BBA - Reviews on Cancer 1868 (2017) 341–358

Contents lists available at ScienceDirect

BBA - Reviews on Cancer

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

Review

Functional analyses of major cancer-related signaling pathways in Alzheimer's disease etiology

Jianping Guo[a,1], Ji Cheng[a,b,1], Brian J. North[a], Wenyi Wei[a,*]

[a] Department of Pathology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA 02215, USA
[b] Department of Gastrointestinal Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China

ARTICLE INFO

Keywords:
Alzheimer's disease
Aging
Tumorigenesis
Cell signaling
Tau
Amyloid

ABSTRACT

Alzheimer's disease (AD) is an aging-related neurodegenerative disease and accounts for majority of human dementia. The hyper-phosphorylated tau-mediated intracellular neurofibrillary tangle and amyloid β-mediated extracellular senile plaque are characterized as major pathological lesions of AD. Different from the dysregulated growth control and ample genetic mutations associated with human cancers, AD displays damage and death of brain neurons in the absence of genomic alterations. Although various biological processes predominately governing tumorigenesis such as inflammation, metabolic alteration, oxidative stress and insulin resistance have been associated with AD genesis, the mechanistic connection of these biological processes and signaling pathways including mTOR, MAPK, SIRT, HIF, and the FOXO pathway controlling aging and the pathological lesions of AD are not well recapitulated. Hence, we performed a thorough review by summarizing the physiological roles of these key cancer-related signaling pathways in AD pathogenesis, comprising of the crosstalk of these pathways with neurofibrillary tangle and senile plaque formation to impact AD phenotypes. Importantly, the pharmaceutical investigations of anti-aging and AD relevant medications have also been highlighted. In summary, in this review, we discuss the potential role that cancer-related signaling pathways may play in governing the pathogenesis of AD, as well as their potential as future targeted strategies to delay or prevent aging-related diseases and combating AD.

1. Introduction

1.1. Aging, cancer and neurodegenerative disorders

Aging has generally been referred to as the progress of becoming older, especially when occurring in animals and in particular mammals such as human beings. Biologically, aging is also referred to cells within organism losing the ability to divide (also termed cellular senescence) [1,2]. Aging represents the accumulation of changes or damage in organs or cells over time, including the increase of DNA damage, misfolding of proteins, and oxidative stress, which carries the greatest risk of human chronical diseases, including cancer, cardiovascular and neurodegenerative disorders [3–5]. Although the damage-related factors (such as DNA-oxidation) or programmed factors (such as apoptosis) are established as the major contributors of aging [3,6], the mechanisms governing the aging process have largely remained elusive.

As two of the major diseases associated aging, cancer and neurodegenerative diseases display rather different properties, and in many aspects exhibit an inverse relationship [7]. For instance, genetic alterations including amplification or gain-of-function (GOF) mutations of oncogenes and deletion or loss-of-function (LOF) mutations of tumor suppressors play critical roles in various types of cancer [8,9]. However, genetic alterations are not common in neurodegenerative disorders, especially in Alzheimer's disease (AD) [10]. Furthermore, tumors display aberrant growth control properties to developing disseminated carcinomatosis, infection or pulmonary embolus ultimately leading to the death of patients [11]. Whereas, the major neurodegenerative diseases are associated with damage or death of neurons, leading to impairment of the patients' movement or mental functioning leading to death [12]. Finally, multiple therapeutic strategies including surgical removal, radio/chemo-therapies, targeted and immune-therapies have been developed to ameliorate or cure cancer patients. In contrast, neurodegenerative disorders, in particular Alzheimer's disease, are currently incurable [13]. To better understand the mechanisms underlying regulation of aging and neurodegenerative diseases, multiple signaling pathways heavily involved and well-studied in tumorigenesis, including FOXO, mTOR, MAPK, SIRT, insulin resistant, autophagy, inflammation, oxidative stress, and metabolic pathways have now been

* Corresponding author.
E-mail address: wwei2@bidmc.harvard.edu (W. Wei).
[1] These authors equally contribute to the works.

http://dx.doi.org/10.1016/j.bbcan.2017.07.001
Received 7 June 2017; Received in revised form 5 July 2017; Accepted 6 July 2017
Available online 08 July 2017
0304-419X/

Table 1
A summary of mouse models for Alzheimer's disease.

Line		Mutation	Genetic pathology	References
APP models	PDAPP	$A\beta PP_{Ind}$	Plaque pathology begins 6–9 months without NFT pathology	[25]
	Tg2576	$A\beta PP_{Swe}$	Plaque pathology begins 9 months without NFT pathology	[338]
	APP23	$A\beta PP_{Swe}$	Plaque pathology begins 6 months with hippocampal neuronal loss without NFT pathology	[339]
	J20	$A\beta PP_{Ind/Swe}$	High levels of $A\beta_{42}$ and plaque	[340]
	TgCRND8	$A\beta PP_{Ind/Swe}$	Plaque pathology begins 3 months	[341]
	TASD-41	$A\beta PP_{Lon/Swe}$	Plaque pathology begins 3–4 months with Tau pathology	[342]
PSEN1 models	*PSEN1*	$PSEN1_{M146V}$	With elevated $A\beta_{42}$ without plaque pathology	[343]
	PSEN1	$PSEN1_{M146L}$	With elevated $A\beta_{42}$ without plaque pathology	[343]
Tau models	*Htau*	*Human tau*	High levels of hyperphosphorylated Tau in 6 months, develop NFT in 15 months	[344]
	JNPL3	Tau_{P301L}	Develop tangle pathology and nerve loss	[345]
	TauP301S	Tau_{P301S}	Develop tangle pathology in 5–6 months	[346]
	rTg4510	*Tet-on Tau*	Develop tangle pathology with cognitive deficits in 2.5 months	[347]
Noncanonical models	*APOE*	$Apoe^{-/-}$	Low levels of $A\beta_{42}$	[348,349]
	$Pin^{-/-}$	$Pin^{-/-}$	High levels of hyperphosphorylated Tau and $A\beta_{42}$	[43,350]
Combinational models	*PSAPP*	$Tg2576/PSEN1_{M146L}$	Plaque pathology begins earlier than *Tg2576* with high levels of $A\beta_{42}$	[34,351]
	TAPP	$Tg2576/Tau_{P301L}$	Tau pathology begins earlier than Tau_{P301L} with plaque pathology	[352]
	3xTg-AD	$PSEN1_{M146L}/A\beta PP_{Swe}/Tau_{P301L}$	Plaque pathology begins 6 months and Tau pathology begins in 12 months	[40]
	APP/APOE	$A\beta PP_{Swe}/Apoe^{-/-}$	High levels of IL1β and GFAP activity compared to *TgCRND8*	[353]

shown to be associated with neurodegenerative diseases as well, especially in the pathogenesis of Alzheimer's disease, and is the focus of this review.

1.2. Alzheimer's disease (AD)

In 2015, approximately 49 million people were diagnosed with AD worldwide, which is anticipated to increase to 115 million by 2050 [14], in which nearly 15% of people over 65 years old and 50% of people over 85 years old will suffer with AD. This supports the notion that aging is the highest risk factor of AD [14]. However, early-onset AD (under the age of 65) also has been reported occurring in approximately 200,000 Americans due to the inherited mutations [15]. As the major cause of dementia, AD accounts for around 70% of dementia cases with symptoms including difficulty remembering new information, and is characterized as the 6th leading cause of death for all Americans without any efficient treatment strategy [13]. Thus, studies leading to early diagnosis and therapies of AD are urgent in the medical field.

Since 1907, two pathological lesions with abnormal structures and parallel spatial distribution, called senile plaques and neurofibrillary tangles (NFT), are suspected to damage neuronal cells, and have been characterized as the major pathological hallmark of AD [16]. Senile plaques are caused by deposition of a protein fragment called amyloid beta (Aβ, 42 and 40 peptides) that build up in the spaces between nerve cells, also referred to "brain amyloidosis". Specifically, Aβ peptides are released by cleavage of the amyloid precursor protein (APP), to form oligomeric Aβ aggregates, that play a crucial role in disrupting the survival of neuronal cells and are considered a leading cause of AD [17]. Neurofibrillary tangles are twisted fibers of tau protein that build up inside cells. Growing reports demonstrate that hyper-phosphorylation of tau form tangles that could subsequently induce the damage of neuronal structure and function, which is a major intracellular pathology of AD [18]. Thus, the development and regulation of these two lesions have been well studied recently as major hallmarks of AD [19,20].

1.3. Biomarkers for Alzheimer's disease

With the difficulty associated with diagnosing AD, identification of biomarkers is necessary for early detection of AD and drug treatment validation. Until now, cognitive assessment is still the primary method for diagnosing AD-induced dementia [21]. Magnetic resonance imaging (MRI) has been developed for the diagnosis of AD, however, the microscopic changes in the brain has been reported to occurring long before the first signs of losing memory [22]. Recently, biomarkers derived from cerebrospinal fluid (CSF) and peripheral blood have been developed for the purpose of early AD symptom detection. Among which, CSF-based biomarkers have been designed for AD detection dependent on the alteration of neuron pathological lesions, including total tau protein (T-tau, reflecting the intensity of neuro axonal degeneration), phosphorylated tau (P-tau, correlating with tangle pathology) and the ratio of Aβ42/40 (correlating inversely with the plaque pathology) as previously reported [23,24].

Although genetic alterations are rare in AD, genetic biomarkers for AD have also been investigated in which mutations of *PSEN1*, *PSEN2* and *APP* have been found to be responsible for a majority of familial early-onset AD cases (1–2% of total AD) [25], and were further validated by the generation of mouse models based on these mutations which lead to the development of AD-like symptoms [26]. Moreover, *APOE ε4* has been characterized as an important genetic risk factor for sporadic AD (98% of total AD), although its alteration is neither necessary nor sufficient for AD pathogenesis [27]. More recently, peripheral plasma proteins have been identified as being associated with AD [28], and blood profile biomarkers derived from lipidomic approaches are may be relevant to the levels of AD [29], in which ten lipid metabolites from plasma could distinguish with 90% accuracy between people remaining cognitively healthy from those appearing cognitively impaired [29].

1.4. Mouse models for Alzheimer's disease

Due to the current dilemma in elucidating pathophysiology and therapeutic strategies of AD, more robust animal models are therefore urgently needed. Mouse models, which feature highly genetic kinship with the human genome, have been widely regarded as a suitable tool for AD researches, similar to their role in other disorders, including cancers (Table 1) [30,31].

Since Games and colleagues firstly succeeded in constructing AD-transgenic mice [32], multiple generations of AD rodents have been developed on basis of pathological hypotheses and mutation sites, which are often produced using knock-in techniques. As a key hallmark during AD pathogenesis, overloaded amyloid plaques are induced by hyperactivity of *AβPP* gene [25], thus the first generation of AD engineered mice were characterized by activating mutations on certain AβPP sites. Interestingly, these engineered mice displayed aberrant amyloid accumulation at 6 months of age and rapidly suffered from learning and memory impairment [33]. After the immunotherapeutic contribution by those first generation products, more transgenic mice have also been designed and produced, mainly concentrating on *Presenilin* (*PSEN1*) mutagenesis [34]. PSEN1 is responsible for the catalytic