Applying Clonal Evolution to Cancer Research

Eric De La Cruz

Authors Note

This paper was prepared for Biology 141 Lab: Evolution taught by Dr. Moran Williams

Abstract

Peter C. Nowell's research continues to help impact how biologist observe tumor cells with using Darwin's Theory of Evolution to help researchers better understand cancer cells and how we can counter their effects on the human body such as chemotherapy and other methods of eliminating them. With chemotherapy being the most known method of treatment, there is another method that is much safer and recently left clinical trials called immunotherapy. By discussing Nowell's research we review clonal evolution in which he explains how tumor cells are produced along with other researchers who have discussed the progression of tumor cells. With these studies explaining more how cancer cells work, will benefit future methods to deliver better and safer treatments for patients.

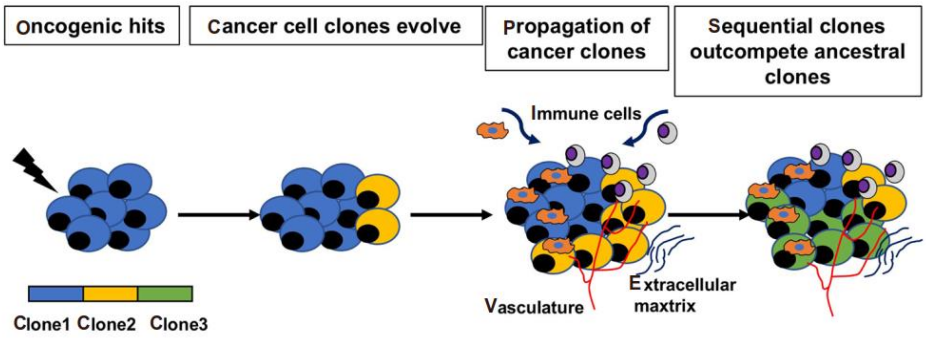
Keywords: Clone (Parent cell), Sub clone, Darwin's Theory of Evolution, Tumor/Cancer cell, Peter Nowell, Immunotherapy**,** Somatic cell

The Theory of Evolution with Tumors

Darwin's Theory of Evolution states that all species of organisms develop through the process of natural selection such as inheritable variation allowing it to diverse to compete for survivability. For natural selection to occur, they must have inheritable variation as stated by Charles Darwin in his theory of evolution. With Nowell's hypothesis, he proposed the process of clonal evolution where a tumor cell for example is made after a damaged DNA coding that mutated and then it splits with the copy obtaining different genetics or mutations. This can be compared to asexual reproduction, but the way somatic cells reproduce allow for inheritable variation which increases survivability compared to asexual reproduction of species. Clonal evolution works like how Darwin sees evolution as survival of the fittest in nature only instead of animals its cells. Like many living organisms, cells grow and stop growing once they mature to eventually begin reproducing offspring. Sometimes cells are damaged and most likely do not move on to the next stage due to requirements the body checks before proceeding and are usually repaired or destroyed. However, sometimes the damaged cells will bypass the checkpoints and end up reproducing and will keep reproducing. Cells that reproduce eventually die after they serve their purpose, but tumor cells do not stop growing until they invade the body. You can compare tumor cells as an animal invading a habitat that was inhabited by another species and eventually drive them to near extinction. These are called parasites and they do whatever they can to survive. In Peter Nowell's paper about clonal evolution of tumor cells, he described how neoplastic cells escape the normal growth mechanism for all somatic cells and how these tumor cells that were not destroyed beforehand will increase the tumor population in the body.

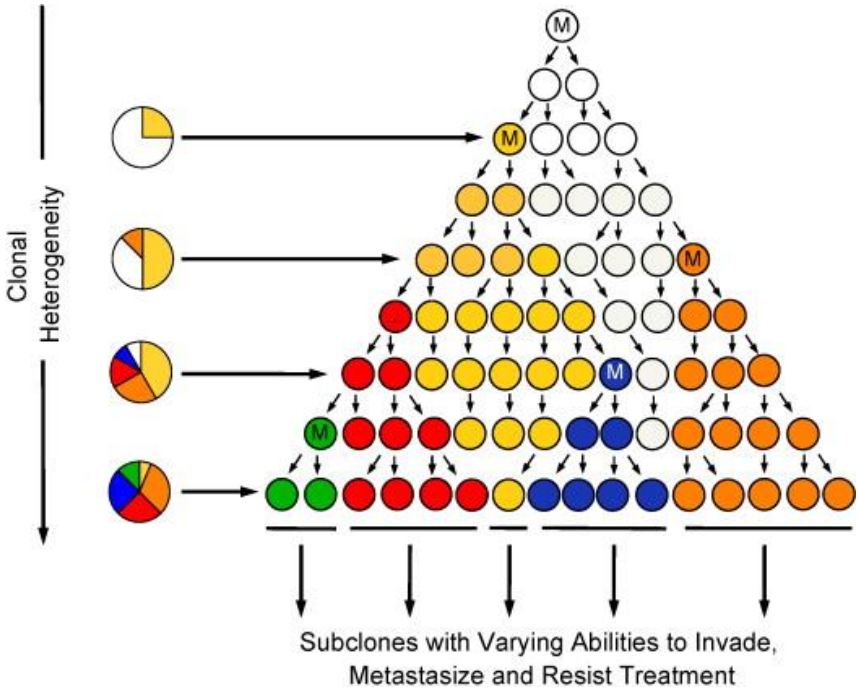
•

The Process of Clonal Evolution in Cancer Cells



In order to explain clonal evolution, I must define the parts that make it up. A clone is a group of cells that come from the same parent cell meaning they have identical ancestry and genetics. If a tumor cell were to be formed, it would reproduce very quickly creating copies of itself and eventually one of the generations will have a mutation and then the following generation will have that same mutation and so on as seen in the figure above. The offspring of the original clone is called a sub clone. From clone to subclone, this is known as clonal evolution in which progression has occurred. Nowell used tumor cells to explain the progression in clonal evolution. Tumor progression is when a tumor cell is created from the result of acquiring genetic variability from the original tumor or a clone and the selection become more aggressive as it evolves. This means that eliminating it is very difficult since it mutates very quickly and most likely that mutation is a resistance towards the first chemo. Eliminating the clones of the original only give a better survival advantage towards their offspring who developed a mutation that resists the chemotherapy that eliminated the parent cells. This is where natural selection comes to take shape since the competition has been wiped out, the subclones can thrive allowing for further mutations to occur. It is explained in Peter Nowells' paper that the elimination of the parent

clone cell is also due to metabolic disadvantage leaving the offspring or the subclone as the dominant until the same pattern occurs. This constant change in their genetic coding make it very difficult to eliminate the cancer cells with one method.



In the figure above, this is the basic principle of clonal selection where it explains the function of the immune system (lymphocytes). This can be considered as the natural selection process of all types of cancer cells. To further explain the process, the parent clone cell or the original clone will reproduce and eventually one of the subclones will obtain a mutation that likely will be an immunity towards a certain treatment such as chemotherapy. As offspring are being produced, the chance of the sub clones has and correlation with the parent clone will eventually be non-existent due to have a metabolic disadvantage or being destroyed by chemotherapy or other similar methods. This occurs like how natural selection works by eliminating the competition and creating inheritable traits in the population. Although the rate of mutation in tumor cells are

low, the rate of reproduction is very fast giving the mutations to resist cancer treatments an increase rate of it appearing in each generation.

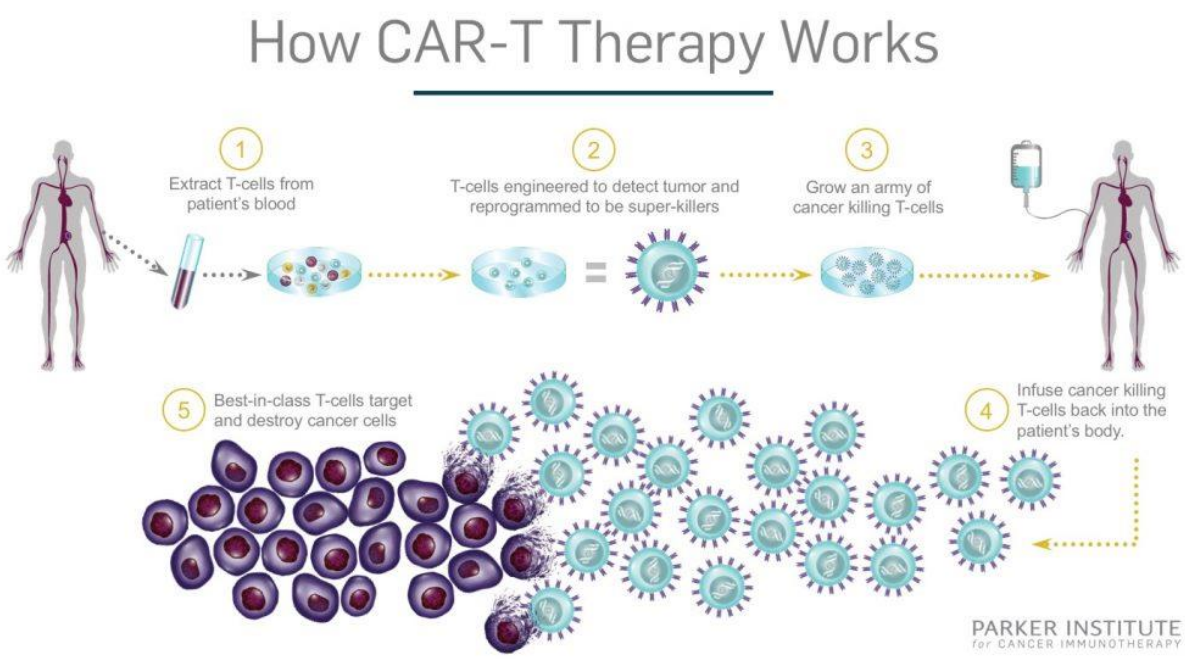
Immunotherapy Advancements and Side Effects

With Nowell's work in cancer research, advancements in cancer treatment have been made with new methods of immunotherapy that create stronger white blood cells that attack the tumor cells without harming the patient. From his passing in 2009 to 10 years later, new information has been discovered to understand what cause cancer cells. It has been theorized that chromosomal abnormalities cause tumor cells, but according to Nowell's paper chromosomal abnormalities result not cause tumor cells. With that information, the search for the cause of tumor cells needs to be broader. As we know today, there are many ways to cause tumor cells such as too much exposure to UV rays or radiation. As of today, immunotherapy has been a turning point for cancer research and treatment as mentioned by Jennifer Couzin-Frankel. There are still other questions left unanswered still to this day, but one core concept has been solved. Fixating our immune system to target tumor cells was the most effective method for patients. Immune therapy treatments have been around since 2002, but only 4-7 years later is when clinic trials began for some new methods such as CAR-T (Chimeric Antigen Receptor T-cell) therapy. CAR-T has been used to target breast cancer or leukemia. Frankel described a situation where in 2006 one of the first trials of immunotherapy contained surprising results where 5 out of the 39 volunteers had their tumor cells shrink within two years. The progress was outstanding and soon led to further studies to increase success rate in immunotherapy. There were roadblocks, however, that prevented immunotherapy to be used with all patients such as issue with cost of the treatment since it rates around $120,000 and the average person does not have that kind of finance. Other than financial issues, there are more challenges to this method explained by C. Lee Ventola like

how unpredictable it is. Immunotherapy buffs out the immune system and assigns T-cells to solely target the tumor cells, but as mentioned before the tested success rate was low and different depending on the type of cancer present.

Side Effects

As research and clinical trials have shown, the benefits of immunotherapy had promising results. Although, there can be negative side effects that can damage the person, similar to chemotherapy. One of the challenges mentioned earlier was how unpredictable immunotherapy was in efficacy. An article from the Cancer Research Institute has listed several side effects from the clinical trials and several brief stories of patients' experiences with immunotherapy. One patient explained he became diabetic while another said that it made her unable to speak in coherent sentences. Other patients said they experienced inflammation in the lung or other symptoms like abnormal skin reactions. Most of these patients who received immunotherapy experienced these side effects during the first week of the treatment. These side effects are usually caused by a hyperactive immune system coherent with developing genetically engineered T-cells or also known as "Super T-cells" which explains the drowsiness, fever, and flue like symptoms.



The image above is a visual representation of how the process of CAR-T therapy works (Parker Institute for Cancer Immunotherapy). The first step is to extract the T-cells of the infected patients' blood and then take the sample to a lab to genetically engineer the T-cells to attack the targeted tumor cells. This will slow down the grow the tumors and will shrink it to control it but will not cure it. Before infusing these genetically advanced T-cells, there needs to be more to contain the cancer cells. Therefore, these new T-cells must reproduce to grow in numbers. Finally, they will enter the body to find the tumor cells they were programmed to target and eliminate the tumor cells.

Glossary(terms)	Definition
Neoplasm	a new and abnormal growth of tissue in some part of the body, especially as a characteristic of cancer.

Clonal Evolution	Suggest an expansion of a population cancer cell, they become heterogenous throughout its' generation and obtain mutations that can be passed on.
Somatic Cells	any cell of a living organism other than the reproductive cells.
Subclone	An offspring of the original parent clone cell.

Conclusion: Impact on Future Cancer Research

Clonal evolution is difficult to predict since evolution is not planned but rather developed within its surroundings. If in the future we can predict which mutations give cancer cells resistance towards several cancer treatments, many lives will be saved, especially with patients who reach stage 4 where most end up hopeless. The purpose of the study is to discover ways to prevent the reproduction of tumor cells and allow better connections toward how to exploit the weakness of the cells. By understanding how tumor cells are created and with further research, we can begin to understand how to remove it and hopefully control the effects it has on the body and how to counter these effects to completely eliminate these tumor cells one day. This topic is still being investigated as of today as we are continuing to discover new methods to contain the spread of cancer in many people who are affected today and for future generations who will sadly be affected as well.

References

Aparicio Samuel & Caldas Carlos, 28 Feb. 2013. "The Implications of Clonal Genome Evolution for Cancer Medicine." Massachusetts Medical Society

Brock Amy, May 2009. "Non-genetic heterogeneity- a mutation-independent driving force for the somatic evolution of tumors." Macmillan Publishers Volume 10

Frankel-Couzin Jennifer, 20 Dec. 2013. "Cancer Immunotherapy" Science Vol. 342, Issue 6165, Pg. 1432-1433.

Garsed W. Dale, 10 Nov. 2014. "The Architecture and Evolution of Cancer Neochromosomes." Elsevier Inc.

Greaves Mel & Maley C. Carlo. 18 Jan. 2012. "Clonal evolution in cancer." Nature 481, 306-313(2012).

Huntly P. J. Brian & Gilliland Gary D., April. 2005. "Leukaemia stem cells and the evolution of cancer-stem-cell research." Nature Publishing Group Volume 5.

Kemp J. Christopher. Dec. 2005. "Multistep skin cancer in mice as a model to study the evolution of cancer cells." Seminars in Cancer Biology 15(2005) 460-473.

Korolev S. Kirill, May 2014. "Turning ecology and evolution against cancer." Macmillan Publishers Volume 14.

Nicholson M. Joshua & Duesberg Peter, 16 May. 2009. "On the karyotypic origin and evolution of cancer cells." Cancer Genetics and Cytogenetics 194 (2009) 96-100.

Nowell C. Peter, 1976. "The Clonal Evolution of Tumor Cell Populations." American Association for the Advancement of Science.

Pepper John W. 27 Jan. 2009. "Cancer research meets evolutionary biology." *Wiley Online Library*.

Selves-Casas Matias & DeGregori James, 2 Dec. 2011. "How Cancer Shapes Evolution and How Evolution Shapes Cancer." Evo Eda Outreach (2011).

Shackleton Mark, 4 Sep. 2009. "Heterogeneity in Cancer: Cancer Stem cells versus clonal evolution." Elsevier Inc.

Stevenson J. Brian, 23 May. 2007. "Rapid evolution of cancer/testis genes on the X chromosomes." BMC Genomics 2007.

Ventola C. Lee, Aug. 2017. "Cancer Immunotherapy, Part 3: Challenges and Future Trends." Pharmacy and Therapeutics (P.T.) PMC article.

Vincent D. Mark, 28 July. 2009. “The Animal Within: Carcinogenesis and the Clonal evolution of cancer cells are speciation events sensu stricto.” Outlook on Evolution and society.