Extrachromosomal DNA: Potential Biomarker and Treatment for Cancer

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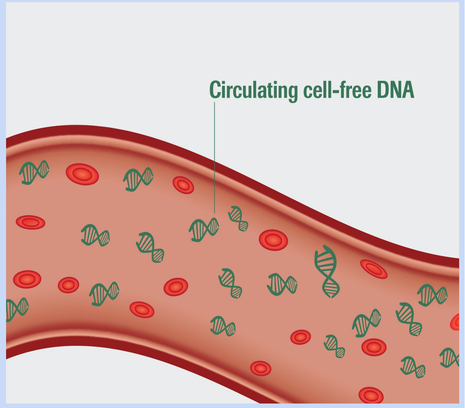
INTRODUCTION

Around 4 in every 10 people will be diagnosed with cancer at some point in their lifetime and the mortality rate is approximately 164 per 100,000 individuals (“Cancer Statistics,” 2018). As a matter of fact, cancer is the second-leading cause of death in the United States alone, directly responsible for more than one-fifth of the total number of deaths in 2017 (“Deaths and Mortality,” 2017). There are many things that scientists cannot explain in regard to cancer, in my research I would like to focus on one area: the common occurrence of circular DNA within the nucleus of tumor cell (Turner et al., 2017) —known as extrachromosomal DNA (ecDNA). Additionally, I would like to explore if there is a possibility that we can use the genetic information in these circles to diagnose and treat cancer in patients because cancer is the result of a mutation the DNA and we can find them in biofluids (Khatami et al., 2018) and if we extract information needed for targeted therapy, it could greatly increase the survival rate of cancer patients.



RESEARCH METHODOLOGIES

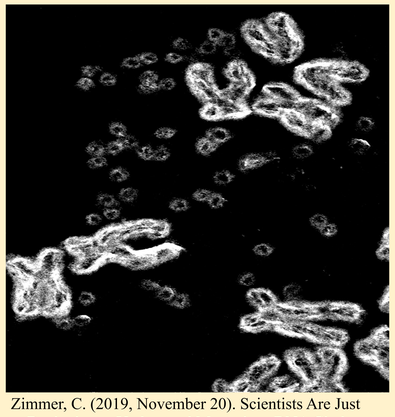
My project was a “descriptive” research where I contacted professors and researchers centered around the topic to interview them about their labs, meaning the type of data I collected was qualitative. I interviewed Dr. Hessen from Charité – Universitätsmedizin Berlin through Skype about his research and I emailed Professor Dutta from the University of Virginia, who has participated in writing papers about extrachromosomal DNA and we did the interview by phone. Dr. Verhaak from the Jackson Lab was then introduced to me via Dr. Hessen and we talked through the phone. In the end I’ve decided “coding” was the best way to present my project.

DATA AND FINDINGS

	Why do extrachromosomal DNA appear?	What should we do to them?	“What do you think is under-researched about extrachromosomal DNA?”
Dr. Henssen	○ Breakage fusion bridge cycles (Barbara Mcclintock) ○ chromothripsis ■ Stuck in micronuclei where ecDNA do occur more frequently mysteriously ○ Replication-induced ■ Replication machinery slips repeats itself and in the loop, causing a circle through replication.	● Needs further studying on purpose ○ If ecDNA is harmless then there’s no point in spending effort to clear it ○ If it's a gene that leads to higher growth or a very powerful driver of cancer development right, remove it from regulatory elements around the gene ● EcDNA in biofluid for diagnosis ● EcDNA from tumor to understand how it interacts	● What is the mechanism of how they are generated? ● What are the consequences of circularization?
Dr. Dutta	● It appears in plasma because it is hard to digest ○ DNA as like just as a strand of thread ○ Exonuclease attaches to the ends of the thread and chews until part that is wrapped around the nucleosome (150bp in length)is left. ○ Circular DNA has no end and so exonuclease cannot digest them	● Use the ecDNA in biofluid to diagnose the patient ● Clear the circles ○ Circles’ functions are unknown ■ Clear if it is junk byproduct ○ Hypothesize it’s not necessary to remove all copies of the circles but most of it ● Hopes that drugs are developed to clear the circles	● How are they made? What is required to produce these guys?
Dr. Verhaak	● Hypothesize it is inherited during mitosis ○ Wants to know the detailed process	● Not sure of its purpose but very frequent in glioblastoma ○ Stopping the inheritance may stop tumor evolution, making it easier to treat	● How is extrachromosomal DNA inherited from one cell to another? ○ Because it’s not like chromosomal DNA

CONCLUSIONS AND ANALYSIS

The thing that all the researchers I have interviewed can agree on is that no one truly understands the function of the extrachromosomal DNA and what it does for the cell. However, they are all treating extrachromosomal DNA with malice because although its functions are unknown, it has been proven time and time again that they are large, meaning that they are capable of gene expressions that can drive tumor evolution, and commonly found in cancer. We also know that they have the capability to survive digestion because they are formed in a way that escapes the enzyme usually digesting DNAs, meaning that they can reveal information a bout the tumor they were part of long after they are discharged through a biofluid.



Zimmer, C. (2019, November 20). Scientists Are Just Beginning to Understand Mysterious DNA Circles Common in Cancer Cells. *The New York Times*. https://www.nytimes.com/2019/11/20/science/dna-genetics-cancer.html

IMPLICATIONS AND NEXT STEPS

Dr. Henssen described several ways in which the extrachromosomal DNA can be generated, namely through breakage fusion bridge cycles, chromothripsis, or error in replication machinery, so there are already some hypotheses that future scientists can test out. There’s also the problem of inheritance like Dr. Verhaak suggested because the extrachromosomal DNA is not just generated on its own, but also inherited from parent cells. There needs to also be further research on circulating tumor DNA because if scientists can find tumor DNA present in biofluids, then early detection of cancer would be extremely helpful in terms of treatment and survival rate; doctors would also be able to sequence it and prescribe the most effective treatment methods.

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