HIGH SCHOOL EDITION
Journal of Student Research
Volume 11 Issue 2 (2022)

Correlation of Cancer and Alzheimer's through Biochemical Pathways

Sanjith Muthu Kumaran[1] and Rajagopal Appavu[#]

[1]West Ranch High School, Stevenson Ranch, CA, USA
[#]Advisor

ABSTRACT

Cancer and Alzheimer's are two diseases that affect the cell life cycle bringing about either improper cell division (abnormal growth) or unnatural cell death due to the change in the cell's mechanisms or environment.
We can confirm that cancer is caused by mutations in genes of cells while Alzheimer's is caused by tau tangles or amyloid beta clumps-caused by mutations to certain genes. But we don't know the biology or inner workings of these causes. While we have speculated and found several causers, we have no actual confirmation on a main culprit. Instead, it must be a multitude of different gene mutations that result in the diseases. But recently we have found several biologic mechanisms where the two diseases find common ground, as we have found consistently that they both share common mechanisms. This can lead to a never explored background that can cure both.

Introduction

Much of cancer and Alzheimer's research has been involved in finding cures that directly target certain mechanisms of each disease respectively. Whether it is the processes of the cancer cell or the tau and amyloid beta tangles that characterize Alzheimer's. Many drugs such as the current drug Aducanumab focus on the amyloid beta and tau factors by using agents that get rid of those tangles. While drugs like Aducanumab focus on other aspects of the neuron for the purpose of working neural networks through increasing acetylcholine. Drugs like Galantamine, rivastigmine, and donepezil fall in this category. Similarly, how drugs involved in cancer, especially ones involved in chemotherapy are focused on killing off tumors or slowing tumor growth. An example being doxorubicin which is a chemotherapy drug that blocks an enzyme known as topo isomerase 2 which is involved in dna replication in mitosis. This pattern is continuous in our research record as we try to find artificial or natural substances that can block certain proteins that help cancer and Alzheimer's thrive, basically trying to slow down or destroy the disease altogether.

However, as we are learning more on the two diseases, we have turned away from focusing on the mechanisms that help cancer thrive and have now begun to prevent it's start by targeting carcinogenic substances and genes in our body that help cause it. We have found new targets in the form of a category of genes known as tumor suppressors and oncogenes that have been known to cause cancer from mutations. Tumor suppressors are genes in the body that regulate mitosis, gene replication, and processes within the cell to prevent abnormalities. While oncogenes are genes if highly expressed from mutations can increase the likelihood of tumor formation and aid in furthering the growth of the tumor. The problem is that we cannot prevent mutations overall in a cell as it grows but we can fix abnormal genes in cancerous cells through gene therapy. Gene therapy works to help either remove genes that help promote cancer growth or to introduce new genes such as tumor suppressor genes to kill the tumor. Other possible treatments are immunotherapy and personalized medicine that works to teach the immune system how to identify the tumor and how to kill it.

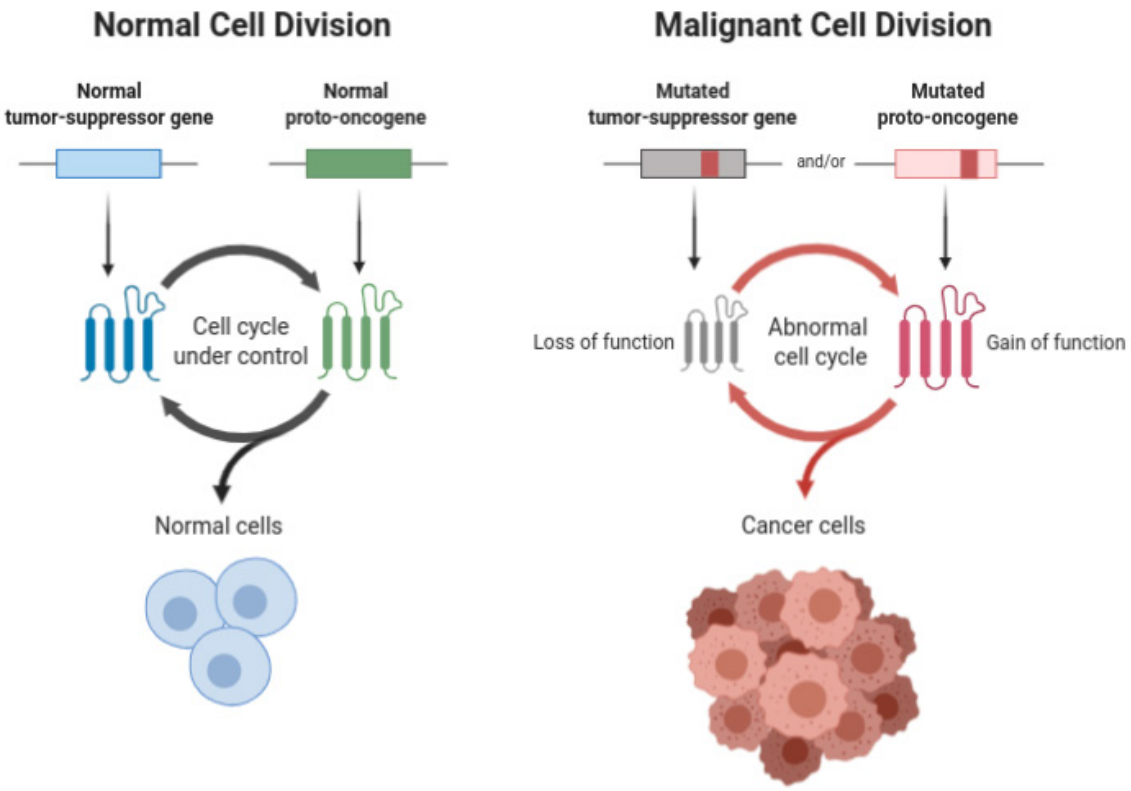

Figure 1. Effects of mutations in tumor suppressors and oncogenes

Gene therapy is also an option for Alzheimer's as well except it targets genes that create the protein amyloid beta or tau to create more stable and functioning amyloid beta and tau proteins (which are a main cause of Alzheimer's). But even Alzheimer researchers are straying away from conventional methods of developing drugs to target proteins and enzymes that aid in the disease progression but instead have looked at the bigger picture focusing on genes and proteins in the brain whose function was altered by the disease (kind of like how current cancer treatments are going). As we get new information about diseases, we then get interesting results as we soon experiment on correlations between diseases. We soon get correlations between two seemingly unrelated diseases like cancer and Alzheimer's as we find a likeness and inverness in biological mechanisms and functions.

Figure 2. New targets of Alzheimer's

Effect of Cell Life Cycle from Cancer and Alzheimer's

Being both disorders affecting the cell life cycle it is only right to look here first. The cell life cycle is essential to the life and death of a cell. A cell starts out its life after mitosis as a replica or duplicate of its parent cell. The cell soon functions as a normal cell, carrying out metabolic processes such as energy production and functioning depending on what kind of cell it is. However, eventually the cell will commence mitosis due to the activation of cyclin dependent kinase (Cdk1) caused by cell signaling. The protein kinase phosphorylates many different substrates those included: downstream effector kinases to prepare the cell for mitosis. Cdk1 also requires the binding of a regulatory cyclin subunit which activates the kinase through changes in the active site allowing kinase to bind to ATP and substrates in an orientation that promotes transfer of terminal phosphate in ATP to its target, serine and threonine residue in the substrate promoting mitosis. Cdk1 is the main regulator of cell life cycle and is a part of the cell signal network to signal cells to go through the next process of mitosis. The process of mitosis has five stages prophase, prometaphase, metaphase, anaphase, and telophase; each phase helps to copy and replicate DNA into the new daughter cells created through cell division.

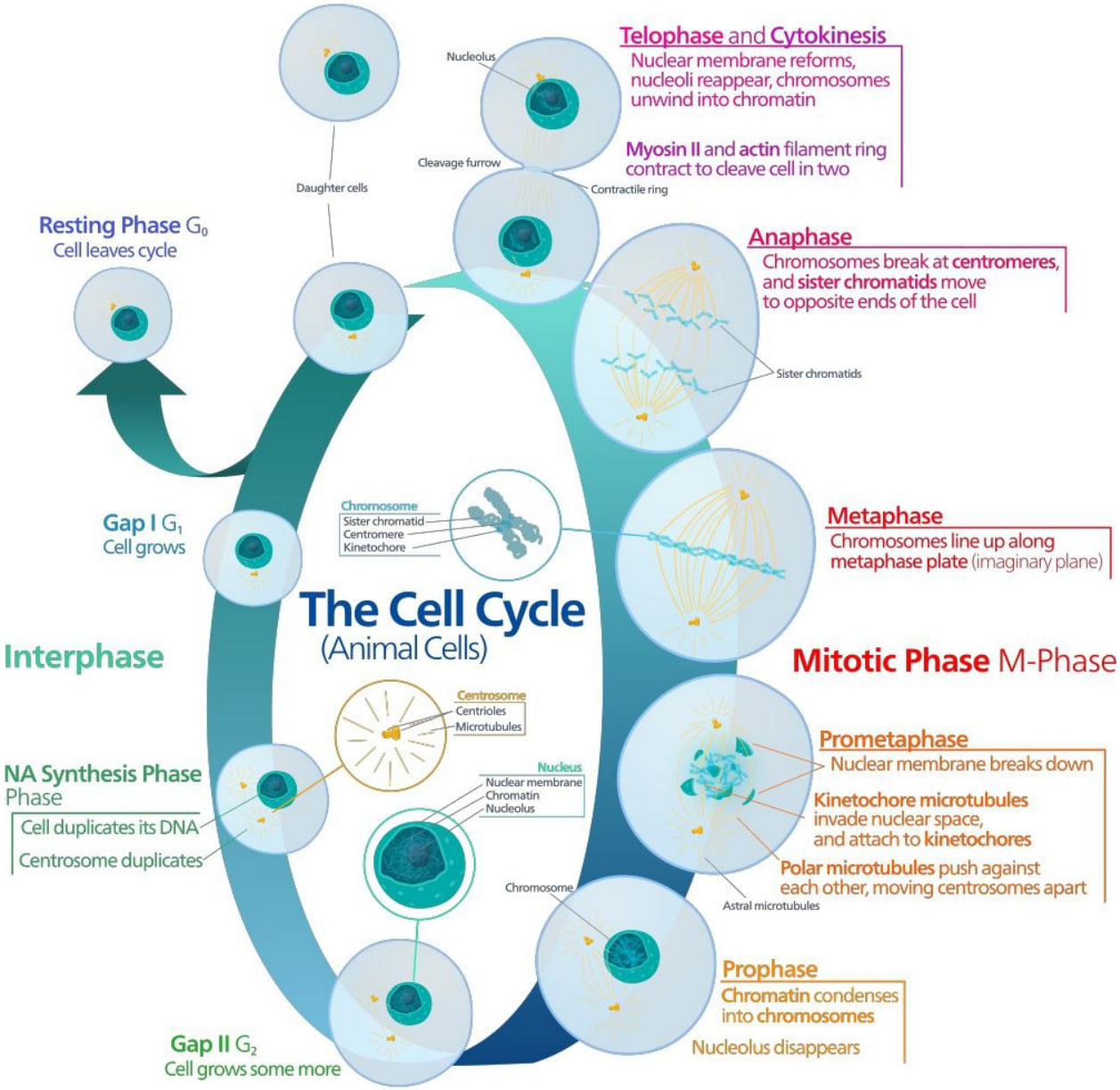

Figure 3. Processes of Mitosis

That's where the problem starts, in cell replication, where the cell is most susceptible to mutations that cause cancer and Alzheimer's. Normally DNA replication is overseen by enzymes like Cdk1, to ensure safe passage into the next part of mitosis, acting like checkpoints to avoid reckless cell division. But other proteins and enzymes also keep the process in check. Proteins like p53 which are tumor suppressor proteins help activate cell cycle arrest and apoptosis whenever necessary while neurons turn off their cell division capabilities. But it's not uncommon for mutations to commonly occur in genes as important as p53. While some of the mutations are harmless, others can turn out as breeding grounds for Alzheimer's and cancer. Mutations to tumor suppressor genes such as p53 can cause uncontrollable cell division and mutations to specific genes regulating cell life cycle.

But neurons have no capability of dividing and replicating. Usually, those genes that promote mitosis are turned off in neurons but there has been known research proving that Alzheimer's can be caused by mutations forcing neurons to go through mitosis, which they cannot go through successfully due to their lack of centrioles. However, that research is still relatively unknown. But one thing for certain is that diseases like cancer and Alzheimer's tend to be caused by genetics as genes have been found to play a huge role in the two.

Genes that Promote both Diseases:

P53:

As explained before there is some genetics involved in the diseases whether it's from mutations from mitosis as DNA replicates or genetic heredity. Cancer especially and Alzheimer's to a certain extent can be caused through genetic predispositions. In cancer there is the case of mutations to genes known as either tumor suppressors or oncogenes. However, the most known gene to consistently be a cause for cancer is p53 which has been found mutated or damaged in over 50% of cancers. P53 is a vital tumor suppressor gene and has links to the cell life cycle as it's known for controlling the division of cells. P53 has been known to slow down cyclin A to stop mitosis from occurring by halting the G1 and G2 phases of mitosis. Or promoting apoptosis in cells by direct transcriptional activation of pro-apoptotic BH3-only proteins or through increased expression of NOXA and PUMA genes that code for pro-apoptotic proteins. P53 thus is a great danger to cancer which explains why all cancer cells usually shut off the gene that codes for its protein. P53 is also known to cause aggregations to neurons in Alzheimer's alike that of tau and amyloid beta protein because p53 protein is usually unstructured, and intrinsically disordered making it easy for it to malform. When p53 malforms it tends to create tangles like tau yet is known to be more toxic as it's oligomeric or an oligomer which are simple molecules that contain few monomers. P53 has just been recently discovered but has shown up in Alzheimer patient brain's and has also been linked to microtubules in the neuron.

Amyloid Precursor Protein (APP):

Amyloid Precursor protein or APP is the most found genetic culprit for Alzheimer's. It is hereditary but also can be caused from mutations in genes. The protein is coded from the APP gene and the normal functioning for amyloid beta is for neural growth and repair. However, later the APP gene can get mutated or ruined in some manner to the point that amyloid beta protein can get misshapen and eventually stick together creating amyloid plaques as the amyloid beta protein loses the ability to function properly. The gene that codes for the protein can also be found on chromosome 21 which when two copies are made can also cause down syndrome. This is essentially a problem as people with familial records of Alzheimer's can have an easier chance of getting the disease. But, luckily only 1% of Alzheimer's cases are genetic as the mutations of the genes that express the disease are rare and can only be found in a few hundred families worldwide.

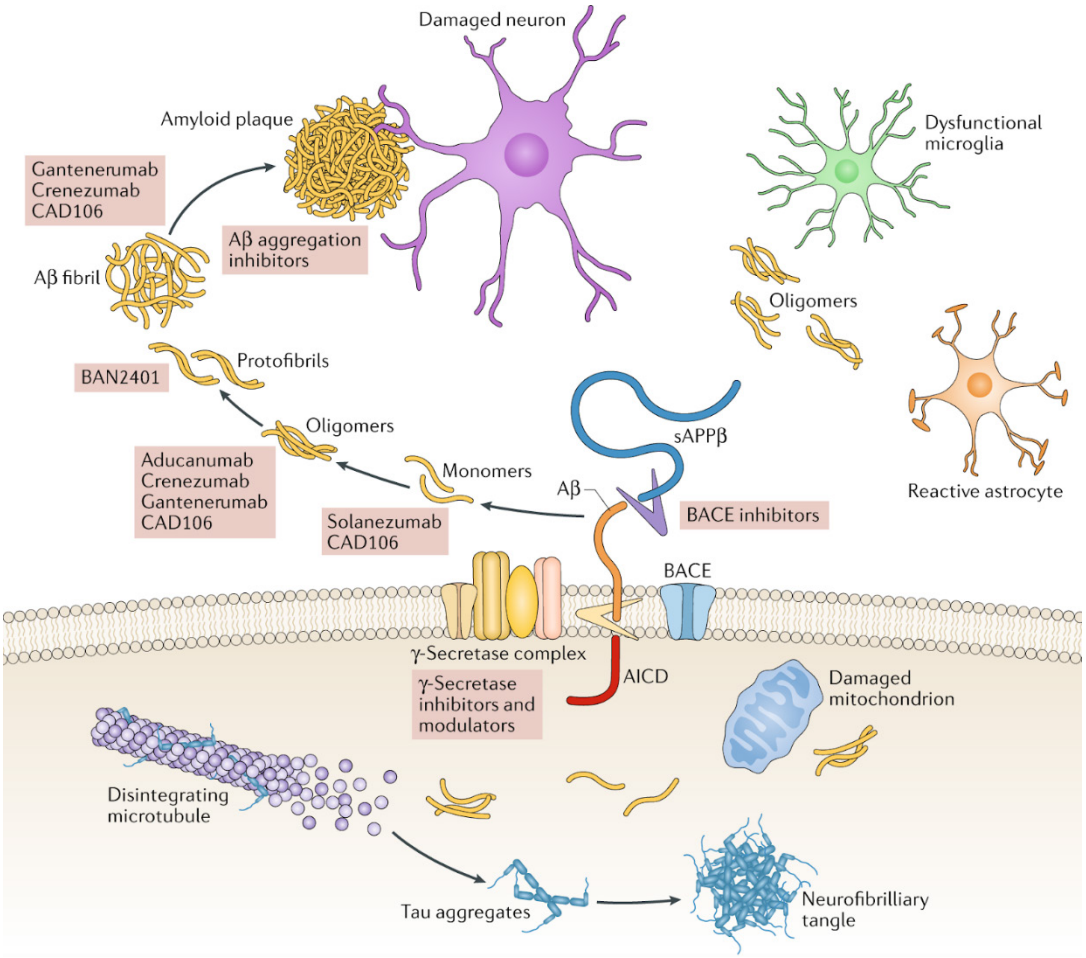

Figure 4. Steps to APP plaques.

However, APP is also found in cancer cells as well. APP belongs to a family of type 1 transmembrane glycoproteins that focus on the cell membrane (where their function usually lies) and many of the proteins in that family such as APLP1 and APLP2 are seen in many cancers. APP has been seen to aid in tumor cell proliferation, migration, and invasion. APP in cancers of breast and prostate have been known to induce androgen-mediated signaling pathways that increase tumor proliferation. APP has also been linked to helping cancers migrate and metastasize by mechanisms such as metalloproteinase and epithelial to mesenchymal transition-related pathways.

Presenilin 1&2:

Presenilin 1 is another protein that when its gene is mutated can cause Alzheimer's. The protein itself helps to prevent Alzheimer's by cleaning up amyloid beta. It is known as one of the four core proteins in the gamma secretase complex. The gamma secretase complex is mostly a complex of transmembrane proteins which cleave amyloid precursor proteins into amyloid beta proteins. This is mostly done by the protein y-secretase which does the actual work in cleaving the APP into its deadly counterpart. Presenilin is known to be a proteolytic subunit of y-secretase and so if mutated then it can cause abnormal processing of APP allowing for amyloid beta to form as its job is to form peptides from larger proteins. Similarly, Presenilin 2 also has a similar function to 1 but also helps process proteins that transmit chemical signals from cell membrane into nucleus.

Presenilin however has been known to be a tumor enhancer if expressed overly. Presenilin has been known to promote cancer growth by stimulating EGFR, a protein that allows for cell growth. In many different cancers such

as colorectal cancer, PS-1 can be proteolytically enhanced and cause processes like cadherin proteolysis and nuclear translocation which allows for the cell membrane of the cancer tumor to change its shape as cadherins promote morphogenesis (shaping of cell membrane by differentiation of cells). This process has been known to cause tumors to be malignant and metastasize. PS-1 also regulates E-cadherin cleavage and beta catenin nuclear accumulation which plays a key role in cell signaling through the Wnt pathway allowing tumor cells to signal for rapid replication.

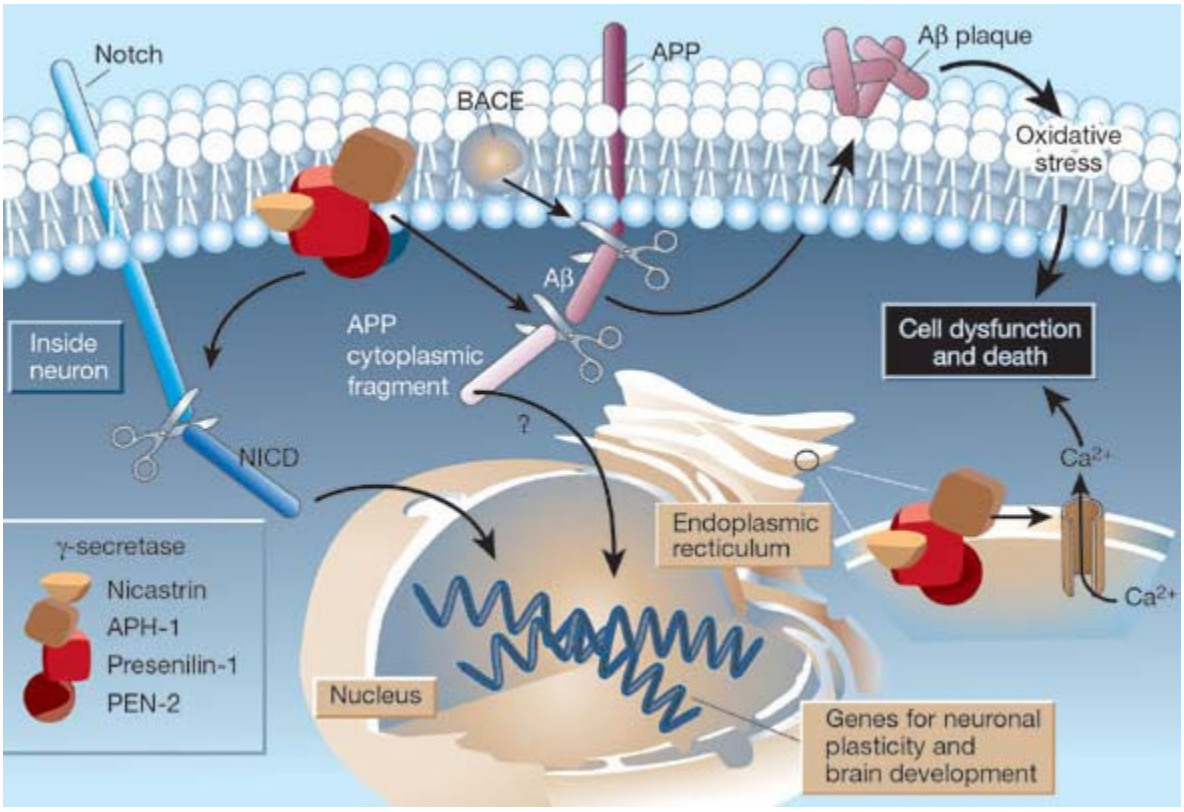

Figure 5. Function of Presenilin 1&2

TERT Gene:

The TERT gene is known as the anti-aging gene and is a factor in cancer. Researchers have found that the gene was expressed in all cancer cells, and it makes sense because the gene gives immortality to cells. The way it's able to do that is by making an enzyme called telomerase that makes telomeres found at the end of chromosomes. These telomeres help prevent degradation or the sticking together of chromosomes which occurs as they replicate more. The TERT gene thus allows the cancer cell to survive longer as the telomeres allow the cell's DNA strands to not shorten quickly and cause apoptosis of the cell. Not only that but telomerase can cause cancers especially when they shorten as it allows for mutations to occur that can promote cancer development. Overall telomerase can be found in 85-95% of tumors which makes it a very important part of cancer to focus and a most targeted area for treatments. TERT has also been found to be in low quantities as the gene tends to be turned off. Telomerase has an ability to protect against tau pathology due to its DNA preservation abilities because telomerase helps lower oxidative stress within a neuron. It has been found that in AD brains that cellular oxidative stress increases due to tau also have a lack of telomerase.

The Common Biological Trigger, p53:

Not only is p53 a gene that is regularly affected in cancer but is also a major factor in Alzheimer's. Since Alzheimer's and cancer tend to be life cycle disorders, it makes sense why p53 would be a critical factor in both. As p53 is a homeostasis and cell life cycle regulator, naturally it's malfunctioning is the cause for cell abnormalities. P53 in neurons serves many important functions such as maintenance of redox homeostasis, regulation of inflammation, control of synaptic function, reduction of amyloid peptides, and inhibition of neuronal cell cycle re-entry. These are important functions for the neuron as amyloid precursor proteins are being spliced into amyloid peptides and never-ending synaptic messages make up the daily routines of a neuron. While neurons also avoid cell cycle due to their natural in capabilities of replication. If p53 was malformed it would lead to chaos in the perfectly balanced life of a neuron as amyloid peptides can freely build up causing plaques and neuronal death occurs as neurons are forcefully sent into cell cycle re-entry. Similarly, this would be the case for cancer cells. As cells normally function with assistance from p53 as it controls mitochondrial processes, ensures normal cell replication, and signals for apoptosis. If p53 were to be malformed or malfunctioning in any other cell than a neuron then the results will be equally chaotic as perfect homeostasis will break down within the cell, as the cell becomes cancerous and divides uncontrollably.

P53 has also been known to interact with tau oligomers and a traced quantity can be identified from within tau tangles and amyloid beta plaques. But not only that but plays an important role in managing healthy aging. The pleiotropic role of p53 in health and disease depends on expression of 12 protein isoforms, more specifically a p53 protein isoform that expresses the full length p53 protein. When the protein N-terminally truncated p53 isoform is overexpressed, it was shown to accelerate aging and aggregate tau. This was most likely due to p53 also being similarly sticky when malformed like tau usually forms when it's malformed. The results of overexpression of this isoform leads to the cognitive impairment and synaptic deficits in Alzheimer's. Another note is that an increase of tau phosphorylation coincides with an increase of the isoform expression which can lead to an assumption that p53 isoforms help in the pathogenesis of AD. Reason for this is because p53 isoforms involve astrocytes which have commonly been known as a factor that causes AD. Astrocytes are usually involved in neuroprotection and protect the neurons from harm. However, due to N-terminally truncated p53 isoform being malformed the astrocytes become misshaped, and astrocytes fail to protect neurons causing AD.

Inverse Relations

Many studies have also pointed out that certain biological mechanisms in one disease also tend to either promote or lower the risk of the other. For example, we have found that cAMP which is a survival signal for neurons also promotes tumor growth as it's a vital homeostatic molecule and EGFR, epidermal growth factor receptor has been found to be highly expressed in tumors while not expressed in AD due to restriction of growth.

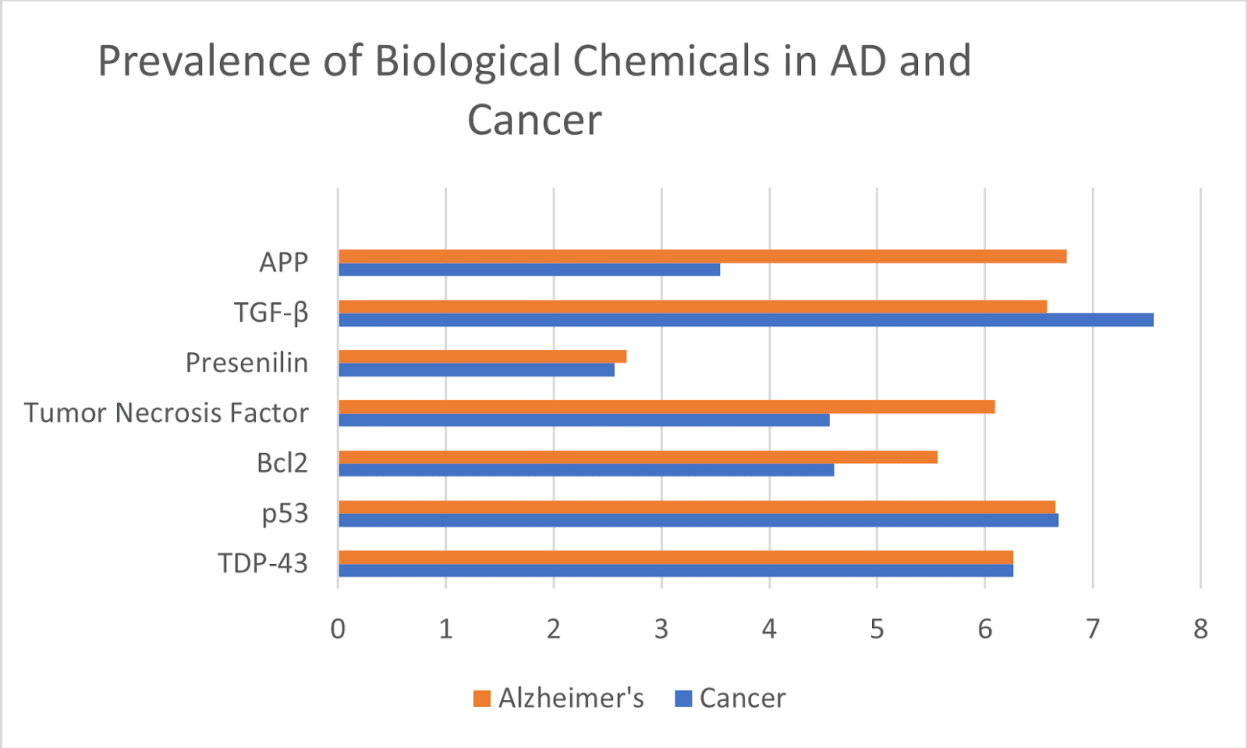

Figure 6. Biological Mechanisms Prevalence in AD and Cancer

There are more biological mechanisms demonstrating an obvious inverse relationship between the diseases, but these biological mechanisms are either more common or more important than others we have found. In the graph we see that APP, the Amyloid Precursor Protein, is more prevalent in Alzheimer's than in cancer due to APP being a promoter for the p53 gene which is an important tumor suppressor. Yet deficit APP is also one of the main causes for Alzheimer's. Similarly, we see this is the case for Presenilin as the transmembrane protein serves a higher role in causation of Alzheimer's as the protein plays the crucial role of splicing APP into amyloid beta peptides. But presenilin is also seen prevalent in cancers like colorectal and prostate as it gives the ability for tumors to metastasize due to its connections with the Wnt pathway for cell signaling. While TDP-43 especially abnormal TDP-43 causes genome instability and increased apoptosis which signals for AD related symptoms while loss of the molecule TDP-43 allows for cancer to take place as the molecule's role is processing mRNA. When the molecule fails it can destroy mRNA and give rise to mutations that can be carcinogenic or apoptosis due to loss of proper processing of mRNA.

This model proves that cancer and AD overlap in biological processes and mechanisms more consistently than we think. This raises factors that we should consider when coming up with drugs or treatments for these diseases as we have learned that some medications can raise AD or cancerous symptoms. But this information also gives us more biological hallmarks or targets that we can use to suppress these diseases.

Conclusion

In conclusion, this information is vital to our current development of cures for these diseases and understanding of them as well. The research presented gives us new scopes to look for cures while also warning us to be careful as we have discovered that cancer/Alzheimer drugs can help increase the risk of the other. While the research is still very unknown to use, it isn't impossible, and we can soon figure out the missing information needed. Much of the reason

why we don't have cures for these two diseases already is because there is a lot, we still don't know about them and so this research is a good base to which we can start new areas of research to gain more knowledge on these diseases.

Acknowledgments

I would like to thank my advisor for helping me with this research.

References

Dai, CQ., Luo, TT., Luo, SC. et al. p53 and mitochondrial dysfunction: novel insight of neurodegenerative diseases. J Bioenerg Biomembr 48, 337–347 (2016). https://doi.org/10.1007/s10863-016-9669-5

Farmer, K.M., Ghag, G., Puangmalai, N. et al. P53 aggregation, interactions with tau, and impaired DNA damage response in Alzheimer's disease. acta neuropathol commun 8, 132 (2020). https://doi.org/10.1186/s40478-020-01012-6
Farmer, K.M., Ghag, G., Puangmalai, N. et al. P53 aggregation, interactions with tau, and impaired DNA damage response in Alzheimer's disease. acta neuropathol commun 8, 132 (2020). https://doi.org/10.1186/s40478-020-01012-6

Li, JM., Liu, C., Hu, X. et al. Inverse correlation between Alzheimer's disease and cancer: implication for a strong impact of regenerative propensity on neurodegeneration? BMC Neurol 14, 211 (2014). https://doi.org/10.1186/s12883-014-0211-2

Kamino, H., Nakamura, Y., Tsuneki, M. et al. Mieap-regulated mitochondrial quality control is frequently inactivated in human colorectal cancer. Oncogenesis 5, e181 (2016). https://doi.org/10.1038/oncsis.2015.43

Majd, S., Power, J., & Majd, Z. (1AD, January 1). Alzheimer's disease and cancer: When two monsters cannot be together. Frontiers. Retrieved January 16, 2022, from https://www.frontiersin.org/articles/10.3389/fnins.2019.00155/full#h8

Moh, C., Kubiak, J. Z., Bajic, V. P., Zhu, X., Smith, M. A., & Lee, H.-G. (2011). Cell cycle deregulation in the neurons of Alzheimer's disease. Results and problems in cell differentiation. Retrieved January 16, 2022, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5925746/

Lanni, C., Masi, M., Racchi, M. et al. Cancer and Alzheimer's disease inverse relationship: an age-associated diverging derailment of shared pathways. Mol Psychiatry 26, 280–295 (2021). https://doi.org/10.1038/s41380-020-0760-2

Shafi, O. Inverse relationship between Alzheimer's disease and cancer, and other factors contributing to Alzheimer's disease: a systematic review. BMC Neurol 16, 236 (2016). https://doi.org/10.1186/s12883-016-0765-2