem cells into specific cell types. Typically, once a cell is completely differentiated (e.g. a skin cell or nerve cell), it can never replicate again. However, stem cells maintain the ability to replicate for the entirety of an organism's life. Evidence suggests that many cancers originate from "Cancer Stem Cells," which retain the capacity to self-renew.

iv. Resource allocation

Within many multicellular species, complex systems, such as the vascular system and the respiratory system, distribute resources throughout the body. Such systems are essential to making larger body sizes possible. Many cancers exploit evolved resource allocation systems, for instance, by hijacking angiogenic signaling.

v. Maintenance of shared extracellular environments

Different cell types share extracellular spaces. Boundaries between these spaces can limit cancer growth. Many cancers evolve mechanisms that destroy these boundaries, paving the way for further spread of the cancer.

2. Cancer and somatic selection

Cells that make up a tumor are not identical epigenetically or genetically. Differences between cells are magnified by mutations that increase mutation rates, causing a constant influx of new mutations and high cell diversity within tumors.

Mutations in tumor cells affect the ability of cells within the tumor to grow, replicate, and metastasize. Importantly, cells in a malignancy compete for energy, space, signals inducing division, and ways to avoid attacks from the hosts' immune system or chemotherapy drugs. Competition between cells and heritable variation within a tumor are the crucial ingredients for selection to take place. Thus, we have to treat a tumor as an evolving population made up of cells best able to survive and out-reproduce others.

This viewpoint is especially important for considering treatment. Much like treating a bacterial infection with antibiotics selects for antibiotic resistance – treating cancer tumors with a single therapy selects for cells resistant to that therapy.

3. Tumor ecology

Tumors exist in a larger ecosystem, and ecological principles are useful for understanding cancer. For example, logistic growth models, where population growth is modeled as a function of current population size and available resources, are often used when considering tumor growth. However, tumor growth can often be density dependent and cannot survive if they are reduced to a threshold number of individuals. Sometimes called the Allee effect, this can occur if a certain population size is required to maintain mutual defense of feeding mechanisms. This can also be true for tumors, when the growth of requires a mass of malignant cells above a certain threshold. When this if the case, it implies special treatment strategies, such as taking advantage of the Allee effect in a cancer, or treating the cancer to reduce its size to a critical threshold, instead of attempting complete extinction.

Another ecological consideration is interactions between tumor and other cells. Tumors rely on other cells in the body that are not necessarily cancer cells, such as immune cells and stromal cells, to behave in ways that support tumor growth. For instance, in some tumors, macrophages are reprogrammed to suppress any attack. This network of interactions is important to consider in tumor growth, and provides potentially new strategies for treatment.

4. Behavioral ecology and cancer

While tumor cells compete for resources as they replicate, they can also help one another grow. For example, mutations that lead to increased signaling for growth factors can increase replication rates. If one cell in a tumor acquires this sort of mutation, other cells nearby can benefit. This may result in a situation where some tumor cells free ride off of the cells producing the local good (in this case, signal for more growth factors). Cooperative dynamics may emerge if other cells in the tumor also produce a public good – for example, they signal for other kinds of growth factors. This kind of cooperative dynamic can lead to particularly aggressive cancers.

5. Natural selection explains why cancer is rare

Cancer will always occur given enough time, however it doesn't occur as quickly or with as high of frequency as one might imagine. This is because evolution has shaped mechanisms that defend against cancer. Cancer is more likely to emerge in species-specific "selection shadows," times later in life when natural selection pressures are weaker because of smaller population sizes and reduced reproduction rates.

Individuals who get cancer before or during their prime reproductive years will have lower reproductive fitness, especially if the cancer causes death. So, individuals who have mechanisms that prevent cancer (e.g. DNA repair mechanisms or cancer elimination mechanisms) will have more offspring on average than those that don't. Individuals with mechanisms that delay cancer have a selection advantage over those that don't, and selection acts on these differences to create species-specific cancer defense mechanisms based on the life history of that species."

6. Peto's Paradox

Cancer occurs when mutations accumulated in the same cell lineage lead to unregulated cell division. This means that the likelihood of cancer occurring for an organism is a function of the number of cells that individual has, and how many times those cells replicate over a lifetime (which is effectively the lifespan of that individual). The more cells and the more cell divisions and the longer the lifetime for a species, the more opportunity there should be for cancer causing mutations to develop. Thus, extremely large and long living-species, like, elephants, should have high rates of cancer compared to small species like mice. However, this is not the case, and in

fact, mice get cancer at higher rates than elephants. This disparity is referred to as Peto's paradox – large long living species tend to have cancer rates much lower than we would predict.

The reason larger species, like elephants, do not get cancer at rates much higher than smaller and shorter-lived species like mice is due to evolved species-specific cancer defenses. For example, elephants have 20 copies of gene TP53, a heavily studied tumor suppressor implicated in many cancers. Humans, on the other hand, only have one copy of TP53.

7. Environmental factors

While cancer happens given enough time, aspects of modern life greatly accelerate mutation rates, and ultimately the onset of cancer. Novel carcinogenetic activities and exposures lead to increased susceptibility to different kinds of cancers. For example, breast and ovarian cancer rates increase with the number of menstrual cycles a woman experiences in her lifetime. Because women who have fewer children have more menstrual cycles, rates of cancer increase with lowered fertility, which is a relatively novel cultural behavior. Likewise, prostate cancer in men is linked to high levels of testosterone, which occur more often in Westernized populations where net energy intake is high. These increased rates of different kinds of cancer are largely caused by a mismatch between our current environment and lifestyle and those of our evolutionary ancestors.

8. Mutations are inevitable

Cancers result from random mutations in cells. Unfortunately, mutations are inevitable. While organisms could evolve a greatly reduced mutation rate in theory, this would come at the cost of a higher energy expenditure towards DNA repair. Organisms must balance how they expend energy, and more energy to DNA repair may come at the cost of reproductive fitness, resulting in an optimal mutation rate that is above zero. Considering that organisms only benefit by delaying cancer to emerge after its reproductive potential is gone, evolving lower and lower mutation rates comes with diminishing returns. Once the mutation rate is low enough for cancer to emerge after reproduction, there is little selective pressure to further delay cancer. At the same rate, any extra energy invested into this further delay may actually be bad for that organism's survival and reproduction.

References

Greaves, M. (2000). Cancer: The Evolutionary Legacy. Oxford ; New York: Oxford University Press.

Aktipis, C. A. (2015). Principles of cooperation across systems: From human sharing to multicellularity and cancer. Evolutionary Applications, n/a-n/a. https://doi.org/10.1111/eva.12303

Aktipis, C. A., Boddy, A. M., Gatenby, R. A., Brown, J. S., & Maley, C. C. (2013). Life history trade-offs in cancer evolution. Nature Reviews Cancer, 13(12), 883–892.

Aktipis, C. A., & Nesse, R. M. (2013). Evolutionary foundations for cancer biology. Evolutionary Applications, 6(1), 144–159.

Enriquez-Navas, P. M., Kam, Y., Das, T., Hassan, S., Silva, A., Foroutan, P., … Gatenby, R. A. (2016). Exploiting evolutionary principles to prolong tumor control in preclinical models of breast cancer. Science Translational Medicine, 8(327), 327ra24-327ra24. https://doi.org/10.1126/scitranslmed.aad7842

Ewald, P. W., & Swain Ewald, H. A. (2012). Infection, mutation, and cancer evolution. Journal of Molecular Medicine, 90(5), 535–541. https://doi.org/10.1007/s00109-012-0891-2

Frank, S. A. (2015). Commentary: The nature of cancer research. International Journal of Epidemiology, dyv200. https://doi.org/10.1093/ije/dyv200

Gatenby, R. A., Brown, J., & Vincent, T. (2009). Lessons from applied ecology: cancer control using an evolutionary double bind. Cancer Research, 69(19), 7499–7502.

Gatenby, R. A., Silva, A. S., Gillies, R. J., & Frieden, B. R. (2009). Adaptive therapy. Cancer Research, 69(11), 4894–4903.

Greaves, M. (2007). Darwinian medicine: a case for cancer. Nature Reviews Cancer, 7(3), 213–221.

Greaves, M. (2014). Was skin cancer a selective force for black pigmentation in early hominin evolution? Proceedings of the Royal Society B: Biological Sciences, 281(1781). https://doi.org/10.1098/rspb.2013.2955

Greaves, M. (2015). Evolutionary Determinants of Cancer. Cancer Discovery, 5(8), 806–820. https://doi.org/10.1158/2159-8290.CD-15-0439

Hanahan, D., & Weinberg, R. A. (2011). Hallmarks of Cancer: The Next Generation. Cell, 144(5), 646–674.

Kokko, H., & Hochberg, M. E. (2015). Towards cancer-aware life-history modelling. Phil. Trans. R. Soc. B, 370(1673), 20140234. https://doi.org/10.1098/rstb.2014.0234

Pepper, J. W., Dunn, B. K., Fagerstrom, R. M., Gohagan, J. K., & Vydelingum, N. A. (2014). Using systems Biology to understand cancer as an evolutionary process. J. Evol. Medicine. 2 2014, 1–8.

Pepper, J. W., Scott Findlay, C., Kassen, R., Spencer, S. L., & Maley, C. C. (2009). SYNTHESIS: cancer research meets evolutionary biology. Evolutionary Applications, 2(1), 62–70.

Aktipis, C. A. (2015). Principles of cooperation across systems: From human sharing to multicellularity and cancer. Evolutionary Applications, n/a-n/a. https://doi.org/10.1111/eva.12303

Aktipis, C. A., Boddy, A. M., Gatenby, R. A., Brown, J. S., & Maley, C. C. (2013). Life history trade-offs in cancer evolution. Nature Reviews Cancer, 13(12), 883–892.

Aktipis, C. A., & Nesse, R. M. (2013). Evolutionary foundations for cancer biology. Evolutionary Applications, 6(1), 144–159.

Enriquez-Navas, P. M., Kam, Y., Das, T., Hassan, S., Silva, A., Foroutan, P., … Gatenby, R. A. (2016). Exploiting evolutionary principles to prolong tumor control in preclinical models of breast cancer. Science Translational Medicine, 8(327), 327ra24-327ra24. https://doi.org/10.1126/scitranslmed.aad7842

Ewald, P. W., & Swain Ewald, H. A. (2012). Infection, mutation, and cancer evolution. Journal of Molecular Medicine, 90(5), 535–541. https://doi.org/10.1007/s00109-012-0891-2

Frank, S. A. (2015). Commentary: The nature of cancer research. International Journal of Epidemiology, dyv200. https://doi.org/10.1093/ije/dyv200

Gatenby, R. A., Brown, J., & Vincent, T. (2009). Lessons from applied ecology: cancer control using an evolutionary double bind. Cancer Research, 69(19), 7499–7502.

Gatenby, R. A., Silva, A. S., Gillies, R. J., & Frieden, B. R. (2009). Adaptive therapy. Cancer Research, 69(11), 4894–4903.

Greaves, M. (2007). Darwinian medicine: a case for cancer. Nature Reviews Cancer, 7(3), 213–221.

Greaves, M. (2014). Was skin cancer a selective force for black pigmentation in early hominin evolution? Proceedings of the Royal Society B: Biological Sciences, 281(1781). https://doi.org/10.1098/rspb.2013.2955

Greaves, M. (2015). Evolutionary Determinants of Cancer. Cancer Discovery, 5(8), 806–820. https://doi.org/10.1158/2159-8290.CD-15-0439

Hanahan, D., & Weinberg, R. A. (2011). Hallmarks of Cancer: The Next Generation. Cell, 144(5), 646–674.

Kokko, H., & Hochberg, M. E. (2015). Towards cancer-aware life-history modelling. Phil. Trans. R. Soc. B, 370(1673), 20140234. https://doi.org/10.1098/rstb.2014.0234

Pepper, J. W., Dunn, B. K., Fagerstrom, R. M., Gohagan, J. K., & Vydelingum, N. A. (2014). Using systems Biology to understand cancer as an evolutionary process. J. Evol. Medicine. 2 2014, 1–8.

Nesse, R. M. (2017). Introduction: Five Evolutionary Principles for Understanding Cancer. In Ecology and Evolution of Cancer (pp. xv–xxi). Elsevier. https://doi.org/10.1016/B978-0-12-804310-3.00028-4

Pepper, J. W., Scott Findlay, C., Kassen, R., Spencer, S. L., & Maley, C. C. (2009). SYNTHESIS: cancer research meets evolutionary biology. Evolutionary Applications, 2(1), 62–70.

Merlo, L. M., Pepper, J. W., Reid, B. J., & Maley, C. C. (2006). Cancer as an evolutionary and ecological process. Nature Reviews Cancer, 6(12), 924-935.

Special 2009 issue of Evolutionary Applications on evolution and cancer.

http://onlinelibrary.wiley.com.proxy.lib.umich.edu/doi/10.1111/eva.2009.2.issue-1/issuetoc

http://www.hhmi.org/biointeractive/evolution-cancer

http://www.bbc.com/earth/story/20160601-is-cancer-inevitable – bbc earth piece

http://evolution.berkeley.edu/evolibrary/news/071001_cancer – info page on

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3660034/ – ev and cancer overview

Berkley's evolution ed resource

https://www.nature.com/collections/yhyydzgkfk – publications

Videos:

https://www.youtube.com/watch?v=u8jMZT0XTkA (Yale course)

https://www.youtube.com/watch?v=xOFWH6_K3f8 (TedX)

https://www.youtube.com/watch?v=BQV5F2tlIZE (TedX ASU Maley)

https://www.youtube.com/watch?v=CjTYYdZQ4is (Nesse and Stearns)