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Review

The amyloid precursor protein (APP) processing as a biological link between Alzheimer's disease and cancer

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ABSTRACT

Aging is a risk factor for several illnesses, such as Alzheimer's Disease and various cancers. However, an inverse correlation between malignancies and Alzheimer's Disease has been suggested. This review addressed the potential role of non-amyloidogenic and amyloidogenic pathways of amyloid precursor protein processing as a relevant biochemical mechanism to clarify this association. Amyloidogenic and non-amyloidogenic pathways have been related to Alzheimer's Disease and certain malignancies, respectively. Several known molecules involved in APP processing, including its regulation and final products, were summarized. Among them some candidate mechanisms emerged, such as extracellular-regulated kinase (Erk) and protein kinase C (PKC). Therefore, the imbalance of APP processing may be involved with the negative correlation between cancer and Alzheimer Disease.

1. Introduction

Aging is a complex process that has been widely recognized as a risk factor for several diseases, such as cognitive impairment and various malignancies (Harman, 1991; Balducci and Ershler, 2005; Bishop et al., 2010). Millions of people around the world are currently affected by dementia (Bos et al., 2018) or cancer (Paltrinieri et al., 2018), representing a growing burden for public health systems, which makes this topic relevant. Cases of Alzheimer's disease (AD) double every 5 years after age 65 (von Strauss et al., 1999; Corrada et al., 2008) and almost 50% of new cancer cases are diagnosed in patients aged 65 years and older (Torre et al., 2015).

Recently, age-related diseases have been the focus of several lines of investigation, and cancer and AD are among the most studied. Epidemiological studies have showed that AD and cancer incidence and prevalence may be inversely related. In accordance, an interesting review highlighted the inverse relationship of several cellular pathways and molecular mechanisms in Alzheimer's disease and Cancer, suggesting that factors related to growth and proliferation are reduced in Alzheimer's disease and raised in cancer, such as neurotrophins and growth factors (Shafi, 2016). The roles of specific signaling molecules, such as Pin-1 enzyme (Driver and Lu, 2010), leptin and adiponectin (Nixon, 2017), have been reviewed as well.

Here we aimed to review the epidemiological data and the involvement of amyloid precursor protein (APP) cleavage pathways, including the final products and regulation systems, related to cell proliferation or survival/death, as divergent/convergent molecular mechanism of cancer and AD.

2. Epidemiological indication

An inverse relationship between neurodegenerative diseases and cancer incidence has been suggested since the fifties. Doshay (1952) demonstrated an inverse correlation between cancer and Parkinson's disease. In agreement, autopsy studies indicated that patients with confirmed AD diagnosis were less likely to have cancer (Corsellis, 1962; Tirumalasetti et al., 1991). Taken together, the data collected by those authors instigated further research to establish the biological basis connecting neurodegenerative diseases and cancer.

The link between AD and cancer has been investigated and an extensive amount of cohort and case-control studies have been published on this subject (Roe et al., 2005, 2010; Driver et al., 2012; Musicco

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Table 1
Epidemiological data on the relationship between Alzheimer Disease (AD) and cancer.*.

Author/Year	Population	Design	Controlled	Risk investigated	Findings
ROE, CM et al. 2005	Individuals with clinical diagnosis of dementia of the Alzheimer type (DAT), followed since April 1992 by the Washington University Alzheimer's Disease Center and neurologically healthy participants were included.	Prospective historical cohort.	No.	AD →Cancer Cancer → AD	Patients diagnosed with DAT were less likely to have cancer; however, no statistical evidence for fewer rates of DAT in patients with cancers was found.
ROE, CM et al. 2010	People aged 65 or older from four north-american communities. The data were obtained from the Cardiovascular Health Study (CHS).	Prospective historical cohort.	No.	AD → Cancer Cancer → AD	In white older adults, prevalent Alzheimer disease (AD) was longitudinally associated with a reduced risk of cancer, and a history of cancer was associated with a reduced risk of AD.
REALMUTO, S et al. 2012	Italian patients with probable AD recruited from the researchers departments between January 2006 and July 2010.	Case-control study.	Yes (each AD case was matched to two neurologically health individuals randomly selected from the municipality).	Cancer →AD AD →Cancer	Inverse association between AD and cancer when cancer precedes AD, but not *vice-versa*
OU, SM et al. 2012	Taiwan patients diagnosed with AD between 1997 and 2006.	Retrospective cohort.	No.	AD →Cancer	Decreased incidence of cancers in AD patients when compared to the general population.
DRIVER, JA et al. 2012	For the cohort study, participants from the original cohort of the Framingham Study (US) aged 65 or more and free of dementia were followed up for 10 years. The case-control population was composed both by members of the original cohort and from its offspring.	Prospective cohort and case-control study.	Yes (each dementia case was matched to three individuals with the same age and sex who were free of dementia by the time of case diagnosis).	Cancer →AD AD →Cancer	Patients who had cancers were less likely to develop AD, as well as patients with diagnosed AD had lower rates of incident cancer.
WHITE, RS et al. 2013	Noninstitutionalized adults aged 70 or older from New York without psychiatric symptoms or signs of dementia	Cohort	No	Non-melanoma skin cancer (NMSC) → AD	Individuals older than 70 years with NMSC have a significantly reduced risk of developing AD compared with individuals without NMSC.
MUSICCO, M. et al 2013	Northern Italy residents with 60 years or more, diagnosed with cancer or AD dementia for the first time from January 1, 2004 to December 31, 2009.	Prospective and retrospective historical cohort.	No	AD → Cancer Cancer → AD	Reduced occurrence of cancers in patients with AD dementia and of AD dementia in persons with cancer.
ROMERO, JP. et al 2014.	Residents from Central Spain aged 65 or older. Data were obtained from the Neurological Diseases in Central Spain (NEDICES) study	Cohort.	No	AD → Cancer	AD patients had reduced risk of mortality from malignant neoplasm.
FREEDMAN, D.M. et al 2016	For the case-control study of risk of cancer in patients with a previous history of AD, cancer cases with at least 66 years and less than 85 years were selected. For the cohort study of AD risk in cancer survivors, a population with the same characteristics was selected.	Case-control study and prospective cohort.	Both for the case-control study and for the cohort, a control population matched by sex and age was selected.	AD → Cancer Cancer → AD	Patients from the case-control study showed reduced risk for developing cancer after AD; however, they also showed reduced risk for cancer after automobile accident, indicating a probable bias. In the cohort study, there was reduced risk for AD among cancer survivors.

*Arrows indicate if the study was on the chances for patients with cancer to develop AD (Cancer → Alzheimer disease) and the other way around (Alzheimer disease → cancer).

et al., 2013; Ou et al., 2013; Romero et al., 2014; Realmuto et al., 2012; White et al., 2013; Freedman et al., 2016 – summarized on Table 1), all of them showing that AD and cancer are inversely related. Although these studies are heterogeneous and have intrinsic limitations to their designs, it is important to note that they bring similar findings and conclusions.

In addition, a systematic review (Driver, 2014) and three meta-analysis (Catalá-López et al., 2014; Ma et al., 2014; Zhang et al., 2015) have summarized the main findings from observational studies. These studies were carefully performed and concluded that cancer and AD are linked. The pooled size effect for the risk of AD patients to have cancer ranged from 0.32 (95% CI: 0.22 - 0.46); 0.59 (95% CI: 0.42-0.82) and 0.59 (95% CI: 0.41-0.85) (Catalá-López et al., 2014; Zhang et al., 2015; Ma et al., 2014, respectively). Regarding the risk for cancer patients to develop AD, a pooled size effect was estimated to be 0.63 (95% CI: 0.56 – 0.72) and 0.62 (95% CI: 0.53 – 0.74) (Ma et al., 2014; Zhang et al., 2015, respectively).

Ma and colleagues (2014) observed the association between specific cancer-sites, such as breast, lung, colorectal and skin cancer, and AD. They reported that AD patients only have lung cancer risk reduction. Nevertheless, this meta-analysis inclusion criteria led to only very large and unspecific studies being included, excluding some works focused on the relationship between AD and specific-site cancers finding an inverse association, such as White and colleagues (2013).

Therefore, it is possible to conclude that further epidemiological research is required for better knowledge about the relationship between specific-site cancer and AD; in spite of that, the findings here summarized provided a comprehensive understanding of the observational evidence for a relation between cancer and AD, leading to the question of which biological basis may be underlying this process.

3. APP processing

APP is a transmembrane protein composed of a large ectodomain, an intramembranous portion and a short intracellular tail. It belongs to an evolutionary conserved family, represented in mammals by APP itself and APP-like proteins (APLPs) 1 and 2 (Weingarten et al., 2017).

The physiological roles of APP have been object of extensive research. Since the 1990s, *in vitro* experiments have shown that APP ectodomain could interact with extracellular matrix components (Clarris et al., 1997; Beher et al., 1996), suggesting its role as an adhesion protein. Later work demonstrated it also has pre-synaptic specialization properties (Wang et al., 2009). In addition, APP acts as a neurotrophic and a synapto-trophic factor (Hérard et al., 2006). Knockdown models resulted in forebrain reduction and corpus callosum agenesis (Zheng et al., 1995; Magara et al., 1999), as well as circadian rhythm impairment and grip strength loss (Zheng et. al, 1995). In spite of this, there are no major phenotype features for APP loss in knockdown models (Magara et al., 1999), probably due to overlapping functions with APLP1 and 2.

APP processing may be canonical and non-canonical; for the purpose of this review, we will focus on the first one (non-canonical processing was reviewed by Andrew et. al, 2016). The so-called canonical secretases are α-secretase, β-secretase and γ-secretase.

β-secretase and γ-secretase are related to the amyloidogenic pathway. There are two β-site APP cleaving enzymes, BACE1 and BACE2. On the other hand, γ -secretase is a complex constituted by presenilin (PS) 1 or 2, nicastrin (Nct), presenilin enhancer 2 (Pen2) and anterior pharynx defective 1 (Aph-1). β-amyloid peptide is produced by sequential actions of β-secretase and γ-secretase. Also, β-secretase activity results in sAPPβ, a peptide involved in synaptic pruning during neuronal development (Nikolaev et al., 2009).

α-secretase activity is mainly performed by the disintegrin and metalloproteinase domain protein (ADAM) family, specially by ADAM 9, 10, 17 and 19 (Asai et al., 2003; Tanabe et al., 2007). There are two main sites for α-secretase activity: the plasma membrane, where there is constitutive activity (de Strooper and Annaert, 2000) and the Golgi apparatus, where its activity is inducible. When APP is cleaved by α-secretase, a product called sAPPα is generated. This product promotes the proliferation of neural progenitors (Caillé et al., 2004; Ohsawa et al., 1999), neuroprotection (Furukawa et al., 1996) and synaptogenesis (Mucke et al., 1994; Bell et al., 2008); also, there is strong evidence that sAPPα is an epithelial growth factor (Hoffmann et al., 2000). However, it is important to note that this family acts over a number of relevant substrates, such as TGFα, TNFα and L-selectin (Le Gall et al., 2009). In addition, a peptide called P3 can be formed when γ-secretase processes the α-secretase product. This pathway is called the non-amyloidogenic. Furthermore, γ-secretase cleavage of APP always results in the amyloid precursor protein intracellular domain (AICD) formation, a molecule which is thought to be a transcription factor (Muller and Zheng, 2012).

4. APP involvement in Alzheimer's disease

APP is widely known as the protein which originates β-amyloid, the component of amyloid plaques, which is thought to be the main pathological feature of AD since its first description was made by Alois Alzheimer. However, it has already been established that these structures do not correlate with the clinical severity of dementia in AD patients (Giannakopoulos et al., 2003; Ingelsson et al., 2004). Therefore, there is recent research concerning another possible mechanism for β-amyloid mediated lesions, the β-amyloid oligomers (Koffie et al., 2009).

β-amyloid peptide is generated by β-secretase and gamma-secretase activities, as described above; when released by cells it aggregates, composing β-amyloid oligomers. These oligomers act as potent neurotoxins (Lambert et al., 1998), targeting specific neurons, such as those present in hippocampal cultures (Chromy et al., 2003). The main regions affected by β-amyloid oligomers are the synapses (Lacor et al, 2004). Considering that they can inhibit long term potentiation (Walsh et al, 2002), a crucial process for memory formation, and their preferential activity over hippocampal neurons and synapses - which are also indispensable for this process - β-amyloid oligomers hypothesis offer a very plausible and sophisticated mechanism for AD dementia (reviewed in Viola et al, 2015).

Several compounds have been described as modulators of amyloidogenic pathway. Glutamatergic NMDA receptor, for example, plays a dual role: when activated under physiological conditions, it induces an increased secretion of sAPPα (Hoey et al., 2009); however, when activation reaches the status of excitotoxicity, the NMDA activity changes and it becomes an inducer of β-amyloid production, with lower α-secretase activity (Lesné et al., 2005). This finding is a possible explanation for the mechanisms by which acute neuronal lesions, which induce harmful NMDA activation (Choi, 1995), can lead to increased AD risk.

Recently, the impact of Advanced Glycation End-products (AGEs) on this molecular machinery has been investigated. Onyango and colleagues (2005) reported that β-amyloid peptide could interact with AGEs receptor (RAGE) and that this interaction induced apoptosis. In addition, AGEs *per se* are capable of inducing APP and β-amyloid expression *in vitro* (Ko et a., 2010, 2015). Clearly, AGEs can have an important role in AD deserving of some consideration, since western diets are closely linked to increased AGEs generation (West et al., 2014).

An important intracellular regulator of APP processing is the extracellular-regulated kinases (Erk) 1/2 mediated pathway. The activation of this cascade is related to inhibition of β-amyloid induced apoptosis (Watson and Fan, 2005) and to reduced gamma-secretase activity (Kim et al., 2006). Interestingly, gamma-secretase activity is inversely related to Erk concentration in a concentration-dependent manner and increased when Erk 1/2 were inhibited by a siRNA (Kim et al., 2006). Other intracellular mechanisms, such as the kinases c-Jun N-terminal kinases (JNK), mitogen-activated protein kinase (MAPK)

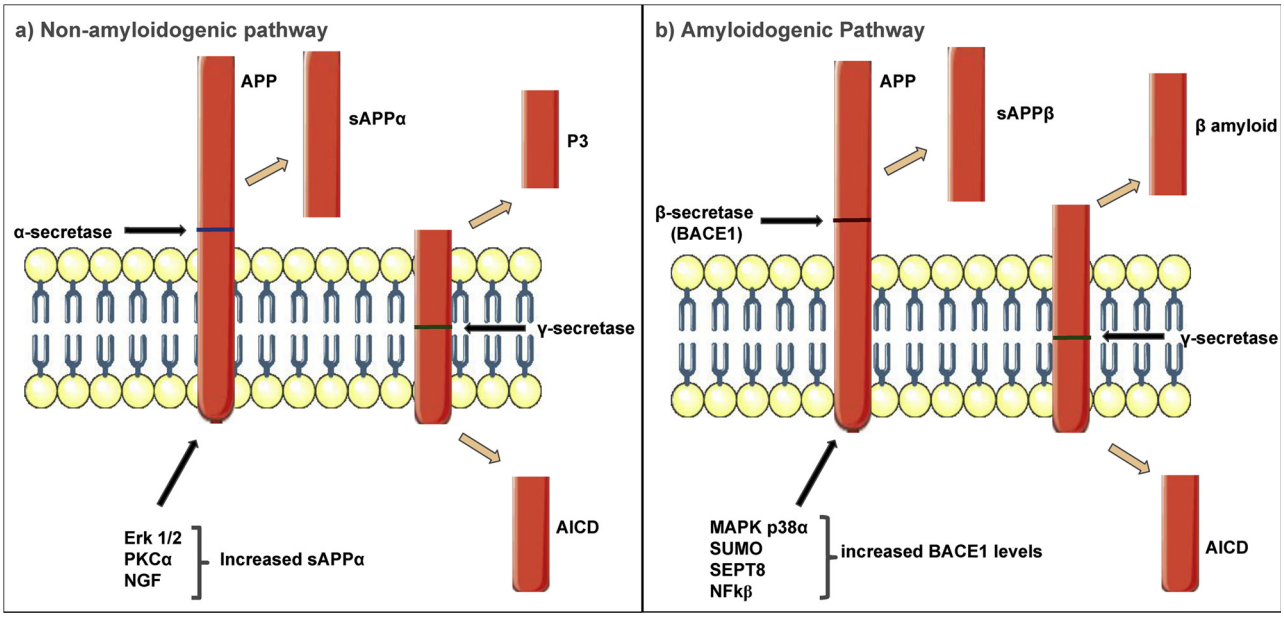

Fig. 1. APP cleavage regulatory mechanisms act mainly on α- and β-secretase activities. Some of them are summarized here. a) Non-amyloidogenic APP cleavage in cancer is stimulated by Erk 1/2 and PKCα activation; other mechanisms have not been investigated on this pathology, but NGF is also known as capable of increasing this process. b) Amyloidogenic pathway regulation occurs mainly at β-secretase activity. All molecules listed have been investigated in Alzheimer disease.

p38α and protein kinase C (PKC) ε are involved in β-amyloid generation as well. MAPK p38α inhibits BACE1 degradation (Schnöder et al, 2016; Fig. 1) and PKCε increases its expression (Du et al., 2018), while JNK directly induces β-amyloid formation (Colombo et al., 2009).

In addition, the involvement of nuclear factor kappa-β (NF-kβ) signaling in AD pathogenesis is noteworthy as it is a key factor in inflammation, oxidative stress and apoptosis and a major regulator of gene expression, which induces BACE1 transcription and increased β-secretase activity (Chen et al., 2012) - Fig. 1. Interestingly, β-amyloid induces NF-kβ activation, leading to cell death (Kuner et al., 1998). Therefore, NF-kβ has a dual role, mediating β-amyloid-induced apoptosis and augmenting β-amyloid generation. Curiously, even though molecules classically related to inflammation (such as NFkβ) are related to AD (Chen, 2012), an *in vitro* study of cells exposed to different cytokines (Il1β, Il6, TGFβ) showed no modification on BACE1 transcription (Satoh and Kuroda, 2000).

Cholesterol is another factor involved in AD. Since the 90's there have been investigations on this connection, leading to the current knowledge that the allele 4 of the apolipoprotein-E (ApoE) is a risk factor for the condition (Urano et al., 2005) and that cholesterol is required for β-amyloid formation, since depleting cells from cholesterol reduced β-secretase activity and caused no changes in α-secretase activity, indicating that β-amyloid reduced production is due to impaired β-secretase function (Simons et al., 1998). This influence of cholesterol on β-amyloid production was observed by another study conducted by Nelson and Alkon (2005) demonstrating that both β-amyloid and APP can oxidize cholesterol to form 7β-hydroxycholesterol, a toxic metabolite and an inhibitor of α-secretase activity. In addition, there is evidence cholesterol plays a role as an enhancer of β-amyloid-induced toxicity, since an experiment conducted by Ferrera et al (2008) showed that cells which had previously incorporated cholesterol, when exposed to β-amyloid, had decreased cell viability. This effect was mediated by reactive oxygen species (ROS) production and attenuated by catalase (Ferrera et al., 2008).

In addition, APP metabolism can be influenced by the membrane lipid composition. Sphingolipids accumulation induces APP degradation and increases γ-secretase activity, leading to augmented β-amyloid production (Tamboli et al., 2011) and its depletion induces increased sAPPα secretion (Sawamura et al., 2004). Also, a glycosphingolipid, specifically GM1 ganglioside, promotes β-amyloid production and decreases sAPPα secretion (Zha et al., 2004) and phosphoglycerides, the main component of plasma membrane, might be involved in BACE1 activity modulation, as suggested by Kalvodova et al. (2005). The role of membrane lipids on APP processing and AD was reviewed elsewhere (Walter and Echten-Deckert, 2013).

Different molecules have been implied in APP processing regulation in amyloidogenic pathway. Some non-coding RNAs, as the circular RNA ciRS-7 (Shi et al., 2017), the miRNAs miR-98-5p (Li et al., 2016), miR-124 (Zhang et al., 2017) and miR-195 (Zhu et al., 2012), regulate Aβ production through different mechanisms involving the APP itself or BACE1 enzyme. Other proteins, as BIN1, SUMO1 and SEPT8 (Fig. 1), are involved in this processing due to their effects on BACE1 intracellular trafficking (Miyagawa et al., 2016; Yum, 2013; Kurkinen, 2016).

Taken together, these data showed interconnected pathways involved in APP processing and their imbalance can contribute to development of AD. All molecules listed in this section and in the next are summarized in Table 2.

5. APP involvement in cancer

Several studies have reported that different products generated during the processing of APP, specifically sAPPα (Meng et al., 2001; Hansel et al., 2003; Ko et al., 2004) and AICD (Zhang et al., 2007; Krause et al., 2008), may have important roles in carcinogenesis.

A product of non-amyloidogenic cleavage of APP, sAPPα, is a known growth factor for epithelial tissue (Hoffmann et al., 2000). In the last twenty years, this has been implied in different steps of cancer progression in a variety of carcinomas, such as pancreatic (Hansel et al., 2003), oral squamous cells (Ko et al., 2004), colon (Meng et al., 2001), thyroid (Popp et al., 1996; Pietrzik et al., 1998) and breast (Lim et al., 2014), acting over cell proliferation and motility. Several research groups have investigated how sAPPα is generated and which regulatory pathways are involved in its generation.

One of the most intriguing findings in this area concerns the relationship between sAPPα and other growth factors, such as epidermal growth factor (EGF). Canet-Aviles and colleagues (2002) showed that sAPPα secretion is increased by EGF, an effect mediated by the Erk 1/2

Table 2
Molecules associated to APP processing and products in cancer (non-amyloidogenic pathway) and/or Alzheimer Disease (amyloidogenic pathway).

Molecule	Proposed mechanism on APP processing	Type of experiment	Alzheimer Disease	Cancer	References
Erk 1/2	EGF increases sAPPα secretion through Erk 1/2 pathway; the activation of this cascade has been related to decreased β-amyloid production.	*In vitro*	↓	↑	Watson and Fan, 2005; Kim et al., 2006; Canet-Aviles et al., 2002; Tang et al., 2010
RNA ciRS-7	ciRS-7 reduces APP and BACE1 cellular levels, promoting their degradation by lysosomal and proteasomal mechanisms.	*In vitro*	↓	↑*	Shi et al., 2017; Pan et al., 2018
NGF	NGF increases ADAM 10, a major α-secretase, expression, inducing non-amyloidogenic cleavage of APP and, therefore, reduced β-amyloid levels.	*In vitro*	↓	↑*	Xie et al., 2015; Bradshaw et al., 2015
FGF2	FGF2 reduces BACE1 expression, inducing impaired β-amyloid production.	*In vitro*	↓	↑*	Xie et al., 2015; Reiland et al., 2006
miR-98-5p	MiR-98-5p downregulation reduces β-amyloid formation through regulation of SNX6 expression.	*In vitro*	↑	↓*	Li et al., 2016; Wu et al., 2018
JNK	JNK phosphorylates APP in a way that lead to β-amyloid formation and inhibits its degradation.	*In vitro*	↑	↑* and ↓*	Colombo et al., 2009; Bubici and Papa, 2014
MAPK p38α	MAPK p38α inhibits BACE1 degradation, thus promoting increased levels of this enzyme and increased activity, leading to increased β-amyloid production.	*In vitro* and *in vivo*	↑	↑* and ↓*	Schnöder et al, 2016; Wagner and Nebreda, 2009
miR-195	miR-195 negatively regulates BACE1 translation, which induces decreased β-amyloid production.	*In vitro*	↓	↓*	Zhu et al., 2012; Itesako et al., 2014
BIN1	BIN1 promotes BACE1 degradation, thus reducing β-amyloid levels; its depletion is related to increased β-amyloid production.	*In vitro*	↓	↓*	Miyagawa et al., 2016; Wang et al., 2017
SUMO	SUMO interacts with BACE1 and induces its accumulation, thus leading to increased β-amyloid formation.	*In vitro* and *in vivo*	↑	↑*	Yun et al., 2013; Han et al., 2018
SEPT8	SEPT8 increased expression of stabilized BACE1, which in turn enhanced its activity and led to increased β-amyloid expression.	*In vitro*	↑	↑*	Kurkinen et al., 2016; Liu et al., 2010
NFkβ	NFkβ expression results in increased BACE1 transcription and enhances β-secretase activity, as well as β-amyloid production.	*In vitro*	↑	↑*	Chen et al., 2012; Tilborghs et al., 2017
PKC	PKC activation induces increased sAPPα generation, but not increased APP expression. This effect is mediated by particular PKC isoforms, as PKCα. Others isoforms, as PKCε, correlate with β-amyloid production.	*In vitro*	↑	↑	Racchi et al., 2003; Krause et al., 2008; Du et al., 2018
NMDA receptor	Under physiological conditions, it induces sAPPα secretion; on excitotoxicity conditions, however, it induces β-amyloid production.	*In vitro*	↑	↑*	Rzeski et al., 2001; Lesneéet al, 2005; Hoey et al., 2009
AGEs	AGEs were shown as capable of inducing β-amyloid production.	*In vitro*	↑	↑*	Ko et al., 2010, 2015; Sharaf et al., 2015
RAGE	β-amyloid interacts with RAGE and triggers apoptosis cascade.	*In vitro*	↑	↑*	Onyango et al., 2005; Sparvero et al., 2009
Cholesterol	Cholesterol-depleted cells showed reduced β-secretase activity and β-amyloid formation. Also, cholesterol increases β-amyloid toxicity and, when metabolized, may decrease α-secretase activity.	*In vitro*	↑	?	Simons et al., 1998; Ferrera et al., 2008; Nelson and Alkon, 2005
Sphingolipids	Sphingolipids accumulation is related to decreased APP degradation, increased γ-secretase activity and increased β-amyloid production	*In vitro*	↑	↓*	Tamboli et al., 2011; Sawamura et al., 2004.
GM1 ganglioside	GM1 increases β-amyloid production through its effects on gamma-secretase; also, it reduces sAPPα secretion.	*In vitro*	↑	?	Zha et al., 2004

↑ indicates that the referred molecule/pathway is positively related to APP processing in the disease, i.e., upregulated.
↓indicates that the referred molecule/pathway is negatively related to APP processing in the disease, i.e., downregulated.
*indicates that there are studies with this molecule/pathway in the disease, but they are not directly related to APP processing.
? indicates that there are no studies to our knowledge studying if the molecule/pathway affects APP processing in the disease.
AD: Alzheimer disease; APP: amyloid precursor protein.

cascade (Fig. 1). These results were reinforced by those from Tang et al. (2010), who demonstrated that stimulation of epidermal growth factor receptor (EGFR) by tumoral growth factor α (TGFα) in a nasopharyngeal carcinoma model induces sAPPα secretion. Also, increased sAPPα secretion was related to cell proliferation and motility, which were effectively reduced by anti-sAPPα antibody.

Another intracellular signaling cascade implied in sAPPα secretion is the one mediated by PKC. The activation of this pathway is related to sAPPα secretion, but not to increased APP expression (Racchi et al., 2003; Krause et al., 2008). Interestingly, it was elegantly evidenced that different PKC isoforms act specifically at different cleavage sites, namely, plasma membrane for PKCα and Golgi network for PKCε (Lanni et al., 2004). Another very important intracellular cascade, the PI3K/Akt pathway, is involved in sAPPα secretion and is capable of inducing APP expression (Krause et al., 2008). This study displays solid evidence that sAPPα has a role, mediated by these pathways, in a thyroid cancer model (Krause et al., 2008).

Another product which arises from APP cleavage and has been related to cancer is AICD. This peptide is the intracellular portion of APP, which is released after protein processing and can be generated for both amyloidogenic and non-amyloidogenic pathways. AICD production is analogous to that of NICD, the intracellular peptide generated by Notch cleavage, which is linked to cancer progression in oral squamous cells carcinoma (Gokulan and Halagowder, 2014) and hepatocellular carcinoma (Luo et al., 2016), among others. Since both APP and Notch are processed by γ-secretase, which is itself related to cancer (Li et al., 2007; Taniguchi et al., 2003), it has been flagged as a possible mechanism implied in carcinogenesis.

AICD may act as a transcriptional factor, connecting to the adaptor protein Fe65 and thus translocating to the nucleus, where the complex AICD/Fe65 binds to Tip60, a histone acetyltransferase (Muller and Zheng, 2012). This mechanism is involved in EGFR expression and transcription, since the mouse with lowered AICD formation showed increased EGFR protein and mRNA (Zhang et al., 2007); therefore, it is possible that this peptide has an important function in suppressing EGFR expression.

Interestingly, it has been described that APP depletion induces cell cycle arrest in breast cancer (Lim et al., 2014). In accordance, an interesting finding was reported by Sobol et al. (2015): the authors demonstrated that APP depletion induces G0 arrest, decreasing proliferation and inducing necrosis in non-small cells lung cancer, a type of malignant neoplasia. In addition to APP protein role in cancer cells cycle, they also showed that AICD, when transfected into these cells, can induce increased proliferation and reduce necrosis. Consequently, it is possible to suggest that intracellular processing of APP is involved in the cell division process.

The studies here summarized provide substantial evidence indicating the role of several pathways and molecules involved on APP processing and their relationship with cancer development and progression. APP cleavage through the non-amyloidogenic pathway is related to a series of malignancies. A report from Siegenthaler et al., 2016 showed that γ-secretase has a negative feedback on α-secretase and that, when γ-secretase activity is impaired, α-secretase becomes more active. This is a possible mechanism linking the two main forms through which APP is implied in cancer, since that impaired γ-secretase activity would be followed by impaired AICD production, which is implied in carcinogenesis, and by increased sAPPα production. This possibility is reinforced by data linking reduced or impaired γ-secretase activity to cancer (Li et al., 2007; Zhang et al., 2007).

6. Discussion and conclusions

Our work brings a potential molecular candidate, APP processing pathways, to explain the epidemiological inverse association between Alzheimer's disease and cancer.

The epidemiological evidence on the association between cancer and AD is compelling; even the study conducted by Freedman and colleagues (2016), which concluded that the reduced risk among patients with AD of developing cancer resulted from ascertainment bias, found that cancer survivors are at reduced risk to develop AD. In spite of the limitations intrinsic to observational studies, these evidences urge researchers to explore any possible links - if not to clearly establish a perfect relation between these diseases, at least to apply the knowledge acquired in research on one of them to the other.

We have reviewed and summarized extensive data on APP processing, a biological event related to both AD and cancer. The findings presented in this review clearly indicate that APP processing is dysregulated in both conditions and that this dysregulation occurs in opposite ways - that is, AD occurs with increased amyloidogenic processing of APP and cancer with increased non-amyloidogenic processing.

Several molecules are likely involved in APP processing dysregulation, from nucleic acids, like miR-195 (Zhu et al., 2012) to circulating compounds like cholesterol (Simons et al., 1998), modulating the fate of APP. Most of them act on α-secretase and β-secretase, altering their expression, function and degradation. This finding is not a trivial one, since there is evidence that β-secretase competes with α-secretase at the Golgi network for intracellular cleavage of APP (Skovronsky et al., 2001).

Interestingly, most of APP processing regulations have been studied in the context of AD physiopathology. In fact, there are few studies analyzing how the increased sAPPα content in cancer is related to APP processing. Therefore, this review may highlight interesting topics to investigate in cancer biology, such as APP processing pathways.

From the molecules summarized here, two were better studied in APP processing in both diseases: Erk 1/2 and PKC. Erk 1/2, when activated by EGF in cancer cells, increases sAPPα secretion and there is an inverse correlation between its activation and β-amyloid production, e.g., increased Erk 1/2 activation is related to non-amyloidogenic pathway. Interestingly, a bioinformatics study by Liu et al. (2013) demonstrated that genes related to Erk-mediated pathways were upregulated in patients with glioblastoma multiform, a central nervous system cancer, and downregulated in AD patients, strongly suggesting that this pathway plays opposite roles in malignancies and neurodegeneration. When it comes to PKC, however, the mechanism is more sophisticated. Increased PKC activation may induce both amyloidogenic and non-amyloidogenic cleavage; however, the isoforms involved in each pathway are different - ε isoform for the amyloidogenic and α for the non-amyloidogenic. These examples show that APP processing may be able to produce controlling factors in cancer and AD, and that mechanisms already described involved in AD physiopathology may provide exciting insights in cancer research.

The present review shows consistent evidence for the involvement of APP processing pathways on the inverse epidemiological correlation between cancer and AD, suggesting that an imbalance in APP processing machinery can be related to cell proliferation or cell damage, respectively, in cancer and AD.

Conflict of interest

The authors report no conflict of interest.

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