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Review

Genetic and environmental factors in cancer and neurodegenerative diseases

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Abstract

The aim of this review is to summarise the recent findings in the fields of carcinogenesis and neurodegenerative diseases, the both disorders are characterised by the contribution of different factors including the inheritance of mutated genes, and the exposure to endogenous or exogenous agents during the life. We first analysed the causative genes until now discovered in both processes, then we focused our attention on the role of environmental exposure, susceptibility factors, oxidative stress, apoptosis and aging to the development of such disorders. The genotype at a particular locus may account for an inter-individual susceptibility that can both increase or decrease the risk to develop the pathology especially after the exposure to environmental agents. The mechanism of apoptosis, that is an excellent strategy in order to eliminate damaged cells, seems to be lost during carcinogenesis, while it seems to be involved in the neuronal death in a lot of neurodegenerative disorders. Oxidative stress can both lead to DNA mutations or to the formation of damaged proteins, so being an important risk factor for the initiation and the progression of a disease: in fact it may be one of the causes or can arise as a consequence of a damage caused by other factors increasing then the first damage. It is well established that carcinogenesis is a multi-step process caused by series of successive mutations occurring into a cell and conferring to this cell a growth advantage, so that age is the largest risk factor for cancer in humans. Pathophysiology of neurodegenerative diseases is complex and likely involves multiple overlapping and perhaps redundant pathways of neuronal damage, characterised by the generation of anomalous proteins, often due to mutations in the corresponding gene, and by their subsequent accumulation into or outside specific areas of the brain.

Keywords: Carcinogenesis; Neurodegeneration; Causative genes; Susceptibility factors; Environmental factors

1. Introduction

An increasingly important health problem in the world is the rising incidence of age-related neurodegenerative diseases. Ironically, this is partly due to the increasing longevity of the populations, which results from better living and working conditions. Even if the aetiology of neurodegeneration is not completely understood, the irregular inheritance pattern found in many neurodegenerative diseases is likely to be the result from the interaction of genetic and environmental factors. Neurodegenerative diseases, including many types of dementia, fall into many groups, ranging from diseases with a clear genetic aetiology (Huntington's disease) to diseases which are believed to be the result of chronic environmental exposure (Guam Parkinson-dementia syndrome), including also inheritable as well as transmissible prion diseases (Kuru, Creutzfeld–Jacob disease), and those whose aetiology is unknown but have a genetic component in at least

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some cases (Parkinson's disease, Alzheimer's disease) [1]. The role of environmental and occupational exposures to neurotoxicants in the pathogenesis of neurodegenerative diseases has not been fully elucidated, but many chemicals can affect the nervous system and some of them require metabolic activation to induce their toxic effects, so that genetic polymorphisms that encode for defective forms of the detoxifying enzymes can further increase the risk of effects from exposure to neurotoxicants [2]. To improve human health and the quality of life, it will be essential to obtain a better understanding of the key biochemical mechanisms and risk factors underlying neurodegeneration. Cancer is now considered a progressive disease characterised by the accumulation of defects in different genes. Cancer-related genes are classified mainly as either oncogenes or tumor suppressor genes. Mutated proto-oncogenes (i.e. oncogenes) contribute to tumor development by enhancing cell growth. Tumor suppressor genes usually inhibit cell growth and transformation, and their loss of function contributes to tumor development. In recent years other types of genes have been found that, if inactivated by mutations, can increase carcinogenesis, for example damaged DNA repair genes affect the carcinogenetic process by destroying the genetic stability of the cells, making them more prone to mutational alterations [3]. Until a few years ago, cancer predisposition was mainly attributed to the level of exposure to carcinogenic agents; at present it is clear that the long process that leads from exposure to a carcinogenic agent to cancer, sometimes more than 20 years later, is subjected to individual modulations: while rare alterations of oncogenes or tumor suppressor genes dramatically raise cancer risk for the single affected subjects, more common polymorphisms in genes encoding for metabolic enzymes are responsible for a small, but rather frequent increase of cancer risk at the population level, especially in people exposed to carcinogens [4].

Table 1
Some examples of causative genes related to cancer and neurodegenerative pathologies

Genes	Disease
(a) Cancer	
Rb	Retinoblastoma
p53	Mutated in over 50% of all tumor types
MYC	Burkitt's lymphoma
BRCA1	Breast cancer
BRCA2	Breast cancer
K-*RAS*	Several cancers (lung, colon,...)
c-*abl*	Chronic myelocytic leukaemia
Bcl-2	Follicular lymphoma
ERB-B	Astrocytomas, glioblastomas
DCC	Colon cancer
APC	Colorectal cancer
(b) Neurodegenerative pathologies	
APP	Autosomal dominant Alzheimer's disease
PS1	Autosomal dominant Alzheimer's disease
PS2	Autosomal dominant Alzheimer's disease
Tau gene	Several (frontotemporal dementia, Pick's disease,...)
PARK1	Autosomal dominant Parkinson's disease
PARK2	Autosomal recessive juvenile Parkinsonism
PARK3	Autosomal dominant Parkinson's disease
UCH-L1	Autosomal dominant Parkinson's disease
ALS-1	Autosomal dominant familial amyotrophic lateral sclerosis
ALS-2	Autosomal recessive familial amyotrophic lateral sclerosis
Huntingtin gene	Huntington's disease
Prion protein genes	Prion diseases (Creutzfeldt–Jacob disease,...)

2. Causative genes

2.1. Causative genes in carcinogenesis

Cancer genes may be involved in the cell division control or in the execution of apoptosis, may code for transcriptional regulators, may be genes involved in signal transduction pathways, may code for growth factors or growth factors receptors, may be genes whose products are important for the cellular adhesion (Table 1a). It is important to note that a function does not exclude another, for example a gene involved in the cell division cycle control may do it acting as a transcriptional regulator [3]. One of the best known tumor suppressor genes is the retinoblastoma gene (*RB*) that codes for a protein involved in the checkpoint control at the G1–S interphase of the cell cycle acting as a transcriptional activator. Loss of *RB* function shortens the cell cycle and does not allow time to correct DNA damage [5]. In response to DNA damage, p53 functions to monitor genomic integrity and to reduce the occurrence of mutations, either by inhibiting the cell from entering the cell cycle, enabling the cell to repair the DNA, or by

triggering apoptosis. Mutations in *p53* have been found in nearly all tumor types, making *p53* one of the most commonly mutated genes in human cancers [6]. Patients with ataxia-telangiectasia (AT) disorder are both significantly predisposed to cancer and hypersensitive to ionising radiations; *ATM* is the gene mutated in AT patients: it was identified on chromosome 11q22–23, through the combined effort of linkage analysis and positional cloning, by the group of Shiloh [7]; this gene was found to be mutated in AT patients from all the four complementation groups previously characterised, leading to the idea that it is probably the sole gene responsible for AT [8]. *ATM* has been strongly implicated in regulating the phosphorylation and the induction of p53 in cells exposed to ionising radiations and the lack of this pathway, due to mutations in the gene, may be one of the causes of the elevated predisposition to cancers in AT patients [9]. Other genes involved in the cell cycle control may also be cancer genes (for a review see Devereux et al. [3]). Transcriptional regulators also play a role in carcinogenesis: *MYC* is an important transcriptional regulator activated by a translocation in Burkitt's lymphoma [10]. *BRCA1* and *BRCA2*, the two genes involved in breast cancer, they both contain regions that can function in transcriptional activation when fused to the DNA-binding domain of another gene [11,12]. Proteins involved in cell cycle control, like p53, explain their function acting as trancriptional activators of several downstream genes [13]. Signal transduction genes are involved in the signal transduction pathways from the cell membrane to the nucleus in order to control the cell growth. Point mutations may lock a receptor in an active state even in the absence of the ligand: one example is that of the K-*RAS* proto-oncogene that is mutated in a lot of human cancers (for a review see Devereux et al [3]). Other genes involved in signal transduction pathways also play a role in the progression of some human cancers: for example a translocation of the proto-oncogene c-*abl* from chromosome 9 to breakpoint cluster region (bcr) on chromosome 22 forms an oncogenic tyrosine kinase that leads to chronic myelocytic leukaemia [14]. *Bcl-2* was discovered as a proto-oncogene via its association with the t(14,18) chromosomal translocation characteristic of follicular lymphoma, this gene was the first identified proto-oncogene which contributes to neoplasia not by increasing cell division, but by suppressing apoptosis and extending cell life span [15]. Growth factors and growth factor receptors genes may be responsible of a specific set of cancers, which is a reflection of the tissue specific action or expression of these genes. For example the epidermal growth factor receptor *ERB-B* gene is overexpressed in some cases of astrocytomas and glioblastomas [16,17]. *DCC*, the gene deleted in colon cancer, codes for a protein involved in the cellular adhesion, which loss may be important for metastasis, the spread of cancer from its origin to other tissues [18]. Defects in DNA repair genes destroy the genetic stability of mutated cells, leading to additional alterations that affect normal cellular growth. Three genes that cause hereditary non-polyposis colorectal cancer (HNPCC) are homologues of bacterial and yeast genes involved in the process of DNA mismatch repair. Cells with defects in mismatch repair may have a mutator phenotype that leads to alteration of certain genes, among them genes important in tumour development [19,20]. Among human diseases associated with cancer predisposition, Bloom and Werner's syndromes are due to defects in a family of DNA helicases. As reviewed by Diffley and Evan, this family of helicases appears to play an important role in both preventing and limiting DNA recombination during S phase [21]. Concluding, the carcinogenic process is characterised by the sequential mutations of proto-oncogenes and tumor suppressor genes determining the transformation of a normal cell into a neoplastic one, and in this context there are genes whose products are critical for protecting proto-oncogenes/tumor suppressor genes against mutations, which may be involved in cancer outcome. Rare individuals are affected by alterations of one allele of a tumor suppressor gene so that in some of their target organs, the number of steps required to complete the process of carcinogenesis is $(n - 1)$ instead of n. These individuals display dramatic increases of cancer susceptibility for both the associated parameters of incidence and age of incidence [4]. Colorectal cancer illustrates the multistage nature of carcinogenesis: *APC* gene on chromosome 5q21 is altered in the earliest stages of more than 80% of all familial and sporadic cases of colorectal cancer, and is responsible for the development of multiple benign polyps in the colorectum. Subsequent mutation of the proto-oncogene K-*RAS* and deletion or functional loss of *DCC* and/or *p53*, the both tumor

suppressor genes, drive the early lesions to malignancy. In late stages of colorectal cancer a variety of other genetic alterations have been identified [22].

2.2. Causative genes in neurodegeneration

Neurodegenerative diseases include a lot of different pathological conditions of specific areas of the brain: Alzheimer disease (AD) is one of the most devastating neurodegenerative disorders that affect several million patients worldwide [23]. Most case of AD are sporadic; however, epidemiological studies indicate that about 30% of AD patients have a family history of disease, and about 10% of familial disease presents as an autosomal dominant mode of transmission. Some studies identified a link between AD and mutations of the amyloid precursor protein (*APP*) gene, which maps to chromosome 21q21.2, and is causal of some early-onset inherited AD due to at least seven missense mutations found in different families: all of them are situated at or near α, β, or γ secretase sites and alter APP proteolysis. APP normal function is still unknown. Since 1995, the Presenilin 1 (*PS1*) gene has been associated with at least 60 different mutations in over 80 families causing early-onset AD. The gene maps on chromosome 14q24.3 and encodes an integral membrane protein with eight transmembrane domains. The Presenilin 2 (*PS2*) gene on chromosome 1q31–q42 encodes for an integral transmembrane protein that has overall homology with the PS1 protein amino acid sequence of 67%. In *PS1* transgenic mice and fibroblast cell cultures with the *PS1* mutations, there is an increased synthesis of $A\beta_{42}$, this form is normally produced by cells in much lower quantities than the 40-residue form ($A\beta_{40}$). The presenilins may function to influence γ-secretase activity or may in fact be γ-secretases. β- and γ-secretases are the postulated enzymes to cleave Aβ from its parent APP peptide. The *APP* and presenilin gene mutations activate β- and γ-secretases to increase Aβ synthesis and it is presumed that environmental or other non-genetic factors will also activate them in sporadic AD. Although, the specific functions of the proteins coded by the *APP* and the *PS1* and *PS2* genes are not completely known, they share a common effect of abnormally processing APP, resulting in a 50% increase in $A\beta_{40}$ or $A\beta_{42}$ peptides, which subsequently aggregate to form the neuritic plaque in the AD patient's brain (for a review see Rosenberg [23]). Another approach to the aetiology of AD takes as a starting point the abnormal accumulation of the paired helical filaments (PHF) or neurofibrillary tangles in neurons. PHF are composed predominately of hyperphosphorylated form of the protein tau. Tau is a microtubule-associated protein that binds to microtubules and promotes their assembly. Filamentous tau protein deposits are also the defining characteristic of other neurodegenerative diseases, many of which are frontotemporal dementias or movement disorders, suck as Pick's disease, progressive supranuclear palsy, and corticobasal degeneration. Six tau isoforms are produced in adult human brain by alternative mRNA splicing from a single gene. The discovery of more than 15 mutations in the tau gene in frontotemporal dementia and Parkinsonism has shown that dysfunction of tau protein causes neurodegeneration [24]. Parkinson's disease (PD) is the second most common neurodegenerative disorder after AD; evidence for the existence of a genetic component in PD is supported by epidemiological and positron emission topography (PET) studies in familial kindred and monozygotic and dizygotic twins [25]. A mutation in exon 4 of the α-synuclein gene (known as *PARK1*) causing an Ala53 → Thr substitution in the protein was found to segregate with the disease in an Italian–American kindred and three Greek kindreds [26]. Another mutation in the *PARK1* gene, leading to an Ala30 → Pro substitution, was subsequently described in a German kindred [27]. Although, *α-SYN* mutations are only a rare genetic cause in PD, α-SYN is the major fibrillar component of the Lewy bodies (LBs) and conformational abnormalities leading to aggregation and deposition of proteins are a common feature of neurodegeneration in several related disorders [25]. The detection of an Ile93 → Met mutation in the ubiquitin carboxy-terminal hydrolase L1 (*UCH-L1*) gene in a German family with autosomal dominant PD [28] leads to the idea that an impaired proteasomal degradation of abnormal proteins may underlie the pathogenesis of PD. Two further loci have been implicated in autosomal-dominant idiopathic PD. A chromosome 2p13 linkage (*PARK3*) was detected in a Danish/German family [29], and a chromosome 4p haplotype segregates with both PD and essential tremor in a North American Iowanian kindred [30]. Autosomal-recessive juvenile Parkinsonism (AR-JP)

is characterised by early-onset (<40 years) and a marked response to levodopa treatment. The genetic locus for AR-JP was identified in Japanese families, which led to identification of homozygous deletions in the Parkin gene (*PARK2*) on chromosome 6q25.2–q27 [31]. In addition to the two homozygous exon deletions first detected in four Japanese families, several other groups have reported exon deletions and mutations in the *PARK2* gene that result in protein truncation or amino acid substitution [25]. Even if the function of Parkin is still unknown, the homologies to ubiquitin suggest a role in the mediation of proteasomal degradation of proteins. Abnormalities in proteasomal degradation may cause the aberrant accumulation of proteins as is indicated by the presence of poly-ubiquitinated proteins in the LBs [31]. Amyotrophic lateral sclerosis (ALS) is a progressive and fatal disease, where neurodegeneration affects primarily, although not exclusively, motor neurons of the cerebral cortex, brain stem, and spinal cord [32].Ten percent of amyotrophic lateral sclerosis cases are of familial origin and 15–20% of such families have point mutations in the gene encoding for cytosolic copper–zinc superoxide dismutase (SOD-1) [32]; the gene maps to chromosome 21q21 (genetic nomenclature: *ALS1*). Autosomal recessive familial amyotrophic lateral sclerosis (RFALS) is rare but has been reported in settings of high consanguinity such as Tunisia. Three clinical variants of RFALS are known. The locus for RFALS type 3 maps to chromosome 2q33 (genetic nomenclature: *ALS2*), while the loci for the other forms remain still unknown [33]. Huntington's disease (HD), dentorubral pallidolysian atrophy (DRPLA), spinobulbar muscular atrophy (SBMA) and the spinocerebellar ataxia types 1–3, 6, 7, and 12 (SCA1, SCA2, SCA3, SCA6, SCA7, and SCA12) result from a CAG trinucleotide repeat expansion which is translated into a polyglutamine stretch in the respective proteins and share a dominant pattern of inheritance [34]. The *HD* gene has been mapped to chromosome 4p16.3 and the underlying mutation was identified as a CAG repeat expansion within exon 1 of the gene [35]; while in the normal population the number of CAG repeats ranges from 6 to 35, in individuals affected by HD it ranges from 40 to121, and the age of onset of HD is inversely correlated with CAG repeat length. All the genes involved in the earlier mentioned polyglutammine disorders have been mapped and for each of them the CAG repeat length ranges in a permitted interval in the normal population, while is expanded in people affected by the disease (for a review see Evert et al. [34]). Friedreich's ataxia is characterised by neurodegeneration involving the spinocerebellar pathways as well as cardiomyopathy [36]. The gene responsible for Friedreich's ataxia codes for a protein called frataxin. Frataxin deficiency is primarily due to an expansion of a GAA trinucleotide repeat situated in the first intron of the corresponding gene causing a reduction in the level of mature mRNA [36]. Creutzfeld–Jakob disease (CJD), fatal familial insomnia (FFI), and Gerstmann–Straussler–Scheinker syndrome (GSS), best known as prion diseases, are a group of neurodegenerative conditions that includes sporadic, inherited, and transmitted forms [37]. The central event in the pathogenesis of prion diseases is though to be a change in protein conformation that results in the conversion of a normal protein, identified as cellular prion protein, into an isoform that is partially resistant to proteases. Genetic factors, such as mutation and amino-acid substitutions in polymorphic sites of the prion protein gene heavily affect the phenotypic expression in prion diseases [37]. (Causative genes for neurodegenerative diseases are listed in Table 1b.)

3. Environmental factors

3.1. Environmental factors in carcinogenesis

Cancers may results from environmental exposure to exogenous agents; epidemiological data on populations indicate an association between many human cancers and lifestyle/diet, moreover detailed studies of mutational events in human cancers have provided evidence for a direct action of environmental carcinogens in the development of certain cancers (Table 2a): an excellent example is lung cancer which has been linked to tobacco smoke, making cigarette smoking one of the major causal factors for lung cancer outcome [38]. Another example is skin cancer linked to sunlight exposure in both normal individuals and individuals with xeroderma pigmentosum (XP) [39,40]. Liver cancer has been linked to human exposure to Aflatoxin [41], and many types of cancer to ionizing radiations exposure (for a review see Setlow [42]). Heterocyclic

Table 2
Some examples of environmental factors linked to cancer and neurodegenerative pathologies

Environmental factors	Diseases
(a) Cancer	
Tobacco smoke	Lung cancer
Sunlight exposure	Skin cancer
Aflatoxin	Liver cancer
Ionizing radiation	Many cancers (skin, leukaemias,...)
Heterocyclic amines	Colorectal cancer
Aromatic amines	Urinary bladder cancer
Viral infections	Several cancers (depending on the viral target)
Inflammation after ulcerative colitis	Colon cancer
Asbestos exposure	Mesothelioma
Inorganic arsenic	Lung cancer, skin cancer
Nickel, cadmium, cobalt	Lung cancer, genito-urinary cancers[a]
Vinyl chloride	Liver angiosarcoma
Fruit and vegetables consumption	Protective role against cancer outcome
Environmental factors	**Increased risk for**
(b) Neurodegenerative pathologies	
1-Methyl-4-phenyl-1,2-5,6-tetrahydropyridine (MPTP)	Parkinsonism
Pesticides (especially paraquat and similar herbicides)	Parkinson's disease[b]
Copper sulphate	Parkinson's disease[b]
Living in rural areas	Parkinson's disease[b]
Head injuries	Parkinson's disease[b]
n-Hexane	Parkinson's disease[c]
Respiratory infections	Parkinson's disease[c]
Copper, zinc and iron	Alzheimer's disease[c]
Zinc depletion	Sporadic amyotrophic lateral sclerosis[c]
Cigarette smoke	Protective role for Parkinson's disease

[a] Conflicting results.
[b] Environmental factors linked to an increased risk for PD only in some papers.
[c] Environmental factors hypothesized to be a risk factor for neuronal illness.

amines arising from the cooking of meat have been linked with an increased colorectal cancer risk [43], while the consumption of fruit and vegetables seems to give protection against cancer outcome [44]. Many carcinogenic chemicals have been identified in the workplace and, even if they usually do not affect the overall population, occupational exposure to carcinogens is a great risk factor for cancer outcome in workers exposed to them every day: one of the best known examples is urinary bladder cancer linked to occupational exposure to aromatic amines [4]; another example is angiosarcoma of the liver causally linked to vinyl chloride occupational exposure; cancers of other sites have been hypothesized to be due to vinyl chloride exposure, but these associations are not consistently supported (for a review see McLaughlin and Lipworth [45]). Also viral infections and inflammation are environmental factors playing an important role in carcinogenesis: as reviewed by Diffley and Evan [21] a group of herpesviruses implicated in cancer is able to encode for cyclins that differ from the host counterparts in being immune to the cellular inhibitors, so promoting an uncontrolled progression of the cell cycle. Examples of cancers arising from chronic inflammation include colon cancer after ulcerative colitis and mesothelioma linked to asbestos exposure [46,47]. Regarding metals epidemiological studies have identified that inorganic arsenic is causally associated with lung cancer via inhalation and skin cancer via ingestion in humans [48]. Compounds of nickel, cadmium and cobalt are well established carcinogens to humans, even if the mechanisms leading to tumor formation are still not completely understood [49]; they have been linked to an increased risk for lung cancer, and conflicting results

have been reported for cancers in other tissues [48]. Nickel(II) has been shown to diminish the removal of UV-induced cyclobutane pyrimidine dimers, and it is now clear that the inhibition of DNA repair processes represent a common mechanism in the genotoxicity of different metal compounds [49]. At present, we know that cancer is due to a series of mutational events that confer to a cell neoplastic properties; environmental agents may both initiate the cancer process and affect the succeeding steps in carcinogenesis.

3.2. Environmental factors in neurodegeneration

A lot of environmental factors have been associated, over the years, with an increased risk for PD. The most known model for PD research is the free radical injury induced by exposure to 1-methyl-4-phenyl-1,2-5,6-tetrahydropyridine (MPTP): this meperidine analogue is metabolised to 1-methyl-phenylpyridinium (MPP+) by the monoamine oxidase B in glial cells. MPP+ is subsequently selectively taken up by dopaminergic terminals and concentrated in neuronal mitochondria in the *Substantia nigra*. MPP+ binds to and inhibits complex I of the mitochondrial electron transport chain, thereby producing the same biochemical defect as detected in PD patients [2]. Paraquat is an herbicide structurally similar to MPTP, and the exposure of humans to it has been associated with an increased risk of PD [2]. From epidemiological studies, it was shown that some risk factors are associated with PD: they were living in rural area, drinking well water, exposure to pesticides and copper sulphate; while negative associations that suggest protective roles, were found for smoking and urban living [50]. Several environmental neurotoxicants are by itself, or are metabolised to become, electrophilic alkylating agents; among them ethylene oxide leads to the disruption of the axonal transport, while workers exposed to normal-hexane (*n*-hexane) are at an increased risk of PD [2]. Also head injuries have been associated with an increased risk for PD [51], while concerning occupational exposure it has been proposed that high exposure to viral (or other) respiratory infections might be one of the risk factors for the excess of PD patients among teachers and healthcare workers [52]. Few environmental risk factors have been identified for AD [53]: an important role for inflammation in the pathogenesis of the disease is suggested by several evidence [54], while it seems that the occupational exposure to solvents and aluminium is not an important risk factor in the aetiology of AD [55]. Although the mechanism(s) causing sporadic ALS remain unknown, several hypotheses, including an abnormal autoimmune mechanism and viral infections, have been proposed [56]. The brain is an organ capable to concentrate metals, so that ingestion or exposure to the metals may cause an abnormal interaction between a protein and a metal ion, leading to neurodegeneration by two generic reactions: a metal–catalysed protein oxidation leading to protein damage, and a metal–protein association leading to protein aggregation [57]. As reported by Bush [57] mutations in Cu/Zn SOD-1 involved in ALS alter the zinc binding site of the protein leading to a decreased zinc affinity, and the enzyme becomes neurotoxic when zinc is removed: SOD-1, without zinc, is capable to produce ROS using oxygen as substrate. For this reason the author speculates on the fact that mutations in the *SOD-1* gene leading to a decreased affinity of the protein for zinc may enhance its ability to produce ROS. The homeostasis of zinc, copper and iron, are altered in AD brain; Cu, Fe, and Zn ions, induce greater Aβ aggregation under mildly acidic conditions, such as those believed to occur in AD brain so that it has been proposed the possibility that Cu and Zn ions play a significant role in the formation of αβ deposits in AD [58]. Prion proteins are Cu^{2+} binding proteins showing SOD activity; like mutant SOD-1, the modified prion protein collected in CJD-affected brain, might induce a Cu^{2+} related alteration of function, leading to abnormal radical formation and oxidative stress [57]. (Environmental factors for neurodegenerative diseases are listed in Table 2b.)

4. Susceptibility factors

4.1. Susceptibility factors in carcinogenesis

Several chemicals require metabolic activation to explain their toxic effect; for this reason differences in metabolic enzymes may account for an inter-individual susceptibility to them; one example is lung cancer: although cigarette smoking is the the predominant cause of lung cancer in US, only about

15% of cigarette smokers develop the disease. Therefore, among cigarette smokers, there exist individuals with high risk for lung cancer whereas others are resistant. The inter-individual difference in metabolism of chemicals from cigarette smoke is the determining factor on who will develop lung cancer from smokers [38]. Metabolic activation is primarily mediated by cytochrome P450 enzymes (CYPs) involved in phase I of the detoxification process. CYPs add an oxygen atom to the parent molecule leading to the formation of an epoxide or ketone, which can then react with phase II enzymes such as glutathione *S*-transferases (GSTs) for excretion in the urine, or with cellular macromolecules including DNA, RNA and proteins to produce their effects; the most relevant metabolic enzymes studied for their polymorphism were P450 1A1 and P450 2D6 cytochromes (CYP1A1, and CYP2D6), GSTs, and *N*-acetyltransferases (NATs) [4]. (Table 3a shows a list of metabolic enzymes linked to an increased risk for human cancers.) CYP1A1 is a P450 isozyme whit a great ability to catalyse the first step in the metabolism of polycyclic aromatic hydrocarbons (PAHs, also present in tobacco smoke) leading to carcinogenic molecules. Considering the structural gene polymorphisms an *Msp*I restriction fragment polymorphism (RFLP) has been identified in the 3′UTR of the *CYP1A1* gene, and a point mutation in exon 7 leading to an Ile–Val substitution, has been described and associated with both increased inducibility and activity of the enzyme; a correlation of either *Msp*I or Ile–Val polymorphisms with lung cancer risk was observed in Japanese, but not in Caucasian or African–American populations, according with the different frequencies of the CYP1A1 polymorphisms existing among ethnic groups (for a review see Taningher et al. [4]). A lot of commonly used drugs are substrates of CYP2D6, so that the lack of its activity can produce severe clinical effects; otherwise in exposure in which metabolites rather than the parent compounds are the cause of cancer, poor metabolizers (PMs), that are determined by the lack of the gene function or even of the gene itself, should be less prone to developing tumors than subjects proficient for CYP2D6 activity. PMs are around 5–10% in Caucasians, 2% in Afro-Americans, and 1% in Orientals (for a review see Pavanello and Clonfero [59]). CYP2D6 high activity increases the risk of squamous and small cell primary lung cancer; and an increased cancer risk, particularly of adenocarcinoma, was associated also with the presence of additional copies of proficient *CYP2D6* gene [4]. GSTs are a family of dimeric proteins, which catalyses the conjugation between electrophiles and the nucleophile-reduced glutathione (GSH). Their primary function is to

Table 3
Some examples of susceptibility factors for cancer and neurodegenerative disorders

Genes	Increased risk for
(a) Cancer	
CYP1A1	Lung cancer
CYP2D6	Lung cancer, adenocarcinoma
GSTM1	Several cancers (lung, urinary bladder, colon,...)
GSTT1	Skin basal cell carcinoma
GSTP1	Lung and urinary bladder cancers
NAT1	Urinary bladder cancer
NAT2	Colorectal cancer
(b) Neurodegenerative disorders	
GSTP1	Parkinson's disease (PD) in people with pesticide exposure
CYP2D6	PD (conflicting results), Alzheimer's disease (AD)
NAT2	PD (in slow acetylators), sporadic late-onset AD
MAO-B	Sporadic amyotrophic lateral sclerosis
NOS3	Late-onset AD
Interleukin-1 gene	AD
Tau gene *A0/A0*	PD (sporadic and familial forms)
APOE-ε4	AD, sporadic PD
α-2-Macroglobulin gene	AD

detoxify electrophiles capable of DNA binding; GSTs also catalyse other reactions including organic hydroperoxide reduction, thus playing an important role in protecting tissues from oxidative stress. The mammalian enzymes can be divided in at least seven classes: α (GSTA), μ (GSTM), π (GSTP), σ (GSTS), θ (GSTT), κ (GSTK) and ζ (GSTZ) [60]. Both GSTM1 and GSTT1 (belonging to μ and θ classes, respectively) are subject to the complete deletion of their encoding genes. The *GSTM1* null genotype (the homozygous genotype for the null allele) leads to an increased risk of cancer in many different tissues [4]. The *GSTT1* null genotype is another common polymorphism, the lack of the enzyme is a risk factor for skin basal cell carcinomas not related to sunlight exposure in males [60] so that individuals null at both GSTM1 and GSTT1 loci are thought to be particularly prone to carcinogenesis. Another polymorphic GST of interest is GSTP1 where an A → G transition at nucleotide 313 in exon 5, and a G → T transition at nucleotide 341 in exon 6, have been associated with reduced activity of the enzyme leading to an increased susceptibility to cancers [61]. NATs can catalyse either detoxifying reactions, such as *N*-acetylations of aromatic amines and hydrazines, or intermediate reactions leading to DNA reactive metabolites, such as *O*-acetylations of *N*-hydroxyarylamines; NAT1 and NAT2 are the two NATs isozymes present in humans. Four common alleles of the *NAT1* gene are known: *NAT1*4* is presumed to be the wild-type allele, the allele named *NAT1*10* has been associated with an increased activity of the enzyme, while another NAT1 polymorphism accounts for a low enzyme activity [4]. More than 25 mutant alleles have been identified for the *NAT2* gene, and some of them lead to a slow acetylator phenotype. Slow acetylators are determined by the homozygous presence of slow-activity alleles, while rapid acetylators include both homozygous and heterozygous carriers of the *NAT2*4* wild-type allele [62]. As reviewed by Taningher et al. [4], NAT2 slow acetylators have an increased urinary bladder cancer risk in both smokers and not-smokers. NAT1 rapid acetylators have an increased urinary bladder cancer risk, while to be both NAT1 slow and NAT2 rapid acetylators give protection against urinary bladder cancer outcome. NAT2 slow acetylators have also an increased colorectal cancer risk associated with smoking, while to be NAT2 rapid acetylators leads to an increased colorectal cancer risk associated with fried meat consumption.

4.2. Susceptibility factors in neurodegeneration

The genes involved in the metabolism of chemicals that have been studied for a possible role in the pathogenesis of neurodegenerative disease include CYPs, GSTs, NATs, and others (Table 3b). CYP2D6 polymorphisms have been associated with the risk of onset of various neuronal illnesses, including PD, AD, schizophrenia and epilepsy [63]. An association between PD and CYP2D6 (in particular for the isoform named *4) has been reported [64]. Also negative studies on the role of CYP2D6 polymorphisms and PD susceptibility are reported [2]. It has been reported that workers exposed to *n*-hexane may be at increased risk of PD; *n*-hexane is metabolised by CYP2E1 and conjugated with GSH by GSTs, suggesting a possible association between environmental exposure and the role of these enzymes in neurodegenerative disorders [2]. The toxic effects of paraquat are attenuated by the conjugation of its free radical metabolites by GSTs, and an association between GSTP1 polymorphisms and PD in a sample population with defined histories of pesticide exposure has been found [65]. Recently studies in workers occupationally exposed to ethylene oxide indicate that individuals who are polymorphic for GSTT1 are at an increased risk of its neurotoxic effects [48]. The NAT2 slow acetylator phenotype has been associated with increased risk of PD [66]. Recent observations indicate that NAT2 is a potential low-penetrance gene in AD pathogenesis, determining an individual susceptibility to this disease [67]. An active role of monoamine oxidase B (MAO-B) in the pathogenesis of neurodegenerative disorders suck as PD has been proposed being the enzyme a generator of free radicals leading to oxidative damage. The influence of MAO-B in the pathogenesis of the sporadic forms of ALS has been evaluated, suggesting an increased MAO-B expression in ALS and supporting the hypotheses that neuronal cell death in neurodegenerative diseases is triggered by astroglial reaction [68]. An association between late-onset AD and a structural polymorphism Glu/Asp at codon 298 in the endothelial nitric-oxide synthase (*NOS3*) gene was found [69]. Interleukin-1 gene polimorphisms have been associated with AD [70]. An association

between the tau gene *A0*/*A0* genotype and PD has been reported recently [71]. *APOE-ε4* heterozygous individuals had a three-fold increased and homozygous persons an eight-fold increased risk for developing AD by age 75 years compared to *APOE-ε3* heterozygous individuals. *APOE* is not a causal gene but is a risk factor for developing AD; it acts as a pathologic chaperone either aiding in the polymerisation of Aβ into β-pleated sheets of amyloid in plaques or by retarding the clearance of Aβ [23]. Studies focused on the α-synuclein gene in sporadic PD have revealed that an allele polymorphism of the promoter sequence is significantly associated with an increased risk of disease development, especially in combination with the apolipoprotein ε (Apoε) allele 4 [54]. The α-2-macroglobulin gene was reported to be associated with AD [72]. Accumulation of neurofilaments in the cell body and proximal axons of motor neurons is a common finding in amyotrophic lateral sclerosis, suggesting a role for neurofilaments in motor neuron pathology. Coding sequences of neurofilaments subunits also show polymorphisms, but so far none have been demonstrated to be significantly associated with familial or sporadic ALS [54]. Examination of the current literature reveals that studies on the association between specific genetic polymorphisms and neurodegenerative diseases are often inconclusive, and sometimes contradictory. The reason could be that the marker genes until now considered in these studies are not the most relevant for the neurodegenerative process. It is likely that when the amount of such molecular epidemiology studies in the field of neurodegenerative diseases will reach that of cancer studies, more definitive conclusions could be drawn.

5. Oxidative stress

5.1. Oxidative stress in carcinogenesis

A wide variety of reactive oxygen species (ROS) can be found in biological systems, and a variety of critical biomolecules, including lipids, proteins and DNA, can be damaged by them. Under normal physiological conditions cells thereby cope with the flux of ROS. Oxidative stress describes a condition in which cellular antioxidant defences are insufficient to keep the levels of ROS below a toxic threshold. This may be either due to excessive production of ROS, loss of antioxidant defences or both [73]. Oxidative stress has been implicated in the formation of many human cancers, it has been shown to induce cancers in animal models, and it can cause a lot of different types of DNA damage, including base modifications, frameshift mutations in microsatellite sequences, base-pair substitutions, strand breaks, and, at the chromosomal level in mammalian cells, discontinuous loss of heterozygosity (for a review see Turker [74]). Therefore, a single event of oxidative stress can induce a variety of mutational events including some observed in human cancers. Kawanishi et al. [75] reported that highly reactive species, such as hydroxyl radical, cause DNA damage at every nucleotide, while less reactive species cause guanine-specific DNA damage due to the fact that the oxidation potential of guanine is lower than the other DNA bases: for this reason 8-oxo-guanine (8-oxo-dG) is the most abundant base oxidation product in DNA. 8-Oxo-dG has altered base pairing properties, leading to transversions, which may account for its potential role in carcinogenesis. For many years the consumption of fruit and vegetables has been associated with a reduced incidence of cancer, principally for the presence of various antioxidant in these foods; antioxidants are supposed to scavenge free radicals, preventing DNA damage and subsequent mutations [44]. In a recent work, the idea that the protection against the disease linked to fruit and vegetables consumption may be due to other agents present in these foods, rather than to antioxidants, has been proposed [76].

5.2. Mitochondrial DNA and carcinogenesis

The mitochondrial genome is more susceptible to oxidative damage and undergoes a higher rate of mutation than does the nuclear genome. Mitochondrial aberrations, including both mitochondrial DNA (mtDNA) mutations and alterations in mitochondrial genomic function, have been identified in cancer of the bladder, breast, colon, head and neck, kidney, liver, lung and stomach, in leukaemia and lymphomas. Cancer may be caused by or may be a consequence of mitochondrial genomic alterations, this is due to the fact that mtDNA code for 13 polypeptides of the mitochondrial respiratory chain; ROS are generated by the activity of the electron transport system and can function in both the initiation and the

promotion of cancer (for a review see Penta et al. [77]).

5.3. Oxidative stress in neurodegeneration

Oxidative stress plays an important role in neurodegenerative disorders: the concept that oxidative stress occurs in PD derives from the fact that the metabolism of dopamine can generate free radicals and other ROS. ROS can then be generated as a consequence of auto-oxidation of dopamine. Oxidative stress may be initiated by a decline in the antioxidative defence system or oxidative stress caused by other factors may decrease the concentrations of antioxidants. Glutathione (GSH) is an important intracellular antioxidant so that the most robust and significant alteration in the antioxidant defence in PD is a decrease in GSH concentration. Another consistent finding in PD patients is a defect in oxidative phosphorylation due to a decrease in complex I activity of the electron transport chain in the *Substantia nigra*. It remains controversial whether a decrease in GSH concentrations precedes the defect of oxidative phosphorylation or vice versa [73]. 4-Hydroxy-2-nonenal (HNE) is a marker of lipid peroxidation that may react with proteins to form stable adducts; it has been found that the 58% of the nigral neurons of PD patients, and only the 9% of the nigral neurons in a control group, contains HNE-modified proteins [78]. We evaluated the presence of spontaneous chromosome and primary or oxidative DNA damage in peripheral blood leukocytes of untreated PD patients, compared with controls; our data support the occurrence of chromosomal, primary DNA damage and oxidative DNA damage at the peripheral level in PD [79]. There are increasing evidences that oxidative stress is involved in the pathogenesis of AD: even if the total brain levels of GSH appeared to be unaffected in AD, the levels of glutathione transferase, a protective enzyme against HNE are decreased in the brain and ventricular CSF of autopsied AD subjects, and HNE, is elevated in AD brain and CSF [80]. A significant increase of 8-hydroxyguanosine, and an oxidised amino acid (nitrotyrosine) has been detected in neurons of patients with AD, moreover the increased oxidative damage is an early event in AD that decreases with the progression of the disease [81]. Patients with probable AD are exposed to oxidative stress, and to an increased metabolism of arachidonic acid-derived products [82]. It is now clear that oxidative stress may play an important role in the pathogenesis of ALS: increased levels of markers of oxidative damage to proteins and DNA have been measured in the motor cortex of sporadic ALS patients; HNE levels were increased in CSF of ALS patients, and increased modification of proteins by HNE was found in the lumbar spinal cord of ALS patients respect to controls; while less clear is the role of the altered glutathione metabolism founded in ALS (for a review, see Schulz et al. [73]).

5.4. Mitochondrial DNA and neurodegeneration

The pathogenesis of mtDNA mutations is not fully understood, but is assumed that their final common pathway involves impaired oxidative phosporylation: complex I deficiency in PD brain was first described in 1989, and there is evidence now emerging that mtDNA abnormalities may determine the complex I defect in a proportion of PD patients [83]. Respiratory chain defects have been identified in Huntington's disease (complex II–III deficiency) and Friedreich's ataxia (complex I–II deficiency), in both these disorders the mitochondrial abnormality is secondary to the primary nuclear mutation: CAG and less GAA repeats, respectively, suggesting that the mitochondrion may be the target of the biochemical defects that are the consequence of these mutations [84]. Also AD has been associated with mtDNA mutations, and has been proposed that the mutations founded in mtDNA of patients with PD or AD may be secondary features of the disorders rather than causal [85].

6. Apoptosis

6.1. Apoptosis in carcinogenesis

Apoptosis or programmed cell death (PCD) is a physiological process necessary for organ development, tissue homeostasis and elimination of defective or potentially dangerous cells without a concomitant inflammatory response in the surrounding tissues [86]. Three classic pathways of apoptotic signalling in mammalian cells are known, and they all require the activation of a family of cysteine proteases, called caspases. The first one is initiated by the withdrawal of growth factors and is regulated by the Bcl-2 family

proteins. This pathway results in cytochrome c release from mitochondria into the cytosol, and the subsequent activation of caspases. The second pathway involves signalling by cell surface death receptors, like as Fas receptor and tumor necrosis factor receptor 1 (TNF-R1), which contains an intracellular domain termed 'death domain' by whom they can interacts with downstream molecules leading to the activation of caspases. The third pathway is initiated by DNA damage; although in part regulated by proteins such as p53, how this pathway results in caspase's activation is still not completely known. At the moment is clear that DNA strand breaks induce p53 upregulation, and the downstream response to its upregulation is mediated through the action of downstream effector genes transactivated by p53, including genes associated with apoptosis [86]. As reported above, altered expression of Bcl-2 family proteins occurs commonly in human cancers, contributing to neoplastic cell expansion by suppressing PCD and extending tumor cell life span, and *Bcl-2* was the first discovered proto-oncogene of this family [15]. Bax is a pro-apoptotic member of the Bcl-2 family proteins and its activity is regulated by p53; an increased *bax* transcription is the consequence of p53 upregulation following DNA damage, so that *bax* may act as a tumor suppressor in a p53 dependent manner. *Bax* is also mutated in colon cancer presumably contributing to tumour progression (for a review see Müllauer et al. [87]). The inhibitors of apoptosis (IAPs) are members of a family of proteins with an emerging role in cancer. The strongest evidence for IAPs involvement in cancer is seen in the fetal IAP called survivin. Survivin is expressed fetally and not in adult differentiated tissues, however, survivin is present in most cancers tested to date; this protein is able to inhibit caspase directly and its levels correlate inversely with 5 years survival rates in colorectal cancer [88]. Deregulated expression of the c-*myc* oncogene not only promotes cell proliferation, but also can induce apoptosis [89]. RB activity has been linked with apoptosis induction in diverse cellular settings, leading to the concept that the inactivation of the RB apoptotic pathway may be a critical regulatory control that is lost during the metastatic progression of some cancers, like as prostate cancer [90]. As reviewed by Müllauer et al. [87] Fas mutations, many of them located in the 'death domain' were detected in bladder cancer, in colon cancer and in gastric cancer.

6.2. Apoptosis in neurodegeneration

Cell proliferation, cell death and differentiation are the key events in the patterning of the CNS during embryogenesis. Relatively little is known about the events that follow the cessation of cell proliferation in the developing CNS and lead to either differentiation or apoptotic death of postmitotic neuronal precursors [91]. In AD, ALS, and PD, the number of DNA fragmented nuclei detected by the TUNEL assay significantly increases in neurons located in frontal and hippocampal cortices, in spinal motor neurons, and nigral dopaminergic neurons, compared with age matched controls, respectively [92]. Morphological features of apoptosis particularly in the *Substantia nigra* have been described in Lewy-body-associated disorders including PD [93]. In AD patients postmortem tissues of the frontal and temporal lobes showed significantly higher levels of p53 and Fas receptor expression, in comparison with controls [94]. Based on studies in AD patients and controls it seems that under certain circumstances neurons in the adult human brain are able to re-enter the cell division cycle [91]; however, it also seems that in control subjects the cell cycle does not progress beyond the G1 phase and cells in G1 are able to re-differentiate without necessarily dying via an apoptotic pathway initiated by the G1 arrest. In AD patients the neuronal cell cycle is allowed to progress as far as the G2 phase, without any evidence of DNA replication. Cell cycle arrest at this stage does not permit re-differentiation, but, depending upon some unknown feature of the neuron type, it will lead either to apoptosis or to the development of Alzheimer-type amyloid deposits and/or to the deposition of PHF [91]. There is an increasing evidence that some CAG repeat disorders involve the induction of apoptotic mechanisms: in HD, an apoptotic mode of cell death appears to be operative, since neurons of HD patients show increased levels of DNA strand breaks typical of apoptotic cells, so that the discovery that Huntingtin is cleaved in a CAG repeat length-dependent manner by caspase-3 led to investigation of potential caspase cleavage sites and their involvement in the disease progression: it has been discovered that seven of the nine polyglutamine repeat proteins involved in CAG expansion diseases, including HD, SBMA, DRPLA and SCAs, contain caspase consensus cleavage sites as predicted by their amino

acid sequence [34]. In most polyglutamine diseases formation of intracellular aggregates by the disease protein and the formation of intranuclear inclusions (Nis) in susceptible neurons appear to be central to the pathogenesis [95]. A commonly held view is that caspase cleavage may generate fragments of mutant proteins that might serve to initiate the formation of aggregates that could recruit other cellular proteins containing a polyglutamine repeat and are capable of entering the nucleus. Despite the generation of proteolytic fragments due to caspase cleavage, evidence has accumulated that specific caspases are activated and recruited in polyglutamine-induced cell death [34]. Endogenous caspase-8 is recruited by polyglutamine inclusions in neurons and this recruitment may result in the activation of caspase-8, suggesting that polyglutamine repeats may promote a pathological mechanism of protein–protein interaction that results in recruitment and activation of caspase-8 [96]. It remains to be determined if other caspases are also recruited into Nis and if these interactions are critical for the induction of cell death in all polyglutamine diseases [34].

7. Aging

7.1. Aging in carcinogenesis

Although many hypotheses have been proposed over the years to explain the aging process, the exact mechanisms are not well defined. Most theories of aging are based on two fundamental concepts: aging is the result of genetic programs akin to those of development and morphogenesis; and aging is due to evolutionary non-adaptative homeostatic failures [97]. Cancer is an age-related disorder, and its frequency increases throughout almost the entire lifespan. The incidence of cancer peaked in the sixth decade and that of multiple cases in the eighth decade, while it seems that the incidence of most kinds of cancers may plateau or decrease in the oldest population [98]. Even if the largest risk factor for cancer in humans is age, and an accumulating body of evidence suggests that mutational events increase during aging in mammals [75], the fact that the incidence of cancer does not increase among centenarians would suggest that certain people among those of advanced age have a special resistance to it [98]. It is important to remember that complex mixtures of mutations affecting multiple cancer-related genes are necessary for any given cells to became malignant, so that mutation accumulation during aging may have an important role in the multi-step process; on the other hand aging enhances apoptosis and susceptibility to apoptosis in several types of intact cells, and age-enhanced apoptosis may be an inherent protective process against age-associated tumorigenesis [92]. In contrast, in certain genetically damaged, initiated, and preneoplastic cells, the apoptotic machinery is suppressed during aging, thereby leading to tumorigenesis [92]. Caloric restriction is a good method for extending life-span and slowing aging in mammals, maintaining a condition of good health [99]. At present a lot of papers demonstrate that reduced energy intake and body size control represent important factors to prevent cancers and other age-related diseases [100–102]. It has been demonstrated that a reduced caloric content of the diet leads to a decreased level of free radicals, and to changes in the level of metabolic enzymes; moreover energy restriction enhances DNA repair and seems to reduce and stabilize oncogene expression (for reviews see Kritchevsky [103], and Hart et al. [104]). Immunosenescence is a progressive loss of immune system function occurring with aging; recently it has been proposed that immunosenescence might create an environment unfavourable for neoplastic growth in centenarians [105]. The analysis of haplotypes, and how they may influence the risk for diseases, suggests that the inheritance of certain alleles of genes encoding for metabolic enzymes may be associated with the prevention of lung cancer outcome in old smokers (for a review see Au et al. [38]). The idea that a good DNA repair system is a prerequisite for longevity is supported by the fact that there exist differences in the frequencies of *BRCA1* polymorphic variants between centenarians and controls [106].

7.2. Aging in neurodegeneration

Even if the loss of neurons is a part of the normal physiological process of aging and has been reported in several regions of the senescent brain in human individuals, it is also closely associated with functional impairments suck as dementia and motor neuron disability in neurodegenerative diseases [92].

Apoptosis seems to play a role in the neuronal loss of specific neurones in patients with neurodegenerative diseases [91]; it also seems that apoptosis is upregulated during aging in various cell, for example in the nigral dopaminergic neurons aging has been associated with enhanced expression of p53, Fas receptor, and Bax protein, as well as increased DNA fragmentation, they all markers of apoptosis [92]. Another important link between neurodegeneration and aging is the evidence that a subset of aged individuals with Down's syndrome (DS) exhibits the clinical features of AD; this is due to the fact that trisomy 21 leads to a dose dependent increase in the APP production, and recently it has been seen that oxidative damage and neuroinflammation may contribute to accelerate this process especially in individuals with DS over the age of 40 years [107]. Current evidence indicates that caloric restriction can reduce the generation of ROS in the mitochondria, so slowing aging, by retarding the age-associated loss of function of complexes I, III, and IV [108]. Recent findings suggest that dietary restriction may enhance resistance of neurons in the brain to metabolic, excitotoxic, and oxidative insults relevant to the pathogenesis of AD and other neurodegenerative disorders; further studies will be required before to recommend caloric restriction as an approach to prevent neurodegeneration [109]; in this context it is important to consider that the benefits associated with decreases in caloric intake only occur in the presence of sufficient nutrient quality and density, and that a proper nutrition is fundamental for human health. Data obtained from susceptibility genes for neurodegenerative diseases, whose polymorphisms have been analysed in gene-longevity association studies, have furnished, in most cases, contradictory results. *APOE* is a locus that can reliably affect longevity, and *APOE-ε4* carriers have an increased rate of mortality compared to the rest of the population [110].

8. Discussion and future prospects

Even if carcinogenesis and neurodegeneration are different pathologies, common factors can be identified in the generation and the progression of both the diseases. The current opinion is that cancer is a multi-step process in which the first mutation may derive from parents or may arise in the genome following the action by endogenous and/or exogenous factors. The successive divisions of the initiated cell generate a clone of cells each of one may be the target for subsequent mutations leading cancer from initiation to a manifest state. At present there is no evidence that neurodegeneration is due to mutations accumulating with elderly; however, a common mechanism in many neurodegenerative disorders involves the accumulation of mutated or modified proteins in neurones. We can so speculate that also neurodegeneration may be due to multiple pathogenetic mechanisms in which an initiator event, due to the inheritance of a particular gene or to the contribution of environmental factors, may lead to the formation of an anomalous protein in some areas of the brain. The subsequent accumulation of this product may continue until the reaching of a concentration critical for cell survival. At this concentration the cells may be enable to scavenge the damage which thus can cause the progression of the degenerative process ending with the death of the cell. It is likely that an aberrant proteasomal degradation of mutated or modified proteins can lead to the abnormal protein accumulation observed in some neurodegenerative diseases ([29,32]), but an aberrant proteasomal degradation might also lead to the activation of other pathways critical for cell survival. The protein misfolding and aggregation, typically found in PD, could be attenuated by the intervention of chaperones in neurons. This has been found in a fly model by Auluck et al. [111]. So that studies on the mechanisms involved in brain protein integrity maintenance such as the role of proteasomes and that of chaperones can be a promising field of investigation in neurodegenerative disorders.

Moreover, it is of fundamental importance the study of familial cases, to better understand the role of other causative genes in the development of the pathologies; although a lot of different genes have been discovered as proto-oncogenes or tumor suppressor genes, other genes involved in cellular adhesion, motility and invasion have surely an important role in carcinogenesis [3], but less is known about their role in the process. Cellular interactions and adhesions could be critical even for neurodegeneration; the recent findings that traumas [51], inflammation [54], and autoimmune response [56] resulted as risk factors in the aetiology of different neurodegenerative disorders, seems to support to this idea.

Environmental agents interact with human tissues in different ways, some of them are metabolised by enzymes. Several studies have been carried out, in recent years, to evaluate the human risk linked to the exposure to a particular agent in people carrying one particular allele at a specific metabolic enzyme locus. Considering the individual variations in the coding part of the human genome, it is now emerging that everyone has got his own pattern of proteins, including metabolic enzymes; this concept leads to the idea that the individual risk due to the exposure to environmental factors is strongly influenced by the inherited combination of alleles coding for metabolic enzymes. The recent development of powerful techniques, like as DNA microarrays, is a promising field in order to evaluate the role of combinations of alleles in an unique experiment. As reported above detoxifying enzymes play an important role also in the metabolism of several drugs, so modulating the individual response to drug treatment [59]. Thus another important field of research is that of pharmacogenomics, a new discipline with the aim to elaborate an effective therapy to individual patients, according to their genetic profile. An increasing number of papers report an association between polymorphisms in genes coding for cellular membrane proteins and diseases: one example is that of the receptor CCR5 used by human immunodeficiency virus-1 (HIV-1) to enter the cell, it has been reported that people carrying a mutated form of the gene are less prone to viral infections [112]; it seems that also genes coding for proteins involved in the uptake of cancer drugs, drugs used in neuronal therapy, carcinogenic agents and neurotoxicants, may exist in polymorphic forms among humans being responsible for an inter-individual response to the exposure to a chemical and to drug treatment.

Unfortunately, the human brain is not an organ easily accessible, and the majority of the studies have been conducted in postmortem brains. Animal models of aging and neurodegeneration seem to offer a good opportunity to obviate the problem. *Drosophila melanogaster* has provided elements on the mechanisms of aging, and recently fly models of PD and polyglutamine diseases have been obtained by the expression of human genes in fly's nervous system [113]. These models are now objects of study in order to evaluate the role of presumed therapeutical molecules on the progression of the diseases [111].

DNA microarrays are used primarily to determine the gene expression profile in normal tissues, compared with that of pathological ones; they have been also employed to determine the gene expression profile of the aging process in the brain of mice models [114]; we think that the use of similar techniques in animal models of dementia and neurodegenerative illness, might be an excellent method to better understand the molecular pathways underlying the dynamic of these diseases.

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