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Review article

CONTRIBUTION OF VARIOUS FACTORS IN THE INVERSE RELATIONSHIP OF ALZHEIMER'S DISEASE AND CANCER

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ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disease of increasing age and Cancer results from uncontrolled proliferation of cells,both of which have a negative impact on quality of life and expectancy .Many risk factors contribute to an inverse relationship between Alzheimer's and Cancer. Previous case-control and cross-sectional studies have reported that there exists an inverse relationship between cancer and dementia of the Alzheimer's type (DAT).It has been reported that the occurrence or prevalence of cancer among individuals with Alzheimer's is comparatively less than its occurrence in nondemented individuals. Conversely, adults of increasing age with a history of cancer may develop Alzheimer's disease(AD) at a rate slower than individuals without cancer history. This hypothesis establishes an inverse relationship between Alzheimer's disease and Cancer. Many factors that are upregulated in any type of cancer to sustain growth and survival of cells are however downregulated in Alzheimer's disease leading to neuronal degeneration. The main objective of this review is to bring together various aspects that are related to cancer and Alzheimer's. Further to stimulate severe investigations to reveal the inverse association between these two major diseases and improve therapeutic targets at the molecular level.

Key Words :- Dementia of Alzheimer's type, neoplasia, neurodegeneration, cognition, transcription, telomerase.

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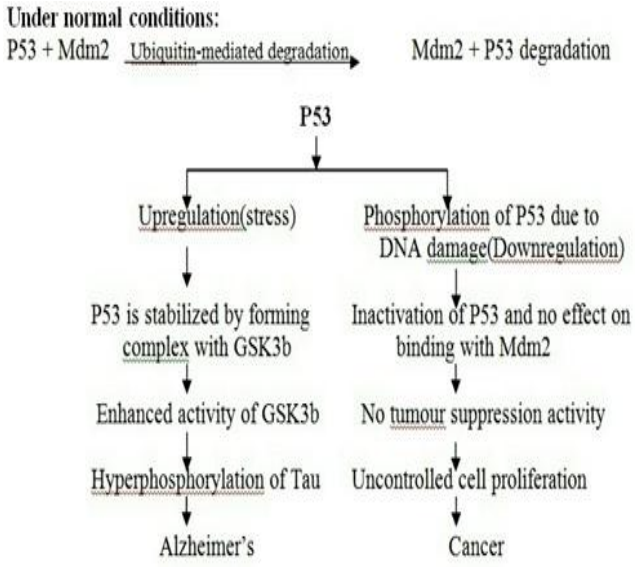
INTRODUCTION

Alzheimer's and cancer are two mysterious diseases that are age related and contribute to many risk factors (Mark Yarchoana *et al.*, 2017). Alzheimer's disease (AD) simply called as Alzheimer's, is an age-linked gradually progressive dementia affecting cognition, behavior and functional status which adversely impacts healthcare system and global economic development.

Although this neurodegenerative disease has been studied for more than 100 years, the exact etiology and pathogenic cascades remained mysterious (Zhinchun Chen, Chunjiu Zhong., 2013). On the other hand, Cancer is largely a disease of older age and are over-proliferative by controlling the fundamental process of cell renovation and tissue repair associated with cellular replication (Galliot B *et al*., 2008). If an inverse relationship exists between these two, then individuals with Alzheimer's should be less likely to develop neoplasia in the future compared with similar individuals without Alzheimer's, and individuals without cancer should be at risk of developing Alzheimer's than individuals with Cancer (C.M Roe *et al*., 2005). Dysregulation of the Wnt/ β-catenin Signaling pathway in normal and cancer cells is associated with numerous cancer types such as intestine, breast and prostate makes it an interesting target for anti-neoplastic therapeutics (Kenneth C *et al*., 2011).Various Confounding issues might underline the observed inverse relationship between cancer and Alzheimer's (David A *et al*., 2010). Firstly, both Alzheimer's and cancer limit the life expectancy of affected

individuals and therefore reduce the occurrence of other diseases by limiting the available lifetime. Secondly, the existence of one disease might hide the diagnosis of other disorders because any new findings in patients with AD or cancer might be represented as a cause of primary disease which was already diagnosed. Finally, cognitive decline due to neurodegeneration in AD may be misinterpreted as an adverse effect of chemotherapy in patients with neoplasia (Hutchinson AD *et al* ., 2012). Many components such as apoptosis pathways, P53, estrogen, neurotrophins and growth factors, cAMP, HSV, EGFR, TDP-43, Bcl-2, IGF-1, APOE variants, notch signals and presenilins, PI3K/ MTOR /AKT pathway, ACE levels, NCAM, TNF alpha, telomerase, ROS, contribute to inverse relationship between cancer and Alzheimer's disease. Alzheimer's occurs when neurons of brain have lost their cell survival responses, growth maintenance and anti-stress responses (Shafi., 2016).

1. Role of P53:



The basic role of P53 is to protect the cells from stress. P53 in humans is encoded by TP53gene and acts as tumour suppressor protein by regulating cell cycle (Naga Deepthi CH *et al* ., 2011). P53 plays a significant role in nucleus and cytoplasm. In cytoplasma it responds to cellular stress. While in nucleus it maintains all cellular responses like Cell –cycle arrest at G1/S regulation point on DNA damage recognition, Apoptosis, Senescence and Differentiation (Kikawa KD *et al*., 2011). P53 is upregulated in Alzheimer's disease and down-regulated in Cancer. Under normal conditions, p53 binds to Mdm2 which is a major regulator of P53 that can trigger the degradation of P53 by the ubiquitin system and targets p53 for proteasomal degradation (Ananymous 1). Under conditions of stress(upregulation), p53 is stabilized and form complex with GSK3b which results in increased activity of GSK3b leading to hyperphosphorylation of tau that results in Alzheimer's. P53 provokes apoptosis by irreversible DNA damage (Carole J Proctor, Douglas A Grayl1., 2000). Activation of P53 leads to cell cycle arrest through p21 and stops cell division after they are being exposed to damaging agents. Upregulation of p21finally results in cell cycle arrest and senescence of cells (Dulic V *et al*., 2000). Phosphorylation of P53 at Ser15,Thr18 or Ser20 will disrupt its binding with Mdm2(Downregulation) and the tumour suppression activity is lost leading to cancer(Driver JA *et al*., 2012).

2. Estrogen, neurotrophins and growth factors:

Estrogen,neurotrophins and growth factors are neuroprotective but promote the risk of developing cancer. Estrogen is well established as neuroprotective and neurotrophic. It even protects neurons from ischemic and hypoglycemic injuries , oxidative stress and from damage by Aβ42; which is involved in the pathogenesis of AD (Shepherd ., 2001). Low levels of a neurotrophin are needed to keep nerve cells alive.A number of neurotrophic factors found in blood stream increases neuronal differentiation and proliferation , influencing synaptic functions and promotes the survival of neurons. In other conditions presence of neurotrophin will have opposite effect and induce cell death (Anonymous 2). Interactions of glutamate and neurotrophic factors are also involved in maintaining developmental and brain plasticity.For example, production of BDNF(Brain-derived neurotrophic factor) is stimulated by Glutamate and BDNF modifies the sensitivity of neurons to glutamate ,brain plasticity and Calcium homeostasis. Neurotrophic factors can also change the expression of receptor subunits of glutamate and calcium regulating proteins and induce production of anti-apoptotic Bcl-2 family members, energy-regulating proteins and antioxidant enzymes that lead to cancer pathogenesis. Metabolic and oxidative stress activate glutamate receptors in excess, may contribute to neurodegeneration and dysfunction in Alzheimer's disease leading to neurotoxicity (Romon R *et al*., 2010).

3) Epidermal growth factor receptors (EGFR):

Several cancer types are associated with overexpression of Epidermal growth factor receptors(EGFR) which play an important role in the pathogenesis of cancer whereas AD neurotic plaques lack EGF (Bodey B , *et al*., 2005).EGF being a mitogen for progenitor cells and neural stem is essential for hippocampal neurogenesis and cognitive improvement (Sun D, *et al., 2010*).

4)IGF-1 and Bcl-2:

IGF – 1 plays an important role in disease states such as cancer along with normal physiological mechanisms. IGF axis promotes cell proliferation and inhibits cell death It is also involved in neuroprotection and also in neuronal development including myelination,

dendritic branching, neurogenesis and synaptogenesis (Westwood AJ, *et al*., 2014). Increased levels of Bcl – 2 lower the tendency of cancer cells to undergo apoptosis. Overexpression of Bcl-2 and other oncogenes is seen in cancer which contributes to cancer cell survival. IGF-1 and Bcl-2 are overexpressed in cancer where as Bcl-2 is downregulated in AD(Paradis E, *et al*., 1996).

5)HSV:

HSV is oncolytic and it also has the capacity to contribute to AD pathogenesis and its development through the pathways that work against cell survival and cell proliferation.HSV 1 DNA has already been found within Amyloid plaques in Alzheimer's disease (Woznail MA, *et al.*,2009).

6)APOE:

Risk of AD is associated with APOE but the underlying mechanisms are not clearly known (Liu C-C, *et al*., 2012). From apoE4 to E3 to E2 the risk of AD gradually decreases but improve growth and survival of cells, neural cell adhesion molecule stain positive in cancer but decrease in AD. APOE is involved in neuroprotection,and regeneration. It plays role in cell remodeling after neuronal injury and restore neuronal function. But APOE4 is unable to do these functions properly and is associated with decrease in hippocampal volume and high risk of AD development.

7)TNF-α :

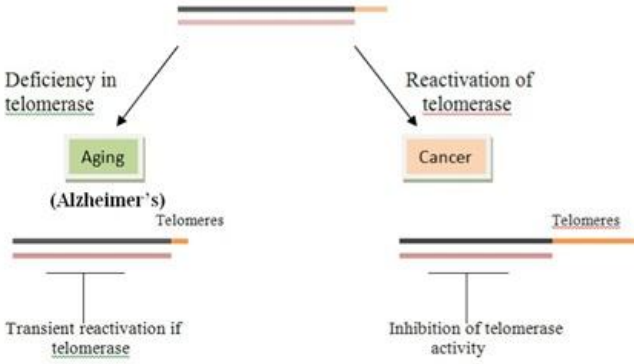
TNF- α has anti-cancer properties and its overexpression causes neurotoxic environment by induction. TNF-α signaling has the tendency to negatively impact neuronal function. TNF- α inhibition improves cognitive status of Alzheimer's patients (Park KM, Bowers WJ, 2010).

8. Role of Telomerase in aging:

Another important aspect is that Telomerase present in cancer cells prevents aging associated death of cells. Reactivation of telomerase enzyme is an essential hallmark of most cancers with the synergistic activation of other oncogenic processes, while deficiency in telomerase and telomeric proteins might lead to senescence and age-related disorders such as Alzheimer's (Mert Burak Ozturk *et al*.,2017). In tumour cells, the function of telomeres that regulate age process is overcome by overexpression of an enzyme known as telomerase which replaces the part of telomeres that is lost in each cell division, thus defending senescence and allowing uncontrollable cell doublings. Whereas AD is associated with accelerated neuronal death with age process due to decreased length of telomeres. The length of telomeres have been examined in samples such as Human blood leucocytes and cancer cells which showed a decreased length of telomeres with the possible mechanisms of increased oxidative stress, Susceptibility genotypes of metabolizing and DNA-repairing genes and DNA alterations (Mirabello *et al*., 2010). Hence Telomerase is definitely a specific target for antineoplastic drug development process to control rapid cell division (Shay JW, Wrigt WE., 2011). The following figure shows the summary of modifying therapeutic targets in age related diseases and cancer:

9)Wnt- signaling:

Defects in the WNT signaling pathway have been identified in a number of ailments, most notably cancer. Dysregulation of WNT signaling has been considered as key mediators in development of many types of cancers and defects which include inactivating mutations in APC, axin, axin 2 or (conductin) proteins, which control ß-catenin degradation and thereby activate TCF/ß-catenin driven transcription (N.I. Khan, L.J. Bendall, 2006).



Other factors:

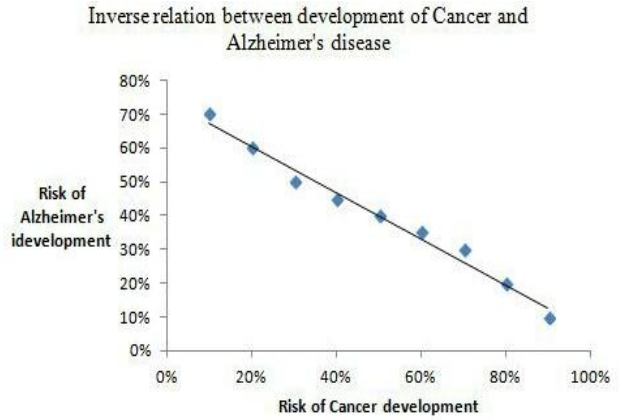
PI3K/AKT/MTOR is an intersignalling pathway which is upregulated and neuroprotective in many cancers, ROS are increased in AD which slows cancer proliferation, ACE levels are elevated in AD but decreased in neoplasia.

The following table shows the variability of factors in Alzheimer's disease and Cancer:

SI.No	**Factor**	**Alzheimer's disease**	**Cancer**
1	P53	Upregulated	Downregulated
2	Estrogen	Downregulated	Upregulated
3	Neurotrophins and growth factors	Levels are decreased	Increased
4	IGF-1 and Bcl-2	Under expressed	Overexpressed
5	APOE association	apo E2 to E3 to E4	apo E4 to E3 to E2
6	TNF- α	Increases risk of AD	Shows anti-cancer properties
7	Telomerase	Under expressed	Overexpressed
8	P13K/AKT/MTOR	Upregulated	Downregulated
9	ACE levels	Increased	Decreased
10	ROS	Excessive	Slows cancer proliferation
11	Carbonic anhydrases	Decreased	Increased
12	Neural cell adhesion molecule (CD56)	Decrease	Increase

There is an exponential rise in the occurrence of both cancer and AD with age. Several previous Epidemiological studies have shown a reciprocal association between these two diseases (Realmuto S, *et al*., 2012). The length of telomeres has been considered as an indicator of age and the decrease in their length is associated with the development of AD (Zhiou Cai, Liang-Jun Yan, 2013). Both alzheimer's and cancer increases mortality rate in affected individuals.

The inverse relation between Cancer and Alzheimer's disease can be shown as:



The above graph shows the inverse association between brain cancer and Alzheimer's disease i.e, risk of Cancer development decreases with the Alzheimer's. In case of brain cancer, the correlation between Alzheimer's and brain cancer has been found to be statistically highly significant (Yashin AI, *et al*., 2009).The standard treatment available for brain cancer is whole-brain irradiation for which the common side effect is Dementia or loss of healthy neurons. Another factor is that many chemotherapeutic agents are considered to be neuro toxic. It is likely that treatment of brain cancer causes dementia that is either mistaken for Alzheimer's disease or increases its severity. The protective effect of other types of cancer is probably caused by the likelihood of pathologists listing a single cause of death at the time of autopsy. For instance, When a patient with both cancer and Alzheimer's expires, the pathologist will frequently list cancer, and not Alzheimer's, as the cause of death. One reason for this is that the standard death certificate form (PHS T-003) only has a single line for the immediate cause of death. However, a small number of studies that did not rely on death certificates still found a small protective effect of cancer from which a group of researchers has raised the interesting possibility of inverse relationship between cancer and Alzheimer's (Stallard, E., 2002).

DISCUSSION

Previous studies have shown that the occurrence of both cancer and AD dementia increases exponentially with age, but with an inverse relationship; older persons with cancer have a reduced risk of AD dementia and vice versa. As Dementia of Alzheimer's type and cancer are negative hallmarks of aging and senescence, we suggest that AD dementia, cancer, and senescence could be manifestations of a unique phenomenon related to human aging (Massimo Musicco, *et al*., 2013). Cell death and cell replication are the two important aspects to be considered in resulting the establishment of inverse relationship between cancer and Alzheimer's which are associated biologically with the length of telomeres and many other factors (viz. P53,estrogen,neurotrophins and growth factors, cAMP, HSV, EGFR, TDP-43,Bcl-2,IGF-1, APOE variants, notch signals and presenilins, PI3K/ MTOR /AKT pathway, ACE levels, NCAM, TNF alpha, telomerase, ROS and apoptosis pathways) can be extensively investigated. An inefficient cellular mitotic cycling in neurons of individuals with Alzheimer's disease is followed by an efficient process of cell death due to cellular senescence being subjected to apoptosis (Vincent I, *et al* ., 1996). This inefficiency of cellular multiplication and efficient tendency of cell aging and apoptosis in Dementia of Alzheimer's type is Complementary to cancer and might provide a biological explanation for the inverse relationship in the incidence of Cancer and Alzheimer's(Copani A, *et al* ., 2007).

CONCLUSION

Regulation of a common pathway that represents a junction between these two age related diseases like Cancer and Alzheimer's should be established and therapy should be aimed at this common pathway in treating both these diseases. As there are many factors involved individualization of therapy by identifying a specific factor in every individual improves life expectancy and greatly reduces mortality rate in elderly with Alzheimer's or cancer.

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