Biochemistry and Biophysics Reports 37 (2024) 101625

Contents lists available at ScienceDirect

Biochemistry and Biophysics Reports

journal homepage: www.elsevier.com/locate/bbrep

A common molecular and cellular pathway in developing Alzheimer and cancer

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ARTICLE INFO

Keywords:
Cancer
Alzheimer's disease
Inflammation
Pin1
Wnt signaling pathway
Oxidative stress

ABSTRACT

Globally cancer and Alzheimer's disease (AD) are two major diseases and still, there is no clearly defined molecular mechanism. There is an opposite relation between cancer and AD which are the proportion of emerging cancer was importantly slower in AD patients, whereas slow emerging AD in patients with cancer. In cancer, regulation of cell mechanisms is interrupted by an increase in cell survival and proliferation, while on the contrary, AD is related to augmented neuronal death, that may be either produced by or associated with amyloid-β (Aβ) and tau deposition. Stated that the probability that disruption of mechanisms takes part in the regulation of cell survival/death and might be implicated in both diseases. The mechanism of actions such as DNA-methylation, genetic polymorphisms, or another mechanism of actions that induce alteration in the action of drugs with significant roles in resolving the finding to repair and live or die might take part in the pathogenesis of these two ailments. The functions of miRNA, p53, Pin1, the Wnt signaling pathway, PI3 KINASE/Akt/mTOR signaling pathway GRK2 signaling pathway, and the pathophysiological role of oxidative stress are presented in this review as potential candidates which hypothetically describe inverse relations between cancer and AD. Innovative materials almost mutual mechanisms in the aetiology of cancer and AD advocates novel treatment approaches. Among these treatment strategies, the most promising use treatment such as tyrosine kinase inhibitor, nilotinib, protein kinase C, and bexarotene.

1. Introduction

According to research, Alzheimer's disease (AD) and cancer are mostly brought on by ageing [1,2]. Cancer can begin at any age, but once it reaches a certain age range, it typically manifests as AD. Even a patient's history of cancer or AD is associated with a significantly lower chance of the other, indicating that these conditions are typically difficult to coexist at the same time [3].

The key pathological result of AD is a huge degeneration of neuronal cells in the brain, whereas the pathology of cancers is based on a significant rise in the number of cells owing to unrestrained mitosis. Assumed how cancer and AD pathogeneses with a substantial figure of mutual characteristics for example active cell-cycle bring about diverse results can show innovative ways of developing treatment methods for one and/or both circumstances. Whereas the cumulative achievement in cancer therapy progress, the harmful impact of chemotherapy on the CNS, as well as CNS toxicity and abridged psychological function has been noticed for centuries [4].

Cancer-associated cognitive impairments (CRCI) distress memory function, verbal capacity, and chief characters [5,6]. Justifying the CNS toxic impacts would significantly enhance prognoses by augmenting QoL [7,8]. Whereas CRCI is a broad area that comprises, cognitive deficits agonized by cancer patients nevertheless of treatment [9]. Reported that Gray matter concentration was found to be abridged in

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https://doi.org/10.1016/j.bbrep.2023.101625
Received 7 October 2023; Received in revised form 18 December 2023; Accepted 20 December 2023

patients one-month post-treatment, and some of that continued after one year [10] and these modify the brain shapes related to mental deficits [11]. CRCI increases in stayers of various cancers [12], while the patients of breast cancer have been the utmost widely distinguished. Investigation of chemo brain in breast cancer patients has reported that chemotherapy significantly decreased vocal memory and cognitive function continuing for several decades [13]. Administration of chemotherapy to breast cancer patients reported significantly lesser outcomes in visual memory compared to patients who are under local therapy and healthy controls [14]. Post-treatment about 5–10 years patients with breast cancer who had completed systemic therapy with cancer chemotherapy which was significantly poor achieved in short-term memory, connected to a decrease in the rate of metabolism levels of sleeping of various regions of the brain as estimated by the scans of 2-Fluoro-2-deoxy-D-glucose, 2-Deoxy-2-fluoro-D-glucose (FDG) and positron emission tomography (PET) [15].

Chemotherapies also can modify the white-matter areas in the brain leads to induce mental improvements [16]. Long-term chemotherapy induces white matter deficits and abridged outcomes on cognitive assessments and changes the gray matter over nine years [17] and 21 years [18]. Overall, the mental deficits caused by cancer chemotherapy are lasting and alters the shape of the brain.

2. Biological processes that contribute to AD and cancer

Cancer and AD are usually believed as illness mechanisms at reverse ends of variety, one because of improved apoptosis resistance and another one owing to early cell death [19,20]. The senile plaques that contain extracellular amyloid-beta (A) and tau intracellular deposits of an extremely high level of phosphorylated microtubule-associated protein tau (MAPT) are the pathological markers of AD [21]. The pathophysiological function of AD further acts through synaptic loss, cell death, and neurodegeneration. Moreover, free radical damage is permanently connected to numerous approaches in AD pathology which induce degeneration of neurons [22,23]. On the other hand, in inverse to AD, cancer is an ailment that is categorized by abnormal cell growth [24].

Literature reported that there is a common defense between cancer and AD were observed. E.g., in cancer patients, the progression of AD was abridged and showed a reduction in the degree of cancer occurrence in patients with AD compared to the reference. This opposite suggestion might be explicated through the fact which multi-function mechanism that controls cell survival is related to both ailments. Nevertheless, the assessment of what way cancer can regulate the degeneration of neurons and vice versa is still uncertain [25].

2.1. Reverse interrelationship between cancer and AD

A complete longitudinal clinical study conducted on one lakh subjects reported that there is an opposite relation between cancer and AD. Also indicated that the probability of AD in cancer patients was lowered to 35 %, while the treatment of cancer subjects with AD was shortened by up to 50 % [26]. Similarly, scientists demonstrated the same result in their study conducted on six thousand subjects for 10 years (1989–1999), reporting that cancer diminished the AD risk, whereas the occurrence of AD was also related to a considerably lesser risk of cancer [27]. An epidemiological study conducted for 15 years in the United States, reported that significantly decrease cancer in the patients who were suffering from AD [28].

Unexpectedly, it is a glioblastoma, and it may have different forms of cancer i.e. lung cancer that abridges AD [29]. Though the molecular mechanism of this variety is unclear, in contrast, the more cell-cycle stimulation revealed a mutual pathological fact between cancer and AD. Cancer is an unrestrained recurrence of cell-cycle. On the other hand, despite an improvement in the degeneration of neurons in AD, the neuronal cells display a significant rise in their cell-cycle-associated kinases [30,31]. These augmented attempts to proliferate neurons are supposed to initiate the occurrence of neurodegeneration, even though its fundamental mechanisms are still contentious. Many mechanisms are in common between cancer and AD found at cellular levels. An example is the contribution of the PI3K/Akt/mTOR signaling pathway, have a significant role in the propagation, metabolism, and development of cells as well as autophagy in the pathogenesis of both diseases [32,33]. It is believable the elements of this signaling pathway, act as one of the common associations between cancer and AD either alone or together, in a similar expedition of aetiology but to several terminuses. Assume that these links may direct us to better treatment approaches.

3. Reduction of cell cycle induce neurodegeneration

The cell cycle is classified into four stages G_1, S, G_2, and M phases. Emerging by several stages is judged through the cellular appearance of specific proteins termed cyclins as well as cyclins reliant on kinases (cdks) [34–36] e.g. G_1 development is regulated through cyclin D-cdk4, D-cdk6, and E-cdk2 [37], whereas cyclin A-cdk2 and cyclin B-cdk1 arise the development of cell through G_2 that enter the M phase [38].

These cdks have been found to raise neurons in AD, which is an uncommon outcome for cells that are accepted as post-mitotic cells. Though pre-mature nerve cells are involved in cell-cycle at the starting of their life because of distinguishing neurons, they permanently persisted in a calm position subsequently up to death [39]. The cause of this permanent leaving from the cell-cycle process is still unknown, though the detail of tumours of the brain have mostly astrocytes backgrounds but not neural source powerfully assists the fact of neural incapability to divide [40].

When redifferentiation is possible, mature nerve cells' re-entry into the cell cycle from G_0 to G_1 in some cases is followed by cell-cycle arrest in the early phase. This fleeting reappears in the cell cycle in a normal brain that can be relevant to synaptic re-modeling [41], nevertheless, in a huge gage, it mostly rises because of invectives i.e. free radical damage and cytotoxicity [42,43]. These circumstances may result in failures in the formation of the control mechanism on the G_1 to S phase as well as frequent cell cycle termination before the synthesis of novel DNA [44]. Few neurons, yet, get away from this termination and arrive in the S phase, reproduce their DNA [45], and then enter to G_2 phase [46].

Reaching the G_2 phase is the greatest phase where neuronal cells can arrive. Stated that hippocampal degenerative neurons and the DNA has been replicated in the forebrain region of AD patients reported either entirely or incompletely. One study demonstrated increased DNA synthesis in neurons in certain areas of the AD brain, but not in areas that were unaffected by the disease [47].

Nonetheless, the cells are unable to develop more to finish their division. Possibly there is a cause that may be imperfect simulated DNA because of the important function of DNA polymerase-b in the adult nerve cells. However, in other kinds of cells DNA polymerase a, g is in control of DNA reproduction, and nerve cell polymerase b slightly confirms this progression. The appearance of DNA polymerase-b an imperfect enzyme is often uncontrolled in AD patients, which is escorted by more appearance of proliferating cell nuclear antigen (PCNA) [48]. Replicated DNA supercoiling and catenation are desired for the separation of daughter coils subsequently DNA reproduction is another cause for the incapability of nerve cells to division [49]. The damaged DNA as well as desegrated reproduction cause cell death [50]. The previous study assumed that further invective protein accumulation is required for causing the apoptosis of neuron cells [51]. This suggestion was accepted by presenting the stimulation of some mechanisms in the G2 phase, arising the development of NFTs as well as amyloid-β plaques [52] in programmed cell death inept neurons. They cause significant augment phosphorylation of amyloid precursor protein (APP) through the CDK2, CDK4, and CDK5, which rises its β-amyloid making as well as APP breakdown through the stimulated caspases enzymes during the process of cell-cycle [53–55]. Overall, irregular re-entry into the cell

cycle is believe to start the pathway causing NFTs, apoptotic evasion, and making amyloid-β [56,57].

4. Role of cancer cell cycle

Cell-cycle is one of the crucial mechanisms to progress the of cancer pathology. Whereas maximum cells either continually live in a post-mitotic position for example nerve cells and/or myocytes, or are conditionally eliminated for example glial cells i.e. epithelial cells frequently occur in an active stage of proliferation [58]. At the fences among the cell-cycle phases, the change is strongly controlled except for nearby monitoring of the accuracy of the genome [59,60]. Deteriorating to repair DNA injury might finish up to cell death though repeating this imperfection in the replication of DNA which causes cancer pathology, offered by over-controlled cell cycles of cell divide [61]. Indicating cell-cycle contribution in the origination and development of both cancer and AD, advocated a similar response to some activities with a likely similar variety. Free radical damage caused by free radicals is extensively exposed in the brain of AD patients [62], on the other hand, metabolic stress, which may be accepted as the causes to induce cell-cycle as well as emerging cancer and AD [63].

Nevertheless, the result is varied in response to related causes. Although cell-cycle re-entry in the AD brain activates emerging AD hallmarks as well as nerve cell death rather than nerve cell proliferation [64,65]. Expected the significance of the cell division process in cancer and AD, evaluating the common reasons which pledge cell-cycles start in both circumstances seems risky. As of now, we believe that the PI3K/Akt/mTOR pathway plays a significant role in the pathophysiology of cancer and AD and links to the cell-cycle.

5. PI3K/Akt/mTOR signaling pathway in cancer and AD

The PI3K/Akt signaling system plays a significant role in controlling cellular growth, progression, and apoptosis [66]. The important downstream target of PI3K/Akt is the serine/threonine protein kinase activity known as mTOR. The mTOR is a member of the phosphatidylinositol 3-kinase-related kinase family that is specifically responsible for controlling cell division and growth by controlling the progression of the cell cycle at various phases [67]. There are two types of mTOR peptide subunits, mTORC1 stimulated through nutrients and energy signals, and growth factors when mTORC2 is lesser sensitive to the status of energy [68]. Whereas mTOR continuously monitors the availability of nutrients, oxygen, and mitogenic indications [69,70], and their stimulation is tremendously controlled by PI3K as well as Akt [71]. The overactivation of the PI3K/Akt pathway is frequently related to the development of cancer [72,73] and is surprisingly involved in the pathology of AD throughout aging [74].

Deregulation of PI3K, Akt, and mTOR in in-vivo and cell culture experiments [75] was reported to develop tumours, whereas criticizing out of PI3K, Akt, or mTOR, impede this oncogenic alteration [76], prevented tumor progression and blocked its invasiveness [77,78]. PI3K/Akt/mTOR involve in the pathology of AD, which was established by many scientific proofs [79]. Activated mTOR is a usual consequence in patients with AD, a likely description of cell cycle re-entry in AD [80,81]. The triggered mTOR job is a cell motivating force to initiate the proliferation that advocates the involvement of mTOR in cell cycle re-entry induces non-apoptotic cell death in cortical neurons of AD brains [82]. mTOR also can rise neurodegeneration related to tau in a cell cycle-dependent mode [83], beneath the unique driving force that might be vigor stress as the creator of irregular cell cycles [84].

6. Common mechanism of action in cancer and AD: PI3K/Akt/mTOR and autophagy

The function of PI3K/Akt/mTOR in the cell cycle starting allocated pathological mechanism action between cancer and AD, basic degeneration of neuron in AD. The appearance of mTOR has an opposite result on the autophagy process, which acts as cytoprotective activity leading to the remove of toxic proteins e.g. Amyloid-beta. While improving autophagy owing to the inhibition of mTOR which declines the mass of misfolded peptides and lead to cause detains degeneration of neuron in an extensive variety of neurodegenerative syndromes [85], improved mTOR signaling involves autophagy inhibition, accumulation of noxious proteins and enhance degeneration of neuron. Earlier pre-clinical investigation reveals that mTOR combined with PI3K/Akt pathway and controls autophagy, is a mechanism that might support the removal of cancer cells and toxic proteins in AD patients [86].

Autophagy is a main degradation pathway for organelles and aggregated proteins [87] such as those cause multiple neurodegenerative diseases i.e. AD. It has been reported that autophagy is activated in AD brains [88]. Rise in Amyloid-beta deposition [89], decrease in its clearance [90], interrupted removal of tau, and the following injury of nerve cleft and mental deficit in AD brain, might increase the consequence of PI3K/Akt/mTOR stimulation [91,92]. A positive effect of mTOR inhibitors in making autophagy, removal of cumulative Amyloid-beta, and declining Amyloid-beta accumulation was formerly recognized [89]. Literature assessed the inhibition of PI3K/Akt/mTOR pathway augmented autophagy as well as successfully abridged the development of cancer [93]. Hence, tumorigenesis is activated once autophagy collaborates.

7. Common causes for cancer and AD progress

An essential mechanism of nerve cell degeneration in AD is the excessive activation of PI3K/Akt/mTOR under conditions of cell stress (Fig. 1). While PI3K/Akt/mTOR functions as a major regulator of cell survival in response to cell stress [94], its continuous instigation leads to attacks on the cells in deleterious mode. Continuous metabolic stress is a common incident for both cancer and AD [95], which could stimulate PI3K/Akt/mTOR instigation, autophagy inhibition, and re-entry of the cell cycle. Instigation of PI3K/Akt/mTOR pathway led to cellular feedback to metabolic stress which encourages survival [66,95].

While Akt activation enhances Cyclin D1 function directly or through mTOR stimulation, mTOR also activates CDK4 at the same time. Overall results suggest that enhanced cyclin D1 and cdk4 activity restarts the

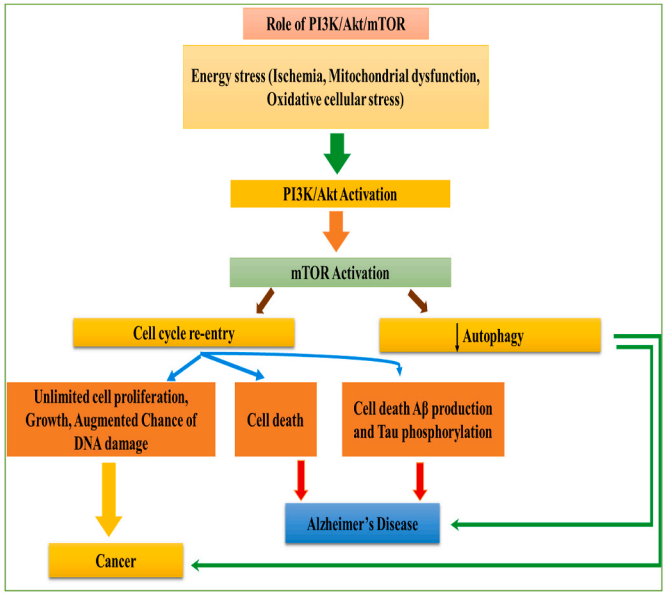

Fig. 1. The function of PI3K/Akt/mTOR in the initiation of AD and neurodegeneration through the stimulation and inhibition of autophagy during the cell cycle. Growth factor depletion and oxidative stress, two types of cellular stress, enhance PI3K/Akt activity.

cell-cycle process, forcing the nerve cell to leave G0 and then enter G1 phase. Cell-cycle kinases are stimulated, increasing APP phosphorylation (cdk2, cdk4, cdk5) to produce a lot of Amyloid-beta, whereas caspases that are activated during the cell-cycle process increase APP proteolysis. Combining APP phosphorylation with proteolysis results in the maximal production and removal of amyloid-beta, along with an increased amount of phosphorylated tau due to the tau kinase activity of cdk2 and cdk5. By inhibiting autophagy and decreasing the clearance of Amyloid-beta, activated mTOR also contributes to plaque formation and amyloid-beta accumulation.

During energy stress situations PI3K and Akt get phosphorylated i.e. the stress related to mitochondria rise survival and avert programmed cell death. To decline the problem of cellular metabolic pressure, boosted phosphorylation of oxidative arises over phosphorylation of subsequent proteins in an Akt-dependent mode. These approaches defend the cells against stress energy. Stimulation of Akt averts the function of some transcription factors i.e. FoxO which are regulating the entrance of antioxidant enzymes i.e. SOD and concurrently it activates mTOR.

Free radical oxidative damage causes a decrease in antioxidant enzyme levels, and when mTOR is activated, it encourages cells to enter the cell cycle and prevents autophagy, which improves the cell cycle and inhibits autophagy. Overall, the cell survival pathway gets instigation of on account of the stress related to energy, which might temporarily release the cells; nevertheless, the long-time impact can pledge or progress the pathology either of cancer or AD [95].

8. Common signaling pathways: p53, wnt, Pin1 in cancer and AD

Amyloid-beta as well as hyperphosphorylated tau protein, interrupt cellular role and offer emerging impaired function and loss of neurons. The main source for the development of cancer is DNA damage. In both cancer and AD, the common mechanisms are involved to modulate cell survival/death (Fig. 2). Tumor suppressors are the main features of controlling the mechanism of cancer development. Which controls the repair of injured DNA, cell-cycle and averts uncontrolled cell proliferation. Moreover, tumor suppressors also remove cancer cells by producing apoptosis. Overall, mostly p53 is an important protein of cell-cycle proteins which is categorized through a short life and stimulated for stress signals for example DNA injury, low blood oxygen (hypoxia), and instigation of oncogenes. The anti-cancer activity of p53 is related to preventing the division of cells as well as contains tissue repair [96,97]. The impaired functional activity of p53 is mutual in various cancer patients for such as leukemia, gastric cancer, and breast cancer [98,99].

It has been reported that modified p53 has innovative transcriptional aspects which alter p53 are contributed to the emergence of cancer via its influence on the regulation of genes accountable for encrypting the transcriptional process of developing cancer [100]. Reported that p53 has a vital role in the elderly and the neurodegenerative disorder i.e. AD [101], where an augmented quantity of p53 action is related to aging as well as senescence [102,103].

Neuropathology of AD that comprises fatal cell-cycle re-entry, excessive DNA damage, and apoptosis are regulated by p53. Reported in the animal experiment that the decline of wild kind of p53 formation declines the re-forming capacity of the brain against deadly damage, ensuring that p53 acts as an essential character in neurogenesis as well as neural regeneration [104]. Mammals are protected against synaptic gene regulation through p53, and p53 has been reported to have neuroprotective effects in animal (rodent) studies of tauopathy [105].

Furthermore, it has been stated that the accumulation of Amyloid-beta in nerve cell stimulate p53-dependent apoptosis. An increase in the level of p53 AD brain may be also connected to the existence of a modified shape of presenilin 1/2 (PS1/2) [101]. Also showed that glutamate-induced a robust association between the expression of p53 as well as excitotoxic nerve cell death. In conclusion, patients with the high rate of tumor suppressors activity would be in dangerous circumstances fort the progression of AD (Fig. 3).

The Wnt signaling pathway plays an important role in maintaining the balance of carbohydrates and lipids, glycolysis, and gluconeogenesis. It also regulates cell survival, proliferation, and differentiation. Likewise, it has been revealed that the Wnt signaling pathway is key in the CNS. Wnt proteins stimulate at least three signaling pathways. This is one of the approved pathways which triggers the transcriptional action of the β-catenin aspect along with pledging the appearance of the gene. Anomalous Wnt signaling is linked to several ailments with cancer and AD (Fig. 4). Glycogen synthase kinase-3β (GSK-3β) is involved in the hyperphosphorylation of tau protein as a result of the amyloid-beta masses that build up in the AD brain [106].

Likewise, literature also reveals that abnormal wnt signaling pathway in neurons is linked to a decline in the level of β-catenin in the cell cytoplasm and augments the appearance of wnt signaling inhibitor

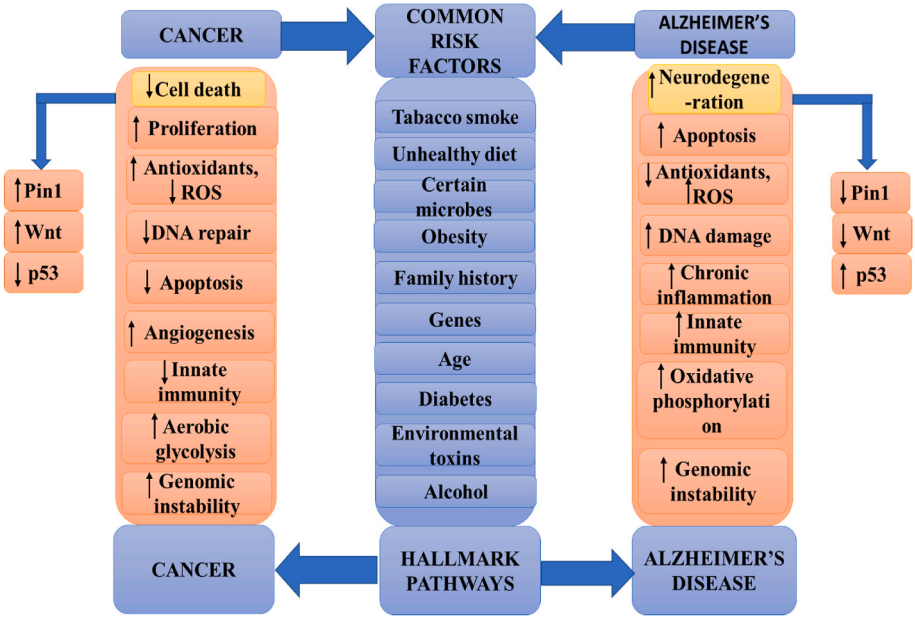

Fig. 2. Representation of the shared risk factors, signaling pathways, and inclination for AD and cancer at the cellular level.

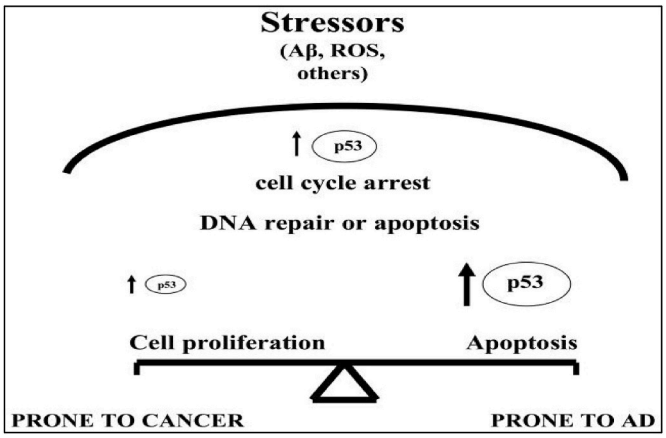

Fig. 3. The function of p53 in cancer and AD is represented. In response to stress signals, post-translational modifications cause p53 to be activated and cause cell-cycle stoppage. If all the body's cells were transferred to high p53 levels in response to stressors, AD may advance because the cells would be more likely to undergo apoptosis. The cells would be more likely to develop cancer if the level of p53 in the cell was low or maybe absent. Reproduced with the permission from Ref. [96] by Copyright Clearance Center (CCC).

DKK1. Thus, the inhibition of Aβ42-arbitrated stimulation of GSK-3β can contribute to the tenacious initiation of the wnt signaling and defend cells of the hippocampal region against amyloid-beta neurotoxicity. Similarly, it has been demonstrated that AD patients with presenilin-1 mutations have much lower levels of -catenin in their brains. Apolipoprotein E4 (APOE4) has been linked to an increased risk of AD and has been shown to block wnt signaling pathways [107].

The inhibitor of β-catenin-dependent Wnt signaling, Dickkopf-1 (DKK1), is released. It was initially identified as a tumor suppressor due to the prevalent belief that Wnt signaling facilitates the development of cancer. Increased GSK-3β activity and consequent tau hyperphosphorylation may occur as a result of the Amyloid beta that appears to be DKK1, an ineffective wnt signaling regulator. Nevertheless, in preclinical models, DKK1 appears to promote tumor growth and metastasis, and a poor prognosis in several cancers is correlated with its higher expression, suggesting that DKK1 has more intricate cellular and biological roles than previously understood. Consequently, Wnt signaling can be activated and the nerve cells protected by relaxing or deactivating DKK1. Advocated that slight alterations cause the defeat of wnt signaling to rise the vulnerability to neuronal death and simultaneously protect in contradiction of cancer emergence. In contrast, the increase of wnt pathway leads to raising the propensity to cancer evolution as well as simultaneously protecting against neurodegeneration (Fig. 4) [108,109].

The cis/trans isomerization of phosphorylated serine/threonine residues, which introduces proline as an amino acid, is catalyzed by the enzyme Pin1. The function and protein building are distressed by changes surrounding the proline. Pin1 adjusts a varied range of molecular methods such as transcription, differentiation, cell cycle, DNA injury feedback, differentiation, and/or survival [110,111]. Pin1 regulation plays a dual role during the cell cycle. In the beginning, it promotes G1/S transition through Cyclin D1 stabilization and cumulative appearance. After that, Pin1 controls DNA synthesis in phase S [112].

Furthermore, expression of Pin1 has connected with the proportion of cell proliferation: showed slight Pin1 expression in cells that are non-proliferating, whereas its over-expression was found in a maximum of the cancers such as colon, breast, lung, and brain in human beings [113]. Abridged Pin1 function was also shown in the pathogenesis of both cancers as well as AD. Stated that the development of cancer through several transforming genes is associated with major Pin1 over-expression in the maximum cancer patients [114]. Based on published data, documented reverse relation between cancer as well as AD. Stated that over-expression of Pin1 in cancers for example lung cancer were related with abridged incidence of AD.

9. Functional microRNAs in Alzheimer's disease and cancer

MicroRNAs (miRNAs) include one of the main post-transcriptional

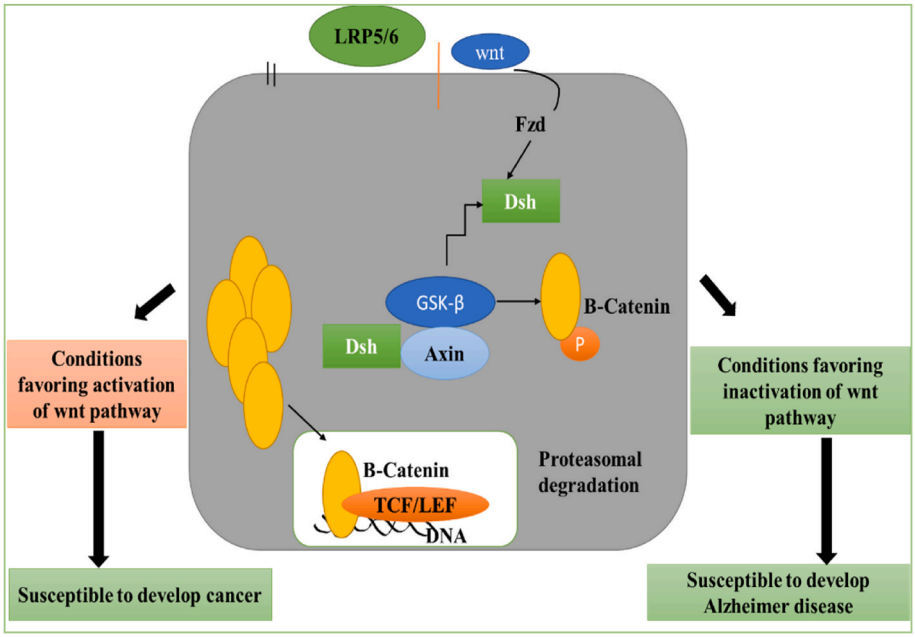

Fig. 4. Wnt signaling pathway involvement in cancer and AD. When wnt binds to the LRP-frizzled receptor on a cell's surface, it stabilizes -catenin, which in turn encourages the expression of wnt target genes and cell growth. imbalance at any point in the pathway's controllable inception stage, for example, an augmented appearance that causes stimulation of wnt or β-catenin may develop cancer and avert degeneration of neurons. In contrast, circumstances that cause defusing of the pathway would favour the AD development, and as an outcome defend from cancer development. Reproduced with the permission from Ref. [96] by Copyright Clearance Center (CCC).

controlling mechanisms concerned with numerous cancers and neurodegenerative diseases [115,116].

Fig. 5 shows how long precursor sequences of miRNA are produced in the nucleus, where certain miRNAs linked to AD and cancer are produced. The pathology of AD is typified by the build-up of intracellular neurofibrillary tangles made of hyperphosphorylated tau protein and extracellular amyloid plaques made of amyloid-beta peptide fragment (Aβ). Additionally, there is a loss of neurons in the frontal, temporal, and hippocampal lobes, as well as increased inflammation and oxidative stress [117,118].

As well as involvement in disease-specific pathways, Holohan et al. noted that miRNAs were involved in cancer and AD in pathways that would be contributing to both illnesses. They also predicted that these miRNAs would be differentially expressed and/or regulated [119].

They also noted that it might be a factor in the variations in disease pathology. We anticipate finding miRNAs linked to invasion, metastasis, inflammation, oxidative stress, and angiogenesis in cancer in addition to the proliferative/anti-apoptotic pathway; since many of these pathways have also been linked to neurodegeneration, we anticipate that these miRNAs will also be linked to the same or related pathways in AD [120–122].

9.1. Pathways

It is evident that AD research to date has centred on the amyloid pathway. Evidence that several miRNAs control the expression of molecules in this pathway includes the following: miR-101 and -153 have been shown to directly inhibit APP protein, while mir-9, -29a/b, −107, and −195 have been predicted or demonstrated to target, or negatively correlate with, BACE1 mRNA or protein levels. These miRNAs may have functional overlap or redundancy (Fig. 6).

Furthermore, the oxidative stress and inflammatory reactions upregulate miR-9, 125b, and 146a, indicating that the amyloid pathway may have a broad regulatory effect through miRNA. Innate immunological and inflammatory pathways have been thoroughly studied in relation to AD and cancer. miRNAs may operate through some of the same processes and seem to have a significant role in these pathways in both disorders (Fig. 7). One common theme among all the miRNAs reviewed here is regulation through the key transcription factor involved in oxidative stress and inflammation, NF-κB [119,123].

This protein has been demonstrated to have a significant impact on cancer and is a crucial signaling molecule in AD since it appears to connect the innate immunity, oxidative stress, inflammation, and amyloid pathways.

Similarly, miRNAs may play a crucial role in both types of disease. For instance, miR-34b/c levels are decreased in PD and SCLC, miR-206 levels are increased as a protective effect to thwart disease development in a rodent model of amyotrophic lateral sclerosis, miR-206 levels are decreased in laryngeal SCC, and miR-132 levels are decreased in frontotemporal dementia and prostate cancer, respectively [124,125]. The role of miRNAs in cancer has received attention thus far. Although the roles of miRNAs in AD diseases have not yet been thoroughly examined, they are currently being investigated extensively [126].

Assuming the excess evidence on controlling mechanisms of cancer comprising miRNA, and the probable contribution to the similar miRNAs in cancer and neurodegenerative, considering the functions of miRNA in cancer may assist to clarify corresponding or differing roles in neurodegenerative disorder. Additional information on the functions of miRNAs in cancer as well as AD may produce ideas in the fundamental pathways intricated in such ailments. The complete range of functions of miRNAs in several kinds of cancer and AD illnesses is a large matter nonetheless out of the scope of this selected assessment; this evaluation emphasizes the scrutiny of excellent miRNAs concerned in cancer and AD. The pathology of AD is categorized by a gathering of extracellular amyloid plaques contained of Aβ peptide fragments and loss of hippocampal cells, augmented free radical-induced oxidative stress [127,128].

After reviewing the literature on miRNAs in AD, there is still more work to be done to fully understand the functions that miRNAs play in all pathogenic pathways. Examining several miRNAs with functional evidence of participation in AD reveals that these molecules may regulate additional pathways outside inflammation and the amyloid pathway, although this has been generally disregarded. Research on miRNAs in AD and cancer was compared, highlighting areas that both diseases could benefit from more study in the future.

10. Inflammation in cancer and AD

Cell injury leads to cause of inflammation, infection, etc. The role of inflammation is to remove the primary source of cell damage and pledge methods of inflammation that cause tissue repair. Inborn immune cells such as dendritic cells, macrophages, NK cells, etc. detect and remove causative organisms through TLR/NF-κB signaling pathways [129,130].

Nevertheless, the response of inflammation is needed for the removal

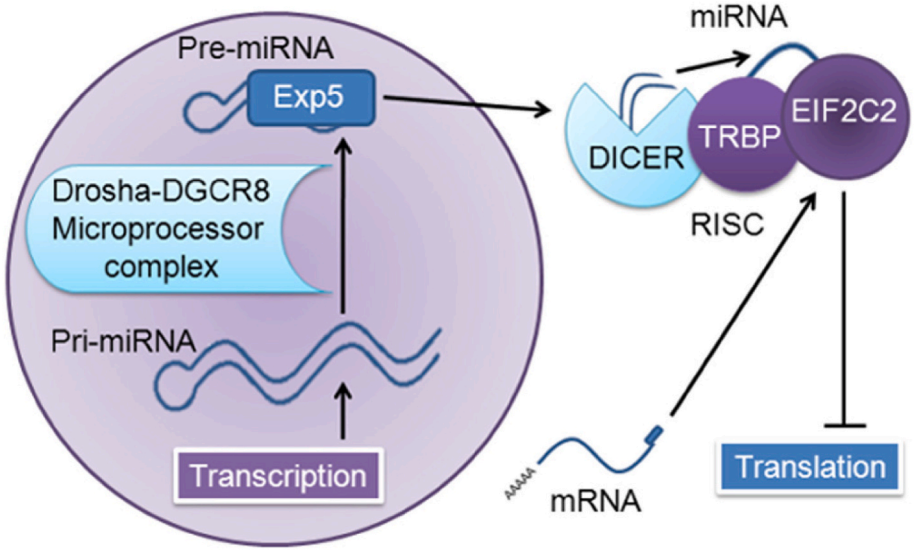

Fig. 5. miRNA production and utilisation. The microprocessor complex (DCGR8 and Drosha) cleaves the nuclear transcript pri-miRNA, which has a length of several kilobases. The result is a short (about 65 nucleotides) stem-loop pre-miRNA. Reproduced with the permission from [119].

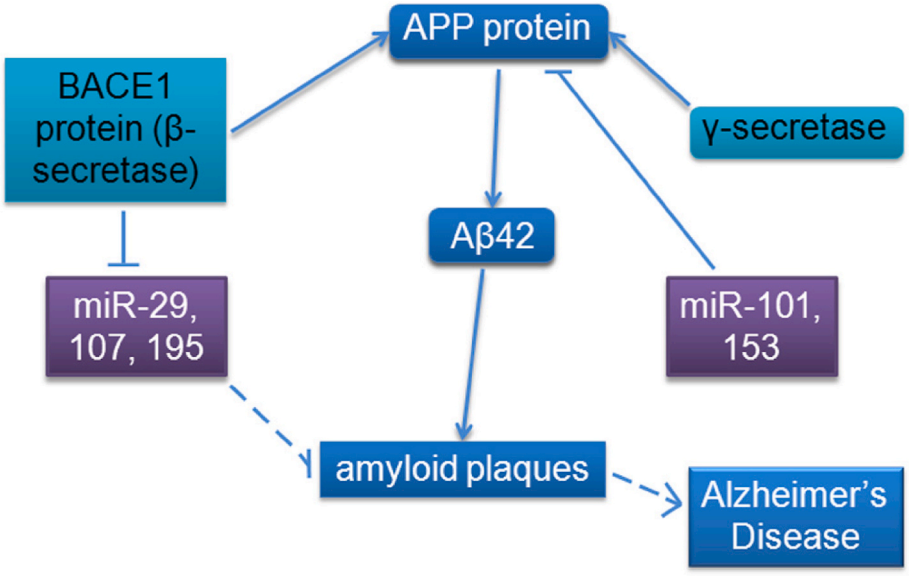

Fig. 6. It suggests that microRNAs have a role in the amyloid pathway and cause AD. Measured correlations are shown by dotted lines; known interactions are indicated by solid lines. Reproduced with the permission from Ref. [119] which was published under a CC BY license.

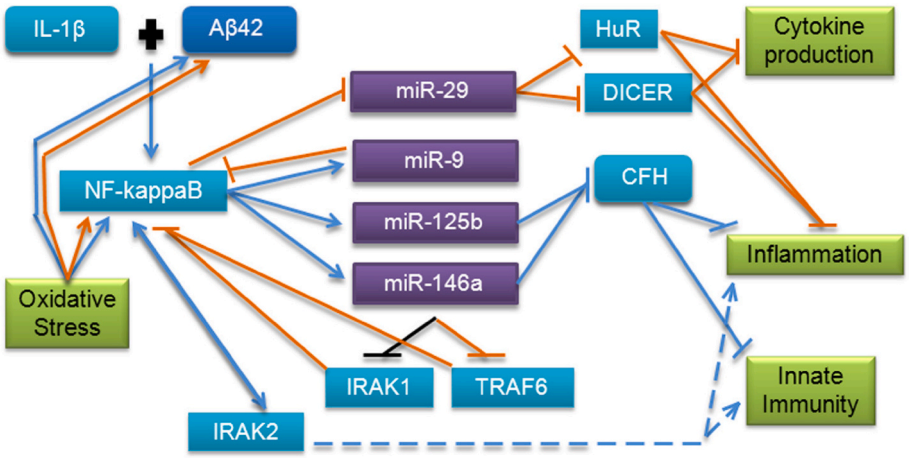

Fig. 7. microRNA participation in the pathways of oxidative stress, innate immunity, and inflammation in cancer and AD. Numerous studies on AD have supported this pathway; however, further data from cancer research suggests that additional molecules may be implicated. Research on AD discovered interactions and effects shown by blue lines; research on cancer revealed interactions and effects shown by orange lines; and discoveries shared by both diseases are indicated by black lines. Reproduced with the permission from Ref. [119] which was published under a CC BY license. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

of causative agents, but an extended method might induce chronic inflammation that may cause nerve cell damage to numerous organs in the body including the brain [131]. The inflammation of the brain is one of the pathological signs of AD. Also known that chronic inflammation can induce the injury of DNA and causes cancer. Increasing age-related decline in inborn as well as adaptive immunity capacity. Immunodegeneration is a serious immune mechanism that occurs in cancer as well as aging [132,133].

The vital structures for host defense are inflammasomes. They indicate a serious inborn immune source of IL-1β, a powerful inflammatory cytokine of which excess production can develop the deficiency of the autoimmune system. The function of inflammasomes in cancer development is so far uncertain, they can inhibit the formation of cancer based on the nature of the cancer [134].

The aggregated A activates the inflammasomes. Increased levels of IL-1, a byproduct of inflammasome stimulation, were observed in AD brain. Treatment interference is a key role for the NLRP3 inflammasome in the emergence of AD [135,136]. A promising correlation between chronic inflammatory AD and cancer was found in several studies. Leukocyte growth in tumours was reported to be the first evidence of a possible link between inflammation and cancer [137]. The gathering of scientific data in recent decades has identified the key factors that support the role of innate immune cells in the development of cancer [138].

The mechanisms by which innate immune cells promote tumor growth are still under ongoing review. The importance of inflammatory responses in several stages of tumor growth, such as initiation, promotion, invasion, and metastasis, is well documented. Both intracellularly and in the cellular response mechanism, which primarily disrupts natural killer (NK) cells, the immune system battles tumor cells. NK cells use markers for the precise chemical presented on tumor cells to identify newly changed cells. Therefore, tumor cells are eliminated. Macrophages and dendritic cells are destroyed after which T and B lymphocytes express tumor-derived fragments [139].

According to published research, inflammation is linked to a variety of neurodegenerative disorders, including AD [140]. The beginnings of AD are connected to a complicated mechanism that happens after neuronal death. The main drivers of AD-related inflammation that contribute to dysfunctional neurons. Neuroprotective mechanisms, amyloid clearance, and antioxidant defense are all effective early on in AD [141]. The neurodegenerative processes are accelerated as we age due to changes in the production and clearance of A-peptide as well as its propensity to form oligomers and extracellular plaques. The over-production of A, which results in the over deposition of senile plaques, has been linked to an anti-microbial response in the brain. A has been found to have an anti-microbial effect on a variety of infections [142]. The infectious theory of AD was given a fresh start by this statement [143].

11. Interrelation between cancer and AD through oxidative stress

Previous literature reveals a potential connection between cancer and AD, and anti-cancer agents were investigated to inhibit the pathology of AD in transgenic mice. The fast growth of cancer and AD performed in rodents simulated human AD that corresponds to the rate of ultrastructural aberrations of mitochondria. Recent research on the cell cycle re-entry of fatally distinct nerve cells indicates that abnormal NO-related mitochondrial activity is not a major contributor to cancer and AD pathogenesis, but it does pave the way for the development of novel therapeutic strategies for these kinds of destructive disorders [144].

11.1. Physiological functions of NO and NO synthase

Well known, NO is one of the important free radicals, documented as a biological signaling substance, as well as a pleiotropic controller in several pathologies comprising the progression of cancer and AD [144, 145]. It is synthesized by NOS through the transformation of L-arginine to L-citrulline. This enzyme includes iNOS, endothelial NOS (eNOS), and neuronal NOS (nNOS). Respectively these three isoforms might be involved in the elevation and/or inhibition of cancer progression in human beings [146].

11.2. Endothelin signaling cascades-GRK2 upstream

Alzheimer dementia (AD) patients experience mitochondrial ultrastructural changes and DNA damage because of nitric oxide (NO-) dependent oxidative stress. Cytosolic proteins known as G protein-coupled receptor kinases (GRKs), including GRK2, aid in the adaption of heptahelical G protein-coupled receptors (GPCRs) and the control of their downstream signals. GPCRs mediate the actions of messengers, which are important vascular and cardiac cell function modulators. The Akt/PKB pathway, which promotes endothelial NOS (eNOS), appears to

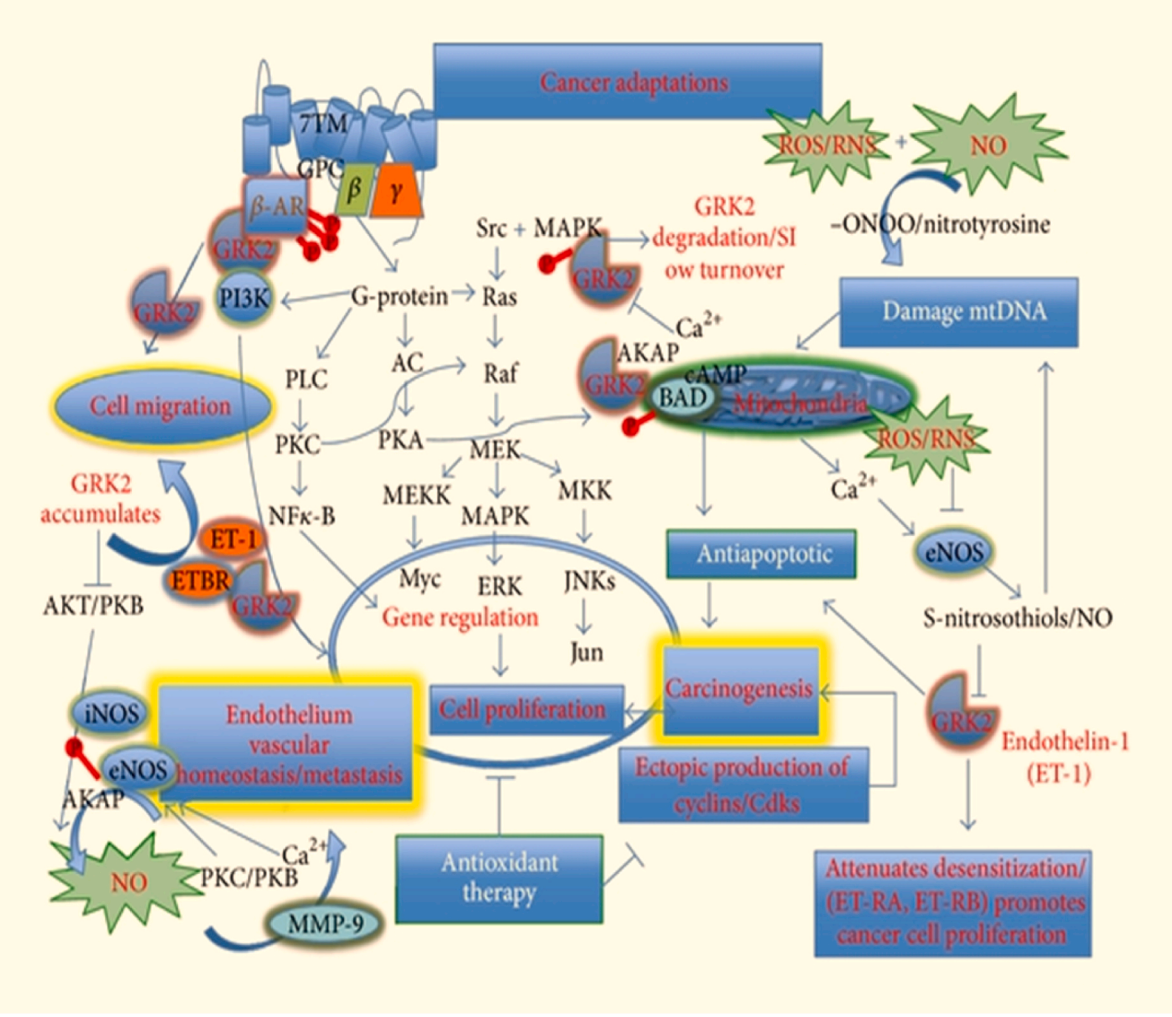

Fig. 8. Diagram showing the significant role that MAPK, JNK, GRK, and p38 play in the emergence and spread of cancer during the adaptive response. Reformed and reproduced from Ref. [150] which was published under a CC BY license.

be regulating endothelial cells' (EC) capacity to create NO. Physically, Akt binds with GRK2 and stops it from being phosphorylated and active, which results in NO production [147]. Suggests that expression GRK2 is augmented in sinusoidal EC from gateway rats under hypertension and reduced GRK2 reinstated Akt phosphorylation, NO production, and stabilized portal hypertension. Therefore, a significant mechanism decreased the action of eNOS in damaged sinusoidal EC which showed imperfect Akt phosphorylation produced by over-expression of GRK2 after injury (Fig. 8). The literature also indicated that GRK2 has a significant role in the endothelin-mediated signaling cascade and that it may regulate several endothelin 1's cancer-related features [148,149] (Fig. 9).

It seems that using GRKs as the goal of a therapeutic intervention is innovative. Additionally, as compared to an existing antagonist of the ET receptor, GRK2 over-expression reduced the formation of SMC caused by ET. TGF-induced expression of GRK2 lowers the production and motility of vascular smooth muscle cells under Angiotensin II regulation, according to reports [41,148]. It is important to consider GRK2's effects on ET-1 receptors, its aftereffects, and its relationship to cancer. The presence of GRK2 in several immune system cell types throughout the body serves as an example of the significance of the strong immunologic relationship to most cancers. The development of T-cells from lymphoid organs and leukocyte migration to inflammatory foci together provide an essential controller of cell responses throughout inflammation. GRK2 independently phosphorylates the chemokines and chemotactic receptors for CCR5, CCR2b, CXCR4, CXCR2, and formyl-peptide [151].

The development of cancer and metastasis are significantly influenced by abnormal epithelial cell motility. In pathological conditions, the expression of GRK2 may alter migrant retorts (Figs. 8 and 9). A possible role for GRK2 in the movement of epithelial cells was investigated, and it was hypothesised that GRK2 alters the actin cytoskeleton, paxillin localisation, and reliable critical bond turnover [152]. Additionally, they discovered that GRK2 promotes increased fibronectin translocation in a variety of epithelial cells and fibroblasts, with these effects being independent of GRK2 kinase activity. The opposite is explained in immune cells, where augmented expression of GRK2 eases relocation to fibronectin and GRK2 decreases the epithelial cells migration [152]. Accordingly, GRK2 levels are normally regulated by cell-cycle machinery and in response to DNA damage, and they differentially contribute to either cell-cycle development or cell arrest in a receptor-independent manner. Pathways may become blocked when DNA is damaged, and in this situation, GRK2 can encourage increased cell survival as a progress factor. The CDK2-arbitrated phosphorylation of GRK2 causes levels of GRK2 to drop swiftly during the G2/M transition, and preventing GRK2 phosphorylation delays typical GRK2 reductions and significantly slows the progression of the cell cycle [152]. Additionally, higher persistent levels of the kinases in cells were negatively linked with the p53 response and the activation of apoptosis [149]. Through an unfavourable feedback ring mechanism, GRK2 inhibits TGF-induced SMAD signaling [153]. By stimulating the TGF

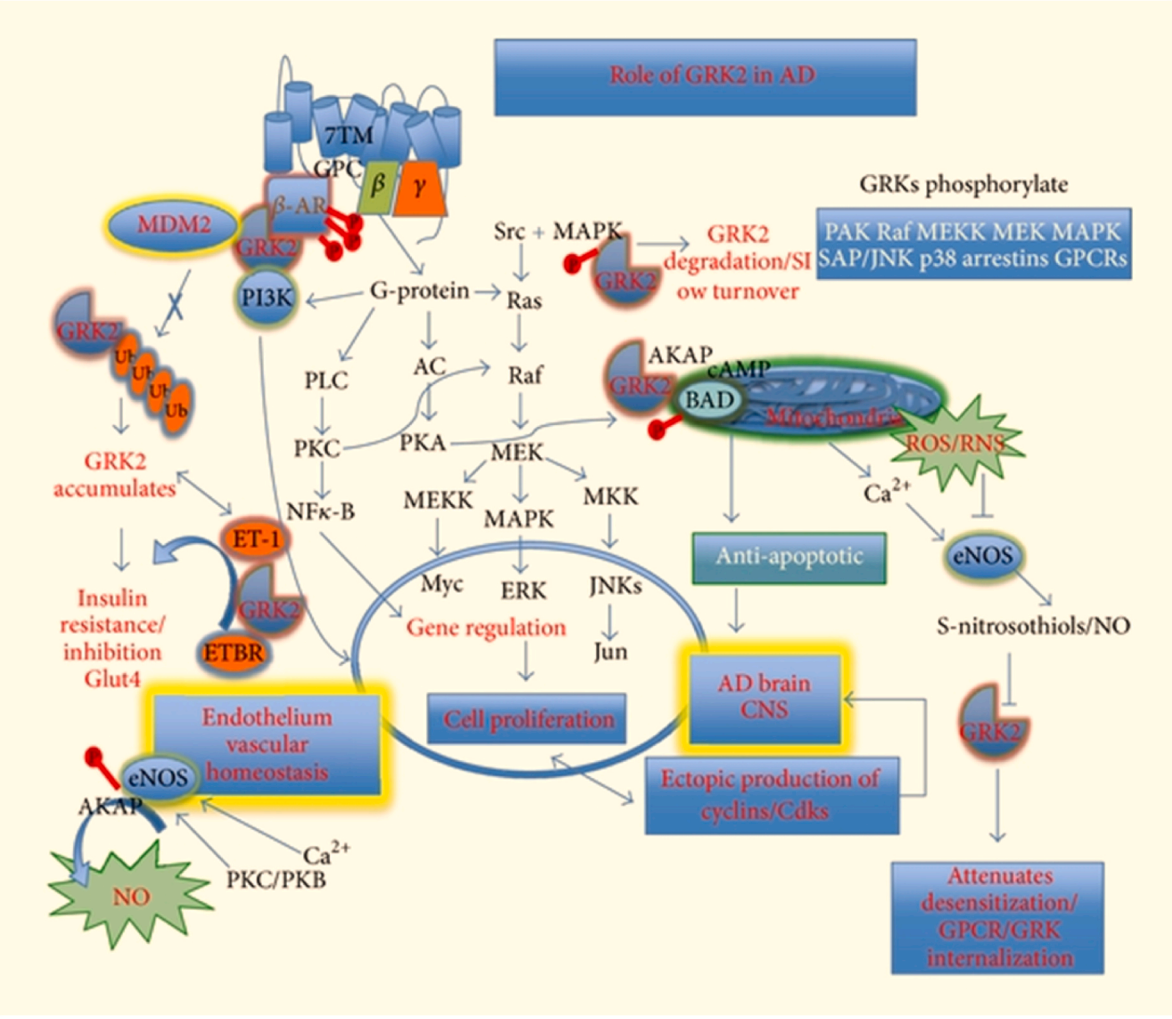

Fig. 9. The GRK2 over-expression seen in the graphical outline likely served as a compensatory response to the free radical stress caused by hypoxia and hypoperfusion, which ensures the development and maturation of AD. Reformed and Reproduced from Ref. [150] which was published under a CC BY license.

signaling cascade in VSMCs, Angiotensin II-induced ERK phosphorylation is blocked, and Angiotensin II-induced VSMC production and translocation at the Mek-Erk interface are inhibited [154].

While ET-1 might result in prolonged physiological reactions, GRKs most likely promise ET-R desensitization. Furthermore, GRK-initiated desensitization may be able to modulate endothelin A and B receptors separately. Additionally, it has been reported that GRK2 inhibits SMC growth [155]. The appearance of GRK2 is described to have a separate effect on cell proliferation and mitogenic signaling. Additionally, it plays a number of regulating roles that are directly related to cancer. The Hedgehog/Smoothened pathway is phosphorylated by GRK2 to boost Smo activity, relieve the Patched-dependent inhibition of cyclin B over the Hedgehog ligand, and activate the regulator of cell proliferation [156]. Additionally, GRK2 performs supervisory functions that depend on outside inputs that encourage cell proliferation [157]. Due to particular signaling pathways that are implicated in various malignancies, the GRK2 protein is expressed at greater levels in cancer cell lines [158,159].

The degree of altered GRK2 expression is known to control abnormal epithelial cell motility, which is crucial for the development and spread of cancer, as well as chemokine-mediated activation of MEK/ERK activity [160]. It has been demonstrated that GRK2 volume has abnormally increased [161] or decreased [162] in a subgroup of prostate tumours, which promotes altered GRK2 appearance in distinct tumor cells, which may overpower relocation in response to particular stimuli and plays a crucial role in fundamental cellular processes such as cell proliferation and differentiation during the emergence of granulose cell tumours in patients with distinct thyroid carcinoma. Additionally, GRK2 suppresses TGF-mediated cell growth arrest and death in human hepatocarcinoma cells. While GRK2 kinase action is essential for IGF-1-activated proliferation and mitogenic signaling in osteoblasts [163,164] and its appearance increases MAPK signaling in response to EGF in HEK-293 cells [164], GRK2 decreases serum or PDGF caused the proliferation of thyroid malignant cell lines as well as smooth muscle cells [155,163].

We noticed elevated GRK2 immunoreactivity in AD patients' susceptible neurons and during ischemia damage. To understand the events that precede amyloid deposition and potentially provide new insights into pharmacological treatments for AD, cellular and subcellular investigations into the mechanisms preceding Aβ deposition and progression, as well as the potential accelerating effects of environmental factors like chronic hypoxia/reperfusion, were therefore essential [165,166].

12. Use of treatments such as tyrosine kinase inhibitor, nilotinib, protein kinase C, and bexarotene

12.1. Tyrosine kinase inhibitor

Additional evidence linking cancer to neurodegenerative conditions including AD and Parkinson's disease (PD) [167] may point to the use of cancer kinases as a means of addressing neurodegeneration. Developing disease-modifying treatments in the field of cancer kinase inhibition for non-oncological purposes, like AD, is becoming more difficult. Tyrosine kinase inhibition does, in fact, have two opposing effects: on the one hand, it manipulates autophagy to prevent tumor growth and cell division in cancer; on the other hand, it causes hazardous protein breakdown and preserves neuronal life in neurodegeneration.

The following describes several anti-cancer EGFR inhibitors that may be used in AD therapy; Table 1 displays the therapeutic effects, safety, and toxicity profiles of EGFR TKIs in AD and cancer.

Table 1
The effects of EGFR inhibitors on cancer and AD.

EGFR Inhibitor	Effects in Cancer	Effects in AD	Ref
Gefitinib	First-generation EGFR TKI for the treatment of lung cancer	Reduces the memory loss caused by Aβ in Drosophila AD model and APP/PS1 transgenic mice Inhibits the levels of extracellular Aβ40/42 and lowers the activity of β-secretase (BACE-1) in N2a cells that overexpress APP. Enhances the cognitive abilities of Swiss albino mice	[168–170]
Erlotinib	Inhibits the development of tumours in human endometrial cancer cell lines HEC-1A	Greatly improves the Drosophila performance index in cases of Aβ42-induced memory loss	[171,172]
Afatinib	Second-generation EGFR-TKI with anti-inflammatory characteristics Inhibits the hepatocellular carcinoma (HCC) cells' ability to proliferate, migrate, and invade prevents the development of brain tumours in glioblastoma cells by controlling EGFRvIII-cMet signaling in combination with temozolomide	stops the activation of astrocytes Lowers the activation of caspase-1 and proinflammatory cytokine levels in CTXTNA2 cells	[173,174]
Varlitinib	FDA-approved inhibitor of EGFR/HER2 Inhibits the development of mammospheres, cell migration, and invasion in triple-negative breast cancer (TNBC) cells	Reduces tau pathology and LPS-mediated neuroinflammatory responses in tau-overexpressing PS19 and wild-type mice	[175,176, 214–216, 219]
Lapatinib	Dual TKI that targets HER2 and EGFR Antitumor actions in breast cancer cells that are positive for HER2	Lowers Aβ1-42 and p-tau levels and improves cognitive impairment in rats with d-galactose/ovariectomized ovaries	[177,178]
Osimertinib	Clinical activity against non-small cell lung cancer (NSCLC) and glioblastoma with EGFR mutation	No research on osimertinib as an AD treatment	[179,180]

12.2. Nilotinib

The Bcr-Abl tyrosine kinase inhibitor nilotinib (Tasigna, AMN107, Novartis, Switzerland) was approved by the European Medicines Agency (EMA) in 2007 and the U.S. Food and Drug Administration (FDA) in 2010 for the treatment of individuals with chronic myeloid leukemia who have the Philadelphia chromosome [181]. Recently, nilotinib has been repurposed in the treatment of several neurodegenerative illnesses, including AD, PD, and Lewy body dementia (LBD). The hyperactivation of this kinase in human AD and PD brains, as well as in a range of tauopathies, provides support for the use of c-Abl inhibition as a therapy for neurodegenerative illnesses [182,183]. Schlatterer et al. consequently observed elevated tyrosine kinase c-Abl activation in both *in vitro* and *in vivo* transgenic AD models [184]. Interestingly, it has been demonstrated that a key mechanism mediating the Aβ-induced synaptic damage is the stimulation of c-Abl signaling [185].

Treating hippocampus neurons exposed to Aβ fibrils with the c-Abl inhibitor STI571 (imatinib mesylate, Gleevec) stopped their neurons

from dying. Furthermore, it has been demonstrated that intraperitoneal injection of STI571 improves spatial learning and memory impairment in 11-month-old APP/PS1 transgenic mice and lessens rat cognitive impairment on spatial memory performance, which is caused by bilateral hippocampal injection of 5 μM Aβ fibrils [186]. Additionally, it has been discovered that Aβ-induced c-Abl activation not only stimulates the proapoptotic signaling cascade through p73, but also promotes tau phosphorylation [187], as it activates the tau kinase Cdk5 (cyclin-dependent kinase 5) and phosphorylates tau directly at tyrosine. Notably, it has been demonstrated that tau phosphorylated at tyrosine is present in pre-tangle neurons in AD brains, lending credence to the theory that c-Abl may play a role in the formation of neurofibrillary tangles and the cognitive deficits they cause [188].

By lowering the activation of the c-Abl/p73 proapoptotic signaling pathway and the c-Abl/Cdk5-mediated tau phosphorylation, nilotinib may be able to reduce Aβ-driven apoptosis and neurodegeneration through c-Abl suppression. This could potentially prevent the creation of neurofibrillary tangles. However, further research is needed to understand how Aβ affects c-Abl activity and the intracellular mechanisms that lead to it.

12.3. Protein kinase C

Protein Kinase C (PKC) isozymes are highly controlled kinases that facilitate the degradation of membrane phospholipids by receptors, hence converting a wide range of signals. They are crucial to the functioning of the brain, and PKC activity dysregulation is linked to neurodegeneration. Alzheimer's dementia (AD) is linked to gain-of-function mutations in PKCα, and spinocerebellar ataxia (SCA) type 14 (SCA14) is caused by mutations in PKCγ.

The brain contains a high concentration of conventional PKC isozymes, with PKCγ mostly located in the cerebellar Purkinje cells [189]. But since PKC was isolated and characterised from brain tissue in the 1970s [190], the main emphasis of oncogenesis-related research on these enzymes has been their function. This is largely because PKC was identified as the primary receptor for the powerful, tumor-promoting phorbol esters, which led to the development of an oncoprotein paradigm for PKC in the early 1980s [191]. This belief has since been disproved, though, as it was discovered that PKC mutations linked to cancer typically result in loss of function [192]. Moreover, higher survival rates are correlated with the steady-state protein levels of traditional PKC isozymes in malignancies such colorectal, non-small cell lung carcinoma, and pancreatic cancer [193].

The idea that reduced PKC activity promotes cellular proliferation and survival is supported by the repositioning of PKC as a tumor suppressor, which would explain why PKC inhibitors have not only failed but, in some cases, also worsened patient outcomes in cancer treatment trials (Fig. 10) [193,217].

Left: Cancer has been linked to loss-of-function somatic mutations in all PKC isozymes. The failure of PKC inhibitors in clinical trials for cancer is probably because PKC should be restored rather than inhibited in this illness. **Right:** Spinocerebellar ataxia is linked to germline mutations in PKCγ, while Alzheimer's disease is linked to gain-of-function germline mutations in PKCα. When neurons are exposed to amyloid-β, their PKC function is abnormal, which results in synaptic depression, neuronal death, and loss of spine density. Repurposing PKC inhibitors that were unsuccessful in clinical trials for cancer may prove to be a successful therapeutic approach for treating neurodegenerative illnesses characterised by hyperactivity of PKC. Reproduced from Ref. [217] which was published under a CC BY license.

PKC is being known as a neurodegenerative disease biomarker and potential treatment target. Specifically, AD and SCA are linked to the brain's PKC isozymes, PKCα and PKCγ, which are Ca^{2+}−regulated and promote synapse loss and neuronal death in these various neurological illnesses. A growing body of research indicates that blocking PKC may be a useful tactic to stop or reduce the neurodegeneration linked to AD. While PKC inhibition with pharmacological inhibitors or aprinocarsen, a PKCα antisense oligonucleotide, did not work well in cancer clinical trials, these same compounds might work better for AD [194].

In fact, antisense strategies have already been successfully applied to reduce PKC in various neurodegenerative diseases, including spinal muscular atrophy [195], amyotrophic lateral sclerosis [196], leucine-rich repeat kinase 2 (LRRK2) protein levels in Parkinson's disease treatment [197], and others. As such, the use of specific PKC antisense oligonucleotides to reduce PKC is an attractive potential treatment of neurodegenerative diseases [198].

A precision medicine strategy that might be helpful for neurodegenerative illnesses where PKC activity needs to be decreased to restore

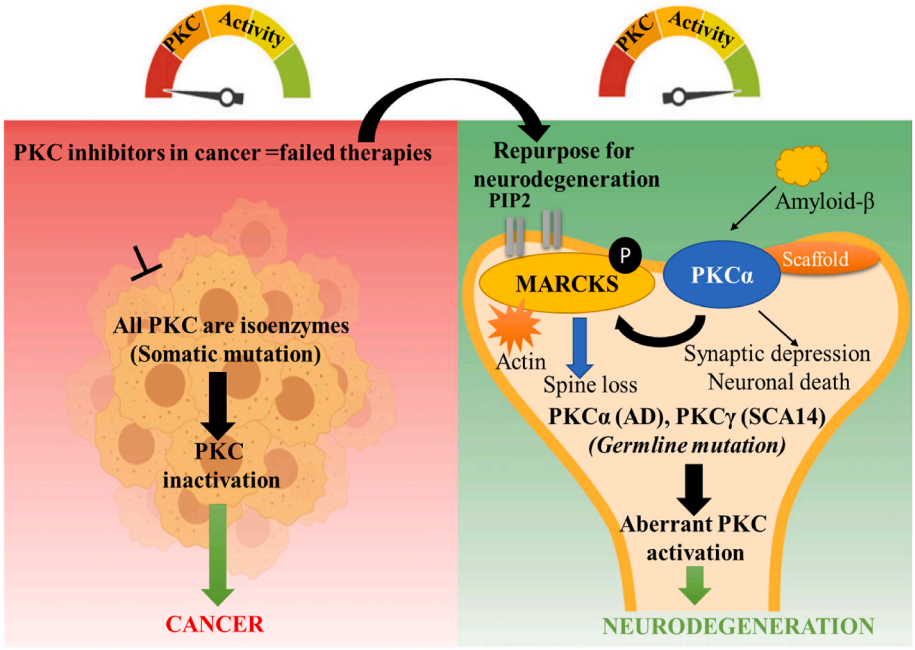

Fig. 10. PKC balance in the cell is crucial.

homeostasis could be achieved by restricting antisense oligonucleotides to the central nervous system (CNS) in order to reduce protein levels only in the brain. Targeting the distinct PDZ ligand contacts of PKCα at the synapse can be an effective way to exploit specificity in inhibition. Indeed, it has been demonstrated in the past that Aβ-induced synaptic depression can be avoided by small molecule binders of PICK1's PDZ domain, which scaffolds PKCα [199].

Crucially, PKC signaling in AD and ataxia just must be adjusted to homeostatic levels—it doesn't need to be completely eliminated. By slightly adjusting activity, the negative consequences of the activity decrease seen in cancer might be avoided.

12.4. Bexarotene

The FDA has approved the retinoid X receptor (RXR) agonist bexarotene for the treatment of cutaneous T-cell lymphoma. But it has also shown encouraging therapeutic potential for neurological conditions like AD, Parkinson's disease, stroke, and traumatic brain injury. In Alzheimer's disease (AD), bexarotene reduces the generation and accumulation of amyloid β (Aβ), triggers Liver X Receptor/RXR heterodimers to boost lipidated apolipoprotein E and eliminate Aβ, lessens the deleterious effects of Aβ, controls neuroinflammation, and eventually enhances cognitive performance.

As an RXR agonist, bexarotene has a variety of side effects and has shown promise as a treatment for several CNS conditions in addition to tumours. Promising findings have been obtained from numerous preclinical investigations examining bexarotene's effectiveness in treating CNS disorders. We think that further thorough research will be helpful in clarifying the possible role of bexarotene in the treatment of cancer and AD, even though the investigation of bexarotene in several CNS illnesses is still in its early phases [200].

13. Aging hallmarks

Given the complexity of ageing as a biological process, it may be necessary to use several biomarkers to predict the physiological mechanisms of ageing that give birth to the range of contradictory outcomes that are often observed in the aged. At initially, telomere shortening—which happens during cell replication—was thought to be indicative of ageing and age-related consequences. However, prior research indicates that an individual's age-related impacts and telomere shortening are quite low [201].

Telomere shortening predicts a person's longevity, health, and clinical and functional outcomes in an inconsistent manner. Thus, to forecast age-related consequences, more biomarkers are needed. Many alterations occur in the organism's cellular and molecular makeup because of ageing. Research has indicated that one important aspect of ageing is epigenetic modifications [202].

Modulation of gene expression without alterations to the genome sequence is referred to as epigenetic modifications. Histone modifications, DNA methylation, and non-coding RNA are examples of well-known epigenetic modifications. The most common epigenetic changes associated with ageing are changes in dynamic DNA methylation. Telomere shortening, genomic instability, epigenetic modifications, mitochondrial dysfunction, loss of proteostasis, deregulated nutrient sensing, stem cell exhaustion, cellular senescence, and altered cellular communication are among the nine well-established hallmarks of the ageing process. Prolonged systemic inflammation has been linked to all of these alterations. Low-grade but persistent inflammation that damages tissues and organs is a form of inflammation that occurs as people age [203].

Ageing and cancer have a complicated relationship, according to a growing body of research. Accordingly, ageing is a major risk factor for cancer because accumulating genetic and epigenetic differences cause mutations or changes in gene expression. Hanahan and Weinberg characterised cancer in 2000 using six distinguishing characteristics: growth signal self-sufficiency, immunity to anti-growth signals, apoptosis avoidance, infinite replicative capacity, persistent angiogenesis, tissue invasion, and metastasis [204].

Four further features were added to the list of hallmarks in 2011 by Hanahan and Weinberg, bringing the total to ten: (vii) deregulating cellular energetics; (viii) avoiding immune destruction; (ix) tumor-promoting inflammation; and (x) genome instability and mutation [205]. By including the following, Hanahan expanded the list to 14 traits in 2022: (xi) polymorphic microbiomes; (xii) non-mutational epigenetic reprogramming; (xiv) releasing phenotypic plasticity. Undoubtedly, the recently updated hallmark features of ageing and cancer demonstrate the close connection between these two processes [206].

14. Oxidative stress and DNA damage can trigger cellular senescence in cancer and AD

By modifying protein shape, catalytic activity, protein-protein and protein-DNA interactions, protein transport, and certain signaling pathways that activate NF-κB and Smad3, oxidative stress plays a major role in senescence. Stressors such as telomere erosion, DNA damage, and oxidative stress act on the p16INk4a/Rb and p53/p21Cip1 pathway, causing cell cycle arrest and cellular senescence. Inhibitors of cyclin-dependent kinase (CDK) include p16INK4a and p21Cip1 [207].

Replicative senescence, stress-induced premature senescence (SIPS), and developmentally programmed senescence (DPS) are the three forms of cellular senescence [208]. Recurrent cellular replication and telomere shortening cause somatic cells' ability to divide to decrease during replicative senescence [209]. UV light, oxidative stress, and oncogene activity are some of the factors that cause SIPS [210]. DPS has been suggested as the evolutionary source of senescence and performs developmental and morphogenetic roles during embryonic development [211]. Given that prolonged oxidative stress causes cellular senescence and antioxidants prevent cellular senescence, oxidative stress causes SIPS in a variety of cell types (Fig. 11) [212,218].

Protein malfunction may be brought on by oxidative damage. In addition to mutations, DNA damage is a significant factor in genetic instability and epigenetic modifications. Furthermore, oxidative stress can alter different kinds of tumor suppressor genes and oncogenes. Alzheimer disease (AD) is characterised by DNA damage and mitochondrial ultrastructural alterations brought on by nitric oxide (NO-) dependent oxidative stress. However, not much is known about these pathways in human cancers, especially in the early stages of primary brain tumour development and metastatic colorectal cancer. Lack of tissue potency, which promotes mitochondrial scratches and the development of hypoxic, smaller mitochondria with ultrastructural abnormalities, is one of the major causes of tumours. There may be a link between AD and cancer, according to recent research, and anti-cancer drugs are being discovered to prevent AD-like pathology in transgenic mice. In animal models of AD that resemble human AD, the degree of mitochondrial ultrastructural abnormalities was linked with the severity of tumor growth, metastasis, and brain damage. Recent developments in the cell-cycle re-entry of the fatally differentiated neurons suggest that mitotic cell division and aberrant NO-dependent mitochondrial activities are not the only important pathogenic elements in the pathophysiology of AD and cancer [213].

The known and proposed functions of these pathways in AD and cancer are summarised in Fig. 12. Comparing the expression and activity of miRNAs may provide more insight into the role that these pathways play in the development and progression of disease.

15. Conclusion

The findings of the inverse association between cancer and AD reveal unique research trajectories that show the emergence of both cancer and AD. If they both have a biological process that, when activated, results in greater cell growth or survival on the one hand and cell death on the

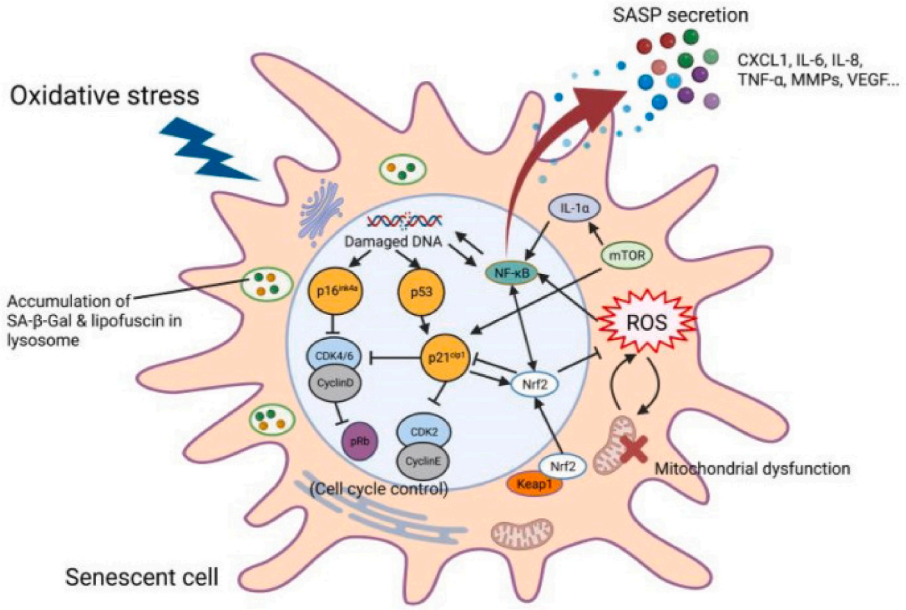

Fig. 11. Senescent cell's molecular signaling network and graphic representation. Reproduced from Ref. [218] which was published under a CC BY license.

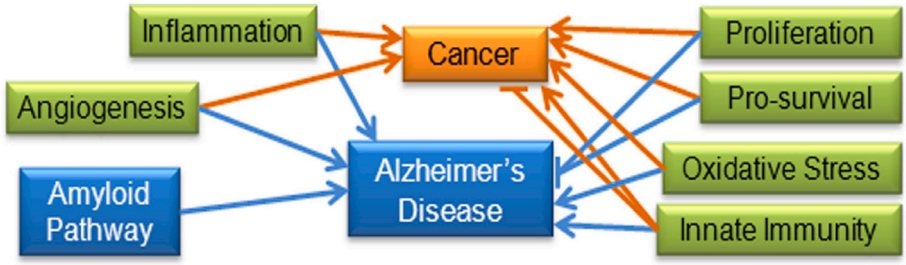

Fig. 12. Important molecular and cellular routes for AD and cancer include elevated oxidative stress and inflammation, which have been favourably linked to both diseases Reproduced from Ref. [119] which was published under a CC BY license.

other. Understanding the relationship between these two diseases is made essential to a greater extent which is considering that presently innovative therapies of both still progress to avert AD that may cause a higher risk for the progression of cancer, in addition, contrarywise the therapies to avert cancer might incline to improv AD.

The outcomes of cell-cycle dysregulation of PI3K/Akt/mTOR pathway stimulation can induce AD, then describes the pathogenesis of cancer and AD in varied circumstance. The mutual biological mechanism can cause an overgrowth of cells as well as proliferation in the circumstance of cancer, however, a vast number of cell death can cause by AD might be described as the opposite relation between both diseases. Several mechanisms i.e. abnormal cell growth as well as survival pathways advised to have a significant role in this reverse relation. The mutual mechanisms, such as p53 signaling, Pin1, and Wnt are working oppositely in cancer and AD, which cause abnormal cell growth in cancer and degeneration of nerve cells in AD. microRNA research in both diseases showed its capacity to control cancer and aging-associated processes and comprised various molecular mechanisms in cancer which might potentially contribute to the pathology of AD. Today, increase interest to concentrate on the impact of various microorganismal infections which have significant roles in AD inflammatory pathways and play a crucial role in the growth of cancer. Regulatory mechanisms of miRNA in both diseases have covered different types of mechanisms detected in cancer which might potentially also involve AD pathology. Though further various features of likely description for AD as well as pathological relationship involving cancer and AD but still not clear. It is looking that cell cycle-associated mechanism has a foremost role in emerging cancer and AD. Previously literature advocates that the vulnerability of cancer may defend against AD and vice versa. Consequently, based on this inverse relation it is well understood that it may progress innovative treatments and should keep continuing strong translational research. According to the literature, cancer and AD can be treated and prevented in novel ways based on biological principles. One of the most advantageous methods of treating cancer is the use of bexarotene, taxanes, cerium oxide nanoparticles like nanoceria, nilotinib, tyrosine kinase inhibitors (TKI), and dasatinib.

Funding

The authors did not receive support from any organization for the submitted work.

CRediT authorship contribution statement

Mohammad Ali: Writing – review & editing, Writing – original draft, Resources, Methodology, Conceptualization. **Shahid Ud Din Wani:** Writing – review & editing, Writing – original draft, Resources, Methodology, Data curation, Conceptualization. **Tathagata Dey:** Resources, Data curation. **Sathvik B. Sridhar:** Resources, Data curation. **Zulfkar Latief Qadrie:** Resources, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgments

We express our gratitude to the Dean of the School of Applied Science and Technology at the University of Kashmir in Srinagar, India, and the East-Point College of Pharmacy in Bengaluru, India, for their unwavering support.

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