CYTOGENETIC ALTERATIONS IN PERIPHERAL CELLS OF ALZHEIMER'S DISEASE PATIENTS

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Alzheimer's disease (AD) is the most frequent progressive neurodegenerative disorder in elderly associated with irreversible cognitive impairment and dementia. The vast majority of AD patients are sporadic (SAD) in which the disease develops after age of 65. Despite of century of research, we lack understanding of the SAD etiology and pathogenesis. Several hypotheses try to explain the main causes of brain degeneration in SAD, one of them assuming that genomic instability and the reentry of certain neurons into the incomplete cell cycle may be the pathogenic basis of the disease. Although the brain is the most affected organ in AD, numerous studies showed structural and functional alterations in peripheral tissues, suggesting that AD is a generalized systemic disorder. Diverse changes in peripheral cells from AD patients are described in literature including cell cycle aberration and chromosome instability, alterations in cell viability, proliferation and apoptosis, oxidative metabolism, amyloid precursor protein and amyloid β protein metabolism, and other cellular processes. The aim of this paper was to summarize and review the results of our investigations and the growing literature data concerning the multiple chromosomal alterations in peripheral cells of AD patients and to consider their possible role in the disease pathogenesis as well as the importance of such investigations.

Key words: Alzheimer's disease, chromosome instability, peripheral cells

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INTRODUCTION

Alzheimer's disease (AD) is the most frequent progressive neurodegenerative disorder in elderly associated with irreversible cognitive impairment and dementia. There are two forms of the disease; 5-10% of all AD cases have an early onset form that starts before the age of 65, while the vast majority of patients are sporadic (SAD) in which the disease develops after age of 65. Up to 50% of early onset cases are familial AD (FAD), diagnosed when a patient has first-degree relative with history of AD (BIALOPIOTROWICZ *et al*., 2011). FAD, as genetically determined AD, seems to be completely explained by pathogenic mutations in three genes, either for amyloid precursor protein (APP) (APP gene on chromosome 21), or enzymes involved in its metabolism: Presenilin 1 gene on chromosome 14, and Presenilin 2 gene on chromosome 1 (SHERRINGTON *et al*., 1995). Presenilins sustain the activity of γ-secretase, a membranous complex that cleaves transmembrane APP to generate amyloid β (Aβ) peptides (Aβ40, Aβ42) known to aggregate and form oligomers that may exert toxic effects on neurons (TAGAMI *et al*., 2008). In contrast to FAD, SAD is a disorder with more heterogeneous and complex causes, which are mostly unknown (BUIZZA *et al*., 2012). Both incidence and prevalence of SAD increase with advanced age, suggesting that age-related physiological changes play a critical role in the majority of subjects affected with AD (CORRADA *et al*., 2008). Although late onset AD is considered sporadic, the fact that affected individuals are more likely to have AD-affected relatives than those without AD means that SAD is not fully sporadic (HENDRIE, 1998). Some risk factor genes has been uncovered, but only the mutation of apolipoprotein E-4 gene is present in considerable number (about 50%) of SAD patients (CORDER *et al*., 1993). Therefore, SAD is multifactorial, genetically complex and heterogeneous disorder modulated by different non-genetic factors (FERRER, 2012).

AD is characterized histopathologically by the degeneration of specific populations of the neurons, extracellular deposits known as senile plaques (SPs) and intracellular deposits known as neurofibrillary tangles (NFTs) within the brain of affected individuals. SPs consist of Aβ42 and/or Aβ40, which originate from the aberrant proteolysis of APP (HARDY, 2006), and it is assumed that Aβ triggers AD-like pathology (KHANDELWAL *et al*., 2011). The NFTs contain structures known as paired helical filaments comprised of hyperphosphorylated tau protein (THOMAS and FENECH, 2007). In addition to Aβ, tau protein is another causal factor for neurodegeneration in AD and other neurodegenerative diseases (GRUNDKE-IQBAL *et al*., 1989).

Over a hundred of years after Alois Alzheimer first characterized the neurological disease that was later named after him, the etiology and pathophysiology of AD are still mostly unknown. Several hypotheses try to explain causes and progression of the disease, especially the SAD form. Since this neurological disorder is complex and multifactorial, a single hypothesis is probably insufficient to cover all aspects of the disease.

According to the "amyloid hypothesis", which is one of the first hypotheses introduced, Aβ has the central role in AD pathogenesis (HARDY, 2006). The similarity of histopathological hallmarks in FAD and SAD led to assumption that a common pathophysiological mechanism underlies both forms of the disease. An elevated level of neurotoxic Aβ in certain brain structures is the primary cause for AD that drives other disease features including tau phosphorylation. However, the amyloid hypothesis emerged out of molecular defects found to be causative primarily in FAD, though not necessary in SAD (SMALL and DUFF, 2008).

The "cell cycle hypothesis" assumes that the pathogenic basis of AD is genomic instability and the aberrant reentry of terminally differentiated postmitotic neurons into the cell

division cycle (ARENDT, 2003; HERNANDEZ-ORTEGA *et al.*, 2007; BAJIC *et al.*, 2008; BONDA *et al.*, 2010; BAJIC *et al.*, 2011; SPREMO-POTPAREVIC *et al.*, 2011). In the hippocampal and cerebral cortex regions of postmortem SAD brains, increased levels of numerous proteins characteristic for G_1/S and G_2 cell cycle phase activation was accompanied by partial or complete DNA replication without signs of mitosis (YANG and HERRUP, 2007; SPREMO-POTPAREVIĆ *et al.*, 2008; BONDA *et al.* 2009). Cells in unaffected brain regions of SAD patients or non-demented control brains show no such anomalies. Data indicate that the G_1/S checkpoint fails in SAD neurons and therefore these cells replicate their DNA and progress to the G_2 phase (MCSHEA *et al.,* 2007). However, the G_2/M checkpoints remain functional and block completion of the cell cycle, i.e. the mitosis, of affected neurons. These changes appear to occur at early stages of SAD, while at the advanced stages the affected neurons exhibit pathological changes characteristic of neurodegeneration and higher susceptibility to death triggered by stress factors (YANG and HERRUP, 2007). The period between the neuronal reentry into the cell cycle and apoptotic death may last for years or even decades (MOSCH *et al.*, 2007).

Although AD is mainly considered a neurodegenerative disorder, there are many indices for additional involvement of cerebrovascular pathology leading to the "neurovascular hypothesis" in AD pathogenesis (ZLOKOVIC, 2005). It is suggested that chronic endothelial dysfunction may be responsible for breakdown of blood brain barrier, impaired cerebrovascular flow, cerebral amyloid angiopathy, atherosclerosis, and other important secondary-related inflammatory phenomena found in AD cases (BELL and ZLOKOVIC, 2009).

Mitochondrial structural and functional perturbations in AD have been recognized for some time (SELFRIDGE *et al.*, 2012) and one of the latest hypotheses is about the potential role of mitochondrial dysfunction in AD pathogenesis, which is not brain-localized, but rather seems to be systemic. Thus, SWERDLOW and KHAN (2004) proposed the "mitochondrial cascade hypothesis", according to which inherited mutation in mitochondrial DNA determined the basal function of mitochondria as well as their ability to respond to and recover from stress that is mediated by molecules such as reactive oxygen species (ROS). At the point at which mitochondrial dysfunction is reached, the histopathology of AD develops. Current data suggest that mitochondrial dysfunction, by influencing cell bioenergetic states and redox system, actually lies upstream of brain amyloidosis (SELFRIDGE *et al.*, 2012)

Until now, AD cannot be diagnosed by a valid clinical method or marker before the disease has progressed to the stage in which dementia is developed and any effective cure is missing. Apart of neuropsychological assessment, several biomarkers are currently available for the clinical diagnosis of dementia of Alzheimer's type: reduced levels of Aβ and increased ratio of phospho-tau/tau in cerebrospinal fluid, increasing atrophy of certain cerebral regions such as hippocampus and amygdala revealed by structural magnetic resonance imaging and increasing positron emission tomography signals of accumulated proteins in the brain, such as Aβ and tau (BLENNOW *et al.*, 2006). Unfortunately, these procedures are either invasive or expensive, which preclude their frequent usage. Extensive investigations for accessible and reliable biomarkers for an early AD diagnosis are in progress.

Although the brain is the most affected organ in AD, numerous studies showed structural and functional alterations in peripheral tissues, suggesting that AD is a generalized systemic disorder (GASPARINI *et al.*, 1998; PALOTAS *et al* 2002; MIGLIORE *et al.*, 2005; HUMPEL, 2011; MIGLIORE, *et al.*, 2011; STIELER, et *al.*, 2012). Due to the inaccessibility of brain tissue in

vivo, peripheral tissues of AD patients that are suitable and most frequently explored are peripheral blood cells, skin fibroblasts and the cells from buccal mucosa.

Diverse changes that occur in peripheral cells from AD subjects include cell cycle aberration and genome or chromosome instability, alterations in cell viability, proliferation and apoptosis, oxidative metabolism, APP and Aβ metabolism, cellular signal transduction systems, calcium homeostasis, and some other cellular processes. The question is rising whether the changes at periphery reflect the situation in AD brain or do they contribute to pathogenesis or even to etiology of AD. It is rather unlikely that all these multiple AD-related changes are independent, and their investigation could lead to a common link to brain cells and peripheral somatic cells (GIBSON and HUANG, 2005). On the other hand, because of their easy accessibility, peripheral cells may be of great importance for identification of biological markers of AD and can be tremendously useful to improve diagnostic accuracy and/or monitor the efficiency of putative therapies (UBERTI *et al*., 2008).

In this review we will summarize the results of our, over a decade long, investigations and the growing literature data concerning the multiple genome/chromosome alterations and abnormalities in peripheral cells of AD patients, compare them with the changes in neurons of AD brain, and consider their putative consequences as well as the possible importance of these investigations.

GENOME/CHROMOSOME INSTABILITY IN ALZHEIMER'S DISEASE

Mounting evidence suggests that the cell cycle disregulation and genomic instability may be the earliest neuropathological event detected in AD thus far (ZHOU and JIA, 2010). These failures are systemic affecting not only neurons but also peripheral somatic cells (STIELER, et *al*., 2012). AD is associated with elevated frequencies of genomic instability markers including cell cycle abnormalities and aneuploidy, and chromosome instability such as premature centromere division, micronuclei and telomere length change (ŻEKANOWSKI and WOJDA, 2009).

The *cell cycle disregulation* is the most prominent failure in AD in both neurons and some peripheral somatic cells (BIALOPIOTROWICZ *et al*., 2011; MOH *et al*., 2011; STIELER et *al*., 2012). Post-mitotic neurons are in a state of terminal differentiation and are unable to divide but they may still retain certain elements that are active during cell cycle maintaining the capability to reactivate various aspects of the replication mechanism when stressed (HERRUP *et al*., *2004*). The most important endogenous genotoxic agent associated with DNA damage in the earliest stage of AD is oxidative stress (NUNOMURA *et al*., 2001). Oxidative stress appears closest to a causal event in AD, acknowledging that previous events may be promoting the oxidative stress itself (MONDRAGON-RODRIGUEZ *et al*., 2010). The presence of Aβ early in the disease also contributes to the oxidative damage of DNA (MAO and REDDY, 2011). According to hypothesis of YUROV and colleagues (2011) incomplete DNA replication, being highly probable in postmitotic cells, causes replication forks to progress slowly or to stall resulting in S phase arrest or replication stress, which leads to DNA damage or improper repair and, thereby, to accumulation of genomic instabilities. The surveillance system of cell cycle checkpoints functions as protective barriers against cytotoxic agents by providing attacked cells additional time, by so called cell cycle arrest, to repair DNA damage before DNA replication or mitosis (SHACKELFORD *et al*., 2000). When damage is severe and irreparable, checkpoint signaling may cause cells to undergo apoptosis, which is the ultimate result of cell cycle aberration in neurons, or enter an irreversible G_0 state.

Examination of cell cycle of peripheral AD cells reveals similar defects with neurons in AD. In the B lymphocytes of SAD, but not FAD, patients a prolongation of the G_1 phase of cell cycle compared to controls was found (BIALOPIOTROWICZ *et al*., 2011). The level of p21 protein, one of the major regulators of G_1/S progression in the cell cycle, was much higher in the SAD cells compared with both control and FAD cells. Cyclin-dependent kinase inhibitor p21 is a p53-inducible protein, which mediates p53-dependent cell cycle arrest (DOTTO, 2000). Cytogenetic anomalies in AD neurons and lymphocytes (MIGLIORE *et al*., 2005; COPPEDÈ and MIGLIORE, 2009) may result in upregulation of p21 in both cell types. Importantly, the results of BIALOPIOTROWICZ *et al.* (2011) directly show differences in the cell cycle regulation between FAD and SAD, as far as lymphocytes concerned. ZHOU and JIA (2010) also observed the abnormality in G_1/S checkpoint of the activated lymphocytes from AD patients. They found that AD lymphocytes were less sensitive to G_1/S transcription blocker rapamycin than control cells. Because of the G_1/S checkpoint dysfunction, the cell cycle of AD lymphocytes was not arrested in G_1 phase and progress to late stages in spite of rapamycin treatment. In addition, AD lymphocytes specifically expressed an anomalous conformationally mutant-like p53 that made these cells distinct from lymphocytes of control subjects. Tumor suppressor protein p53, which promotes transcription of p21, has therefore a critical role in regulation G_1/S cell cycle arrest (KUERBITZ *et al*., 1992). Exposure to multiple signals, including radiation, genotoxic chemicals, hypoxia and oxidative stress, induces p53 to accumulate in the nucleus, to bind to specific DNA sequences and to transactivate several genes most of them involved in cell-cycle control, DNA repair, and apoptosis (ALMONG and ROTTER, 1997). On the other hand, conformational changes of p53 in AD might be one possible reason for p53 inactivation and multiple disturbances in affected cells. Based on their results, ZHOU and JIA (2010) propose two potential biomarkers in blood lymphocytes from AD patients: the G_1/S checkpoint dysfunction and the presence of conformationally mutant-like p53 protein. Of note, recent data demonstrated that combination of p53 phosphorylated at ser 15 and p21 in peripheral blood lymphocytes have high diagnostic power and could differentiate AD from controls and other types of dementia, indicating these proteins as potential biomarkers for improving diagnostic accuracy of AD (TAN *et al*., 2012).

Aneuploidy, a state of non-diploid chromosome number, is a form of genomic instability and may be one of the hallmarks of aging and neurological disorders (BAJIĆ *et al*., 2012; ŽIVKOVIĆ *et al*., 2013). Aneuploidy is defined as the loss or gain of chromosomes to produce a numerical deviation from multiples of the haploid chromosomal complement (KING and STANSFIELD, 1990). A correlation between aneuploidy and aging has been reported (MOSCH *et al*., 2007; THOMAS and FENECH, 2007), but exact role of aneuploidy in etiology of age-related neuronal degeneration is yet unclear (GRANIC *et al*., *2010;* FAGGIOLI, 2011). One of the consequences of aneuploidy could be a predisposition to disease and in this respect aneuploidy has been implicated in the most common cause of dementia in AD. Aneuploidy is a feature of dividing cells, but it is present in neurons in both forms of AD (MOSCH *et al*., 2007), as well as in some peripheral cells of AD patients. The study of THOMAS and FENECH (2007) showed that SAD patients exhibit an abnormally high rate of chromosome 17 and 21 aneuploidy in buccal cells compared to controls. Buccal cells are of interest because they originate from ectoderm during embryogenesis, the germinal layer from which brain tissue and fibroblasts are derived (MIGLIORE, *et al*., 2011) and accordingly may exhibit genetic defects common to brain tissue. An increased aneuploidy was also detected in fibroblast culture from sporadic and familial AD patients (GELLER and POTTER, 1999); a significant approximately twofold increase was found in

the number of trisomy 21 cells compared to control cultures. Trisomy was not limited to chromosome 21 but extended at least to chromosome 18 as well. These data suggest that trisomy 21 mosaicism may contribute to forms of AD that are not caused by presenilin mutation.

Premature centromere division **(PCD)** could be a manifestation of chromosome instability (MEHES and BUHLER, 1995) that leads to aneuploidy. Centromere is a chromosomal region, which holds sister chromatids between the end of replication and the start of segregation, playing a fundamental role in accurate chromosome segregation during mitosis and meiosis. PCD is connected with a loss of control over sequential separation and segregation of sister chromatids. Like aneuploidy, PCD has been correlating with both aging and AD in peripheral somatic cells (KORMANN-BORTOLOTTO *et al*., 1993; MIGLIORE *et al*., 1997; SPREMO-POTPAREVIC *et al*., 2004; ZIVKOVIC *et al*., 2010, 2013b). We have demonstrated, using the FISH technique, the PCD on X chromosome in the interphase neurons in the frontal cerebral cortex of female AD patients (SPREMO-POTPAREVIC *et al*., 2006, 2008; BAJIC *et al*., 2009). The presence of PCD on interphase chromosome is a proof that affected cells perform DNA replication and reenter into the cell cycle, because only replicated chromosomes can exhibit the phenomenon of PCD. Later on, a higher rate of PCD on chromosome X was found in lymphocytes from AD women in respect to healthy age-matched controls (ZIVKOVIC *et al.,* 2006). KORMANN-BORTOLOTTO et al. (1993) were among the first to investigate peripheral blood lymphocytes from AD patients by cytogenetic probes. They found that aneuploidy, PCD and C-anaphase were not significantly different in AD patients comparing to age-matched controls, probably due to the small study population. In contrast, later results of other researchers consistently demonstrated an increased frequency of PCD in different chromosomes of AD lymphocytes, i.e., in acrocentrics (MIGLIORE *et al*., 1997; ZIVKOVIC *et al*., 2010) and chromosome 18 (ZIVKOVIC *et al*., 2006).

Micronuclei **(MNi)** originate from acentric chromosome fragments or whole chromosomes that lag behind in anaphase and are left outside the daughter nuclei. Either they can originate from chromosome breakage or chromosome malsegregation events. Therefore, MNi are ideal biomarkers to investigate DNA damage at chromosomal levels (FENECH, 2000; DJELIC *et al*., 2006). MNi have been shown to be elevated in peripheral blood lymphocytes and skin fibroblasts in AD patients (MIGLIORE *et al*., 1999; PETROZZI *et al*., 2002; TRIPPI *et al*., 2011). Analysis of sensitivity of peripheral blood lymphocytes from AD patients to an aneuploidogenic drug griseofulvin, whose supposed target is microtubule-associated protein(s), showed that AD lymphocytes were characterized by lower levels of MN induction compare to controls (MIGLIORE *et al*., 1997), indicating that microtubule impairment might be associated with the disease. In the peripheral blood lymphocytes of AD patients, FISH data showed higher frequencies of chromosome 13 and 21 loss, evaluated as fluorescently labeled MNi, compared to control lymphocytes (MIGLIORE *et al*., 1999). More frequent chromosome 21 than chromosome 13 malsegregation in somatic cells of AD subjects raised the hypothesis that mosaicism for chromosome 21 could underlie the dementia of AD phenotype (PETROZZI *et al*., 2002). Elevated MNi in AD lymphocytes were shown to be centromere positive, which indicates whole chromosome loss (TRIPPI *et al*., 2011). In addition, the results of TRIPPI *et al.* (2011) confirmed that spontaneous frequency of MNi is increased in AD lymphocytes, but also showed that this phenomenon occurs in the skin fibroblasts of AD patients with either sporadic or familial form of disease. The authors supposed that different types of peripheral somatic cells of AD patients, irrespective of form of the disease, share similar feature leading to the occurrence at the same extent of cytogenetic anomalies. However, MNi frequency in buccal mucosa did not show a

significant difference between AD and control subjects (THOMAS *et al.*, 2007), indicating that different types of peripheral AD cells do not necessarily express the same forms of chromosome instability.

Telomere length may serve as an effective biomarker of a cell replicative history, aging and disease (ALLSOPP *et al.*, 1992). Telomeres undergo shortening not only with each cell division, but also with aging and oxidative stress, all-important factors in AD. Moreover, telomere loss results in chromosomal instability (THOMAS and FENECH, 2007). Since SAD is highly related to age, examination of telomere length in AD neurons and peripheral cells seemed a promising technique to find the possible relationship between the telomere length and AD pathogenesis. However, conflicting results of hitherto investigations for the most part failed to establish such an association.

Significantly shorter telomeres were found in hippocampal neurons in AD patients compared with that in control subjects, and they were not related to age either in control or AD subjects, as well as to amyloid deposits in AD patients (FRANCO *et al.*, 2006). By contrast, THOMAS *et al.* (2008) reported that the mean telomere length in the brain hippocampal tissue was significantly longer in AD brains compared to normal brain tissue, which could be ascribed to a weaker proliferative capacity in cells within the dentate gyrus of the hippocampus, which continue to divide throughout adult life (ERIKSSON *et al.*, 1998), or by telomere to telomere end fusions and amplification of telomere sequences due to breakage/fusion/bridge cycles (FENECH. and CROTT, 2002) after initial telomere shortening.

Regarding the telomere length changing in peripheral cells from AD patients data are also inconclusive. In peripheral blood monocytes from AD subjects, significant telomere shortening was found in comparison to controls (PANOSSIAN *et al.*, 2003). Telomere length of T lymphocytes, but not of B cells, has been correlated with AD status, suggesting possible immune alterations in AD pathogenesis. Similarly, telomere length in peripheral blood leukocytes and buccal cells from AD subjects were significantly shorter relative to corresponding values found in healthy age-matched controls (THOMAS *et al.*, 2008). Recent work, in which telomere lengths were measured in leukocytes from patients with AD or mild cognitive impairment (MCI), displayed that patients with stable MCI that did not progress to AD had reduced telomere length compared to controls, whereas those with AD or MCI that later converted to AD have similar leukocyte telomere length as healthy controls (MOVERARE-SKRTIC *et al.*, 2012). Furthermore, no correlations were found between leukocyte telomere lengths of AD patients arbitrary defined as highly positive for the core AD biomarkers, i.e., the cerebrospinal fluid levels of $A\beta1$-42, total tau and phosphorylated tau and the remaining patients or healthy controls. More recently, significantly shorter telomere length was found in peripheral blood monocytes in AD patients compared to controls, whereas telomeres of patients with MCI were not altered (HOCHSTRASSER *et al.*, 2012). The discrepancy between these and results above may be explained, at least partly, by the fact that first group (MOVERARE-SKRTIC *et al.*, 2012) analyzed telomere length in the whole population of leukocytes, which is a mixture of different cell types. However, in another study, in which peripheral blood lymphocytes were investigated, no significant difference in telomere length was observed among large groups of cognitively normal subjects, demented patients (mixed dementia, AD and vascular dementia) and patients with MCI (ZEKRY *et al.*, 2010). Similarly, no significant changes were found between patients with different etiologies or severity of dementia. These results suggest that telomere length could not be used to distinguish

between demented and non-demented subjects, regardless of type of dementia, or to predict dementia or mild cognitive impairment progression to dementia.

Susceptibility to apoptosis and proliferative activity. Vast majority of experimental data demonstrate that peripheral cells in AD patients, primarily certain leukocyte subtypes, are more sensitive to spontaneous and induced apoptosis, and consequently more vulnerable than corresponding cells of age-matched control subjects. AD lymphocytes in culture exposed to DNA damaging chemical agents (bleomycin or methylmethane sulfonate) exhibit significantly enhanced DNA breakage rates for both drugs (CHERRY *et al*., 1992). The time course accumulation of apoptotic DNA fragments in lymphocytes from AD patients has also been reported in response to apoptotic stimuli (ECKERT *et al*., 1998). Lymphocytes of patients affected by SAD or FAD share an increased sensitivity to cell death, and enhanced vulnerability was most strongly developed in the CD4+ T-cell subtype (SCHINDOWSKI *et al*., 2003). The impact of SAD on CD4+ cell vulnerability was greater than that of FAD. Normal aging has also been shown to increase T cell susceptibility to apoptosis, but in contrast to AD it affected both CD4+ and CD8+ cells. Increased apoptosis was found in natural killer cells (SCHINDOWSKI *et al*., 2006) and in the peripheral blood monocytes from AD patients (BERGMAN *et al*., 2002) as well.

Increased sensitivity of AD lymphocytes to apoptosis is accompanied by a decreased proliferative activity. Peripheral blood lymphocytes, stimulated with mitogen compounds, were less able to express CD69, an early proliferative marker, and expression level of CD69 of both T- and B-cells correlated inversely with the disease progress (STIELER *et al*., 2001). Proliferation activity of peripheral blood mononuclear cells to phytohemagglutinin has been shown to be significantly decreased in AD subjects (ZHANG *et al*., 2003), although Pannasonian et al. (2003) found that T-cells from AD patients respond more robustly to ***phytohemagglutinin*** than control cells.

Possible causes of AD lymphocyte higher sensitivity to apoptosis are not clear. An investigation of the expression of some of apoptosis-related proteins (Bcl-2, Bax and caspase-3) in peripheral blood mononuclear cells from AD patients and healthy controls revealed no evidence of these proteins in AD cells (COSENTINO *et al*., 2009). On the other hand, a significant increase in the activity of caspase-3, -8 and -9, enzymes that play vital roles in the induction, transduction and amplification of intracellular apoptotic signals, was found in peripheral blood mononuclear cells of SAD patients relative to controls. This increased activity was not associated with increase in apoptosis, but was associated with a higher proliferative response to mitogens, suggesting that both altered caspase activation and altered proliferative response of peripheral blood mononuclear cells might reflect a general dysfunction of the cell cycle in AD (TACCONI *et al*., 2004). An extensive study of UBERTI and colleagues (2002) demonstrated a specific alteration of an intracellular pathway involved in sensing and repairing DNA damage in fibroblast from AD patients. AD fibroblast were shown to be less vulnerable to oxidative injury than non-AD cells and the protective mechanism was related to an impairment of H_2O_2-induced cell cycle arrest and characterized by an accelerated re-entry into the cell cycle and a diminished induction of apoptosis. Fibroblasts from AD patients also had a profound impairment in the H_2O_2-activated, p53-dependent pathway, which results in a lack of activation of p53 or p53-target genes, including p21, GADD45 and bax. In addition, AD fibroblasts have been found to express a mutant-like p53 phenotype, which is virtually undetectable in fibroblasts of non-AD subjects (UBERTI *et al*., 2006).

PUTATIVE CONSEQUENCES OF PERIPHERAL CELL
GENOMIC/CHROMOSOME INSTABILITY

Functional consequences of the enhanced genome/chromosome instabilities in different types of peripheral somatic cells in AD patients, with the exception of blood mononuclear cells, at present are far from being understood. However, a prominent immune response, manifested as local inflammatory process has been shown to be associated with Aβ deposition and plaque formation in the central nervous system (BLASKO and GRUBECK-LOEBENSTEIN, 2003). Recent evidence suggest that inflammatory mechanisms represent, besides SPs and NFTs, a third component that may significantly contribute to AD progression and chronicity (HENEKA *et al*., 2007). Abnormalities of both peripheral humoral and cellular immune responses in AD were reported, suggesting an association of immune deregulation and AD pathogenesis (LUGARESI *et al*., 2004; IARLORI *et al*., 2005). A variety of studies have shown that T lymphocytes isolated from peripheral blood of AD patients express alterations in distribution, proliferation, apoptosis and function, including expression of activation markers, disturbed calcium homeostasis and cytokine secretion (SCHINDOWSKI *et al*., 2007). T cells are activated and mainly display a memory phenotype (CD4). These T-cells are present both in the periphery and in the brain in AD patients (TOGO *et al*., 2002; TOWN *et al*., 2005), although they might play a role in AD without necessarily entering and/or taking up residence in the brain (PANOSSIAN *et al*., 2003). The exact roles of peripheral and T cells that entered the central nervous system in AD are still unclear. The presence of activated CD4+T cells might be the result of Aβ-specific chronic T cell stimulation, creating a pro-inflammatory environment, and enhancing disease progression (PELLICANO *et al*., 2012). The same authors conclude that there is a common peripheral immune profile for Alzheimer's disease which mainly involves CD4+ T cells, changes to which are consistent with chronic antigenic stress leading to immune exhaustion. Importantly, the changes in T lymphocyte phenotype and function could potentially affect vaccine-based efforts to modulate AD, and Aβ-reactive T-cell subsets seem to be major components of deleterious central nervous system response to active Aβ vaccination (GIUNTA *et al*., 2010).

REFERENCES

ALLSOPP, R.C., H. VAZIRI, C. PATTERSON, S. GOLDSTEIN, E.V. YOUNGLAI, A.B. FUTCHER, C.W. GREIDER and C.B. HARLEY (1992): Telomere length predicts replicative capacity of human fibroblasts. PNAS, *89*: 10114-10118.

ALMONG, N. and V. ROTTER (1997): Involvement of p53 in cell differentiation and development. Biochem. Biophys. Acta., Volume *1333*: F1-F27.

ARENDT, T. *(*2003): *Synaptic plasticity and cell cycle activation in neurons are alternative effector pathways: the 'Dr. Jekyll and Mr. Hyde concept' of Alzheimer's disease or the yin and yang of neuroplasticity. Prog. Neurobiol., 71*: 83-248.

BAJIC, V.P., B. SPREMO-POTPAREVIC, L. ZIVKOVIC, N. DJELIC and M.A. SMITH (2008): Is the time dimension of the cell cycle re-entry in AD regulated by centromere cohesion dynamics? Biosci. Hypotheses, *1*: 156-161.

BAJIC, V.P., B. SPREMO-POTPAREVIC, L. ZIVKOVIC, D.J. BONDA, S.L. SIEDLAK, G. CASADESUS, H.G. LEE and M.A. SMITH (2009): *The X-chromosome instability phenotype in Alzheimer's disease: a clinical sign of accelerating aging? Med. Hypotheses*, *73*: 917-920.

BAJIC, V.P., B. SU, H.G. LEE, W. KUDO, S.L. SIEDLAK, L. ZIVKOVIC, B. SPREMO-POTPAREVIC, N. DJELIC, Z. MILICEVIC, A.K. SINGH *et al.* (2011): *Mislocalization of CDK11/PITSLRE, a regulator of the G2/M phase of the cell cycle, in Alzheimer disease. Cell Mol. Biol. Lett.,* 16: 359-372.

BAJIC, V.P., D.J. BONDA, L. ŽIVKOVIC, Z. MILICEVIC, B. PLECAS-SOLAROVIC, X. ZHU and B. SPREMO-POTPAREVIC (2012): The Role of Centromere Cohesion and Assocciated Proteins in Alzheimer's Disease: A relation to Aneuploidy? In: Aneuploidy: Etiology, Disorders and Risk Factors. Editors: S. de Rossi and F. Bianchi. Nova Science Publishers, Inc. New york. pp: 77-90.

BELL, R.D. and B.V. ZLOKOVIC (2009): *Neurovascular mechanisms and blood-brain barrier disorder in Alzheimer's disease. Acta Neuropathol., 118*: 103-113.

BERGMAN, M., H. SALMAN, Y. BELOOSESKY, M. DJALDETTI and H. BESSLER (2002): *Are peripheral blood cells from patients with Alzheimer disease more sensitive to apoptotic stimuli? Alzheimer Dis. Assoc. Disord., 16*: 156-160.

BIALOPIOTROWICZ, E., B. KUZNIEWSKA, N. KACHAMAKOVA-TROJANOWSKA, M. BARCIKOWSKA, J. KUZNICKI and U. WOJDA (2011): *Cell cycle regulation distinguishes lymphocytes from sporadic and familial Alzheimer's disease patients. Neurobiol. Aging, 32*: 2319.e13-26.

BLASKO, I. and B. GRUBECK-LOEBENSTEIN (2003): Role of the immune system in the pathogenesis, prevention and treatment of Alzheimer's disease. Drugs Aging, *20*: 101–113.

BLENNOW, K., M.J. DE LEON and H. ZETTERBERG (2006): *Alzheimer's disease. Lancet, 368*: 387-403.

BONDA D.J., T.A. EVANS, C. SANTOCANALE, J.C. LLOSÁ, J. VIÑA, V. BAJIC, R.J. CASTELLANI, S.L. SIEDLAK, G. PERRY, M.A. SMITH and H.G. LEE (2009): Evidence for the progression through S-phase in the ectopic cell cycle re-entry of neurons in Alzheimer disease. Aging, *1*: 382-388.

BONDA, D.J., V.P. BAJIC, B. SPREMO-POTPAREVIC, G. CASADESUS, X. ZHU, M.A. SMITH and H.G. LEE (2010): *Review: cell cycle aberrations and neurodegeneration. Neuropathol. Appl. Neurobiol., 36*: 157-163.

BUIZZA, L., G. CENINI, C. LANNI, G. FERRARI-TONINELLI, C. PRANDELLI, S. GOVONI, E. BUOSO, M. RACCHI, M. BARCIKOWSKA, M. STYCZYNSKA, A. SZYBINSKA, D.A. BUTTERFIELD, M. MEMO and D. UBERTI (2012): *Conformational altered p53 as an early marker of oxidative stress in Alzheimer's disease. PLoS One, 7*: e29789.

CHERRY, L.M., J. FUNK, J.M. LESSER and M. LESAM (1992): *Gender differences and the interpretation of genetic instability in Alzheimer's disease. Mutat. Res., 275*: 57-67.

COPPEDÈ, F. and L. MIGLIORE (2009): DNA damage and repair in Alzheimer's disease. Curr. Alzheimer Res., *6*: 36-47.

CORDER, E.H., A.M. SAUNDERS, W.J. STRITTMATTER, D.E. SCHMECHEL, P.C. GASKELL, G.W. SMALL *et al.* (1993): Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science, *261*: 921-923.

CORRADA, M.M., R. BROOKMEYER, D. BERLAU, A. PAGANINI-HILL and C.H. KAWAS (2008): *Prevalence of dementia after age 90: Results from The 90+ Study. Neurology, 71*: 337-343.

COSENTINO, M., C. OLOMBO, M. MAURI, M. FERRARI, S. CORBETTA, F. MARINO, G. BONO and S. LECCHINI (2009): *Expression of apoptosis-related proteins and of mRNA for dopaminergic receptors in peripheral blood mononuclear cells from patients with Alzheimer disease. Alzheimer Dis. Assoc. Disord., 23*: 88-90.

DOTTO, G.P. (2000): p21(WAF1/Cip1): more than a break to the cell cycle? Biochim. Biophys. Acta, *1471*: M43–M56.

DJELIĆ, N., B. SPREMO-POTPAREVIĆ, V. BAJIĆ and D. DJELIĆ (2006): Sister chromatid exchange and micronuclei in human peripheral blood lymphocytes treated with thyroxine in vitro. Mutat. Res., *604*: 1-7.

ECKERT, A., C.W. COTMAN, R. ZERFASS, M. HENNERICI and W.E. MULLER (1998): *Lymphocytes as cell model to study apoptosis in Alzheimer's disease: vulnerability to programmed cell death appears to be altered. J. Neural. Transm. Suppl., 54*: 259-267.

ERIKSSON, P.S., E. PERFILIEVA, T. BJORK-ERIKSSON, A.M. ALBORN, C. NORDBORG, D.A. PETERSON and F.H. GAGE (1998): *Neurogenesis in the adult human hippocampus. Nat. Med., 4*: 1313-1317.

FAGGIOLI, F., J. VIJG and C. MONTAGNA *(*2011): *Chromosomal aneuploidy in the aging brain. Mech. Ageing Dev., 132*: 429-436.

FENECH, M. (2000): The in vitro micronucleus technique. Mutat. Res., *455*: 81-95.

FENECH, M. and J.W. CROTT (2002): Micronuclei, nucleoplasmic bridges and nuclear buds induced in folic acid deficient human lymphocytes-evidence for breakage-fusion-bridge cycles in the cytokinesis-block micronucleus assay. Mutat. Res*., 504*: 131-136.

FERRER, I. *(*2012): Defining Alzheimer as a common age-related neurodegenerative process not inevitably leading to dementia. *Prog. Neurobiol., 97*: 38-51.

FRANCO, S, M.A. BLASCO, S.L. SIEDLAK, P.L. HARRIS, P.I. MOREIRA, G. PERRY and M.A. SMITH *(*2006): *Telomeres and telomerase in Alzheimer's disease: epiphenomena or a new focus for therapeutic strategy? Alzheimer   s Dement., 2*: 164-168.

GASPARINI, L., M. RACCHI, G. BINETTI, M. TRABUCCHI, S.B. SOLERTE, D. ALKON, R. ETCHEBERRIGARAY, G. GIBSON, J. BLASS, R. PAOLETTI and S. GOVONI *(*1998): *Peripheral markers in testing pathophysiological hypotheses and diagnosing Alzheimer's disease. FASEB J., 12*: 17-34.

GELLER, L.N. and H. POTTER (1999): *Chromosome missegregation and trisomy 21 mosaicism in Alzheimer's disease. Neurobiol. Dis., 6*: 167-179.

GIBSON, G.E. and H.M. HUANG (2005): *Oxidative stress in Alzheimer's disease. Neurobiol. Aging,* Volume *26*: 575-578.

GIUNTA, B., A. RUSCIN, D. OBREGON, J. SALEMI, A. WOLFSON, F. FERNANDEZ and J. TAN (2010): The Central Role of T-Cell memory in Alzheimer's disease vaccination. Ageing Res., *2*: e5 http://www.pagepress.org/journals/index.php/ar/article/view/ar.2010.e5

GRANIC, A., J. PADMANABHAN, M. NORDEN and H. POTTER (2010): *Alzheimer Aβ peptide induces chromosome mis-segregation and aneuploidy, including trisomy 21: requirement for tau and APP. Mol. Biol. Cell,* 21*: 511-520.*

GRUNDKE-IQBAL, I., K. IQBAL, L. GEORGE, Y.C. TUNG, K.S. KIM and H.M. WISNIEWSKI (1989): *Amyloid protein and neurofibrillary tangles coexist in the same neuron in Alzheimer disease. PNAS, 86*: 2853-2857.

HARDY, J. (2006): *Has the amyloid cascade hypothesis for Alzheimer's disease been proved? Curr. Alzheimer Res., 3*: 71-73.

HENDRIE, H.C. (1998): Epidemiology of dementia and Alzheimer's disease. Am. J. Geriatr. Psychiatry, *6* (2 Suppl. 1): S3-S18.

HENEKA, M.T. and M.K. O'BANION (2007): Inflammatory processes in Alzheimer's disease. J. Neuroimmunol., *184*: 69-91.

HERNANDEZ-ORTEGA, K., P. FERRERA and C. ARIAS (2007): Sequential expression of cell-cycle regulators and Alzheimer's disease-related proteins in entorhinal cortex after hippocampal excitotoxic damage. J. Neurosci. Res*., 85*: 1744-1751.

HERRUP, K., R. NEVE, S.L. ACKERMAN and A. COPANI (2004): Divide and die: cell cycle events as triggers of nerve cell death. J. Neurosci., 24: 9232–9239.

HOCHSTRASSER, T., J. MARKSTEINER and C. HUMPEL (*2012):* Telomere length is age-dependent and reduced in monocytes of Alzheimer patients. Exp. Gerontol., *47: 160-163.*

HUMPEL, C. *(*2011): Identifying and validating biomarkers for Alzheimer's disease*. Trends Biotechnol., 29*: 26-32.

IARLORI, C., D. GAMBI, F. GAMBI, I. LUCCI, C. FELICIANI, M. SALVATORE and M. REALE (2005): Expression and production of two selected betachemokines in peripheral blood mononuclear cells from patients with Alzheimer's disease. Exp. Gerontol., *40*: 605-611.

KHANDELWAL, P.J., A.M. HERMAN and C.E. MOUSSA (2011): Inflammation in the early stages of neurodegenerative pathology. J. Neuroimmunol., *238:* 1-11.

KING, R.C. and W.D. STANSFIELD (1990): A Dictionary of Genetics (4th edition). Oxford University Press, New York.

KORMANN-BORTOLOTTO, M.H., M. DE ARRUDA CARDOSO SMITH and J. TONIOLO NETO (1993): *Alzheimer's disease and ageing: a chromosomal approach. Gerontology, 39*: 1-6.

KUERBITZ, S.J., B.S. PLUNKETT, W.V. WALSH and M.B. KASTAN (1992): *Wild-type p53 is a cell cycle checkpoint determinant following irradiation. PNAS, 89*: 7491-7495.

LUGARESI, A., A. DI IORIO, C. IARLORI, M. REALE, G. DE LUCA, E. SPARVIERI, A. MICHETTI, P. CONTI, D. GAMBI, G. ABATE and R. PAGANELLI (2004): IL-4 in vitro production is upregulated in Alzheimer's disease patients treated with acetylcholinesterase inhibitors. Exp. Gerontol., *39*: 653-657.

MAO, P. and P.H. REDDY (2011): Aging and amyloid beta-induced oxidative DNA damage and mitochondrial dysfunction in Alzheimer's disease: implications for early intervention and therapeutics. Biochim. Biophys. Acta, *1812*: 1359-1370.

MCSHEA, A., H,G. LEE, B.R. PETERSEN, G. CASADESUS, I. VINCENT, N.J. LINFORD, J.O. FUNK, R.A. SHAPIRO and M.A. SMITH (2007): Neuronal cell cycle re-entry mediates Alzheimer disease-type changes. Biochim. Biophys. Acta, *1772: 467-472.*

MEHES, K. and E.M. BUHLER (1995): Premature centromere division: a possible manifestation of chromosome instability. Am. J. Med. Genet., *56: 76-79.*

MIGLIORE, L., A. TESTA, R. SCARPATO, N. PAVESE, L. PETROZZI and U. BONUCCELLI (1997): Spontaneous and induced aneuploidy in peripheral blood lymphocytes of patients with Alzheimer's disease. Hum. Genet., *101*: 299-305.

MIGLIORE, L, N. BOTTO, R. SCARPATO, L. PETROZZI, G. CIPRIANI and U. BONUCELLI (1999): Preferential occurrence of chromosome 21 malsegregation in peripheral blood lymphocytes of Alzheimer's disease patients. Cytogenet. Cell Genet. *87*: 41-46.

MIGLIORE, L., I. FONTANA, F. TRIPPI, R. COLOGNATO, F. COPPEDE, G. TOGNONI, B. NUCCIARONE and G SICILIANO (2005): *Oxidative DNA damage in peripheral leukocytes of mild cognitive impairment and AD patients. Neurobiol. Aging, 26*: 567-573.

MIGLIORE, L., F. COPPEDÈ, M. FENECH, P. THOMAS (2011): Association of micronucleus frequency with neurodegenerative diseases. Mutagenesis, *26*: 85-92.

MOH C., J.Z. KUBIAK, V.P. BAJIC, X. ZHU, M.A. SMITH and H.G. LEE (2011): Cell cycle deregulation in the neurons of Alzheimer's disease. Results Probl. Cell Differ., *53*: 565-576.

MONDRAGON-RODRIGUEZ, S., G. BASURTO-ISLAS, H.G. LEE, G. PERRY, X. ZHU, R.J. CASTELLANI and M.A. SMITH (2010): Causes versus effects: the increasing complexities of Alzheimer's disease pathogenesis. Expert. Rev. Neurother.*, 10*: 683-691.

MOSCH, B., M. MORAWSKI, A. MITTAG, D. LENZ, A. TARNOK and T. ARENDT (2007): Aneuploidy and DNA replication in the normal human brain and Alzheimer's disease. J. Neurosci., 27, 6859-6867.

MOVERARE-SKRTIC, S., P. JOHANSSON, N. MATTSSON, O. HANSSON, A. WALLIN, J.O. JOHANSSON, H. ZETTERBERG, K. BLENNOW and J. SVENSSON (2012): Leukocyte telomere length (LTL) is reduced in stable mild cognitive impairment but low LTL is not associated with conversion to Alzheimer's disease: a pilot study. Exp. Gerontol.*, 47*: 179-182.

NUNOMURA, A., G. PERRY, G. ALIEV, K. HIRAI, A. TAKEDA, E.K. BALRAJ, P.K. JONES, H. GHANBARI, T. WATAYA, S. SHIMOHAMA, S. CHIBA, C.S. ATWOOD, R.B. PETERSEN and M.A. SMITH (2001): Oxidative damage is the earliest event in Alzheimer disease. J. Neuropathol. Exp. Neurol., 60: 759-767.

PALOTAS, A., J. KALMAN, M. PALOTAS, A. JUHASZ, Z. JANKA and B. PENKE *(*2002*)*: Fibroblasts and lymphocytes from Alzheimer patients are resistant to beta-amyloid-induced increase in the intracellular calcium concentration. Prog. Neuropsychopharmacol. Biol. Psychiatry*, 26*: 971-974.

PANOSSIAN, L.A., V.R. PORTER, H.F. VALENZUELA, X. ZHU, E. REBACK, D. MASTERMAN, J.L. CUMMINGS and R.B. EFFROS (2003): Telomere shortening in T cells correlates with Alzheimer's disease status. Neurobiol. Aging, *24*: 77-84.

PELLICANO, M., A. LARBI, D. GOLDECK, G. COLONNA-ROMANO, S. BUFFA, M. BULATI, G. RUBINO, F. IEMOLO, G. CANDORE, C. CARUSO, E. DERHOVANESSIAN and G. PAWELEC (2012): Immune profiling of Alzheimer patients. J. Neuroimmunol*., 242*: 52-59.

PETROZZI, L., C. LUCETTI, R. SCARPATO, G. GAMBACCINI, F. TRIPPI, S. BERNADINI, P. DEL DOTTO, L. MIGLIORE and U. BONUCCELLI (2002): Cytogenetic alterations in lymphocytes of Alzheimer's disease and Parkinson's patients. Neurol. Sci., *23* (Suppl 2): S97-S98.

SCHINDOWSKI, K., T. KRATZSCH, J. PETERS, B. STEINER, S. LEUTNER, N. TOUCHET, K. MAURER, C. CZECH, L. PRADIER, L. FROLICH, W.E. MULLER and A. ECKERT (2003): Impact of aging: Sporadic, and genetic risk factors on vulnerability to apoptosis in Alzheimer's disease. Neuromolecular Med., 4, 161-178.

SCHINDOWSKI, K., J. PETERS, C. GORRIZ, U. SCHRAMM, T. WEINANDI, S. LEUTNER, K. MAURER, L. FROLICH, W.E. MULLER and A. ECKERT (2006): Apoptosis of CD4+ T and natural killer cells in Alzheimer's disease. Pharmacopsychiatry, *39*, 220-228.

SCHINDOWSKI, K., A. ECKERT, J. PETERS, C. GORRIZ, U. SCHRAMM, T. WEINANDI, K. MAURER, L. FROLICH and W.E. MULLER (2007): Increased T-cell reactivity and elevated levels of CD8+ memory T-cells in Alzheimer's disease-patients and T-cell hyporeactivity in an Alzheimer's disease-mouse model: implications for immunotherapy. Neuromolecular Med., *9*: 340-354.

SELFRIDGE, J.E., E. LEZI, J. LU and R.H. SWERDLOW (2012): Role of mitochondrial homeostasis and dynamics in Alzheimer's disease. Neurobiol. Dis*., 51*: 3-12.

SHACKELFORD, R.E., W. K. KAUFMANN and R.S. PAULES *(*2000): Oxidative stress and cell cycle checkpoint function. Free Radic. Biol. Med., *28:* 1387-1404.

SHERRINGTON, R., E.I ROGAEV, Y. LIANG, E.A. ROGAEVA, G. LEVESQUE, M. IKEDA, H. CHI, C. LIN, G. LI, K. HOLMAN *et al*. (1995): Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease. Nature*, 375*: 754-760.

SMALL, S.A. and K. DUFF (2008): Linking Aβ and tau in late-onset Alzheimer's disease: a dual pathway hypothesis. Neuron, *60*: 534-542.

SPREMO-POTPAREVIC, B., L. ZIVKOVIC, N. DJELIC and V. BAJIC (2004): Analysis of premature centromere division (PCD) of the X chromosome in Alzheimer patients through the cell cycle. Exp. Gerontol*., 39*: 849-854.

SPREMO-POTPAREVIĆ B., L. ŽIVKOVIĆ, D. DRAKULIĆ, V. BAJIĆ and N. DJELIĆ (2006): Premature centromere division (PCD) of the X chromosome as a bio-marker of the brain cells re-entry into the cell division cycle in Alzheimer's disease. In: Frontiers in Alzheimer's Disease Research, Nova Science Publishers, Inc., New York. Editor E.M.Welsh. pp: 163-177.

SPREMO-POTPAREVIC, B., L. ZIVKOVIC, N. DJELIC, B. PLECAS-SOLAROVIC, M.A. SMITH and V. BAJIC *(*2008*)*: Premature centromere division of the X chromosome in neurons in Alzheimer's disease. J. Neurochem*., 106*: 2218-2223.

SPREMO-POTPAREVIC, B., L. ZIVKOVIC, B. PLECAS-SOLAROVIC and V.P. BAJIC (2011): Chromosome instability in Alzheimer's disease. Arch. Biol. Sci. *63*: 603–608.

STIELER, J.T., C. LEDERER, M.K. BRUCKNER, H. WOLF, M. HOLZER, H.J. GERTZ and T. ARENDT (2001): Impairment of mitogenic activation of peripheral blood lymphocytes in Alzheimer's disease. Neuroreport*, 12*: 3969-3672.

STIELER, J., R. GRIMES, D. WEBER, W. GARTNER, M. SABBAGH and T. ARENDT *(*2012): Multivariate analysis of differential lymphocyte cell cycle activity in Alzheimer's disease. Neurobiol. Aging, *33*: 234-241.

SWERDLOW, R and S.M. KHAN *(*2004): A "mitochondrial cascade hypothesis" for sporadic Alzheimer's disease. Med. Hypotheses, *63*: 8-20.

TACCONI, S., R. PERRI, E. BALESTRIERI, S. GRELLI, S. BERNARDINI, R. ANNICHIARICO, A. MASTINO, C. CALTAGIRONE and B. MACCHI (2004): Increased caspase activation in peripheral blood mononuclear cells of patients with Alzheimer's disease. Exp. Neurol*., 190*: 254-262.

TAGAMI, S., M. OKOCHI, A. FUKUMORI, J. JIANG, K. YANAGIDA, T. NAKAYAMA, T. MORIHARA, T. TANAKA, T. KUDO and M. TAKEDA (2008): Processes of beta-amyloid and intracellular cytoplasmic domain generation by presenilin/gamma-secretase. Neurodegener. Dis., *5*: 160–162.

TAN, M., S. WANG, J. SONG and J. JIA (2012): Combination of p53(ser15) and p21/p21(thr145) in peripheral blood lymphocytes as potential Alzheimer's disease biomarkers. Neurosci Lett., *516*: 226-231.

THOMAS, P. and *M.* FENECH *(*2007): A review of genome mutation and Alzheimer's disease. Mutagenesis*, 22*: 15-33.

THOMAS, P., J. HECKER, J. FAUNT and M. FENECH (2007): Buccal micronucleus cytome biomarkers may be associated with Alzheimer's disease. Mutagenesis, 22: 371-379.

THOMAS, P., N.J. O' CALLAGHAN and M. FENECH *(*2008): Telomere length in white blood cells, buccal cells and brain tissue and its variation with ageing and Alzheimer's disease. Mech. Ageing Dev*., 129*: 183-190.

TOGO, T., H. AKIYAMA, E. ISEKI, H. KONDO, K. IKEDA, M. KATO, T. ODA, K. TSUCHIYA and K KOSAKA (2002): Occurrence of T cells in the brain of Alzheimer's disease and other neurological diseases. J. Neuroimmunol., *124*: 83-92.

TOWN, T., J. TAN, R.A. FLAVELL and M. MULLAN (2005): T-cells in Alzheimer's disease. Neuromolecular Med., *7*: 255-264.

TRIPPI, F., N. BOTTO, R. SCARPATO, L. PETROZZI, U. BONUCELLI, S. LATORRACA, S. SORBI and L. MIGLIORE (2011): Spontaneous and induced chromosome damage in somatic cells of sporadic and familial Alzheimer's disease patients. Mutagenesis, *6*: 323-327.

UBERTI, D., T. CARSANA, E. BERNARDI, L. RODELLA, P. GRIGOLATO, C. LANNI *et al*. (2002): Selective impairment of p53-mediated cell death in fibroblasts from sporadic Alzheimer's disease patients. J. Cell Sci., *115*: 3131-3138.

UBERTI, D., C. LANNI, T. CARSANA, S. FRANCISCONI, C. MISSALE, M RACCHI, S. GOVONI and M. MEMO (2006): Identification of a mutant-like conformation of p53 in fibroblasts from sporadic Alzheimer's disease patients. Neurobiol. Aging, *27*: 1193-1201.

UBERTI, D., C. LANNI, M. RACCHI, S. GOVONI and M. MEMO (2008): Conformationally altered p53: a putative peripheral marker for Alzheimer's disease. Neurodegener. Dis*., 5*: 209-211.

YANG, Y. and K. HERRUP (2007): Cell division in the CNS: protective response or lethal event in post-mitotic neurons? Biochim. Biophys. Acta, *1772*: 457-466.

YUROV, Y.B., S.G. VORSANOVA and I.Y. IOUROV (2011): The DNA replication stress hypothesis of Alzheimer's disease. ScientificWorldJournal*, 11*: 2602-2612.

ŻEKANOWSKI, C. and U. WOJDA (2009): Aneuploidy, chromosomal missegregation, and cell cycle reentry in Alzheimer s disease. Acta Neurobiol. Exp., *69*: 232–253.

ZEKRY, D., F.R. HERRMANN, I. IRMINGER-FINGER, L. ORTOLAN, C. GENET, A.M. VITALE, J.P. MICHEL, G. GOLD and K.H. KRAUSE *(*2010): Telomere length is not predictive of dementia or MCI conversion in the oldest old. Neurobiol. Aging, *31*: 719-720.

ZHANG, J., Q. KONG, Z. ZHANG, P. GE, D. BA, W. HE (2003): Telomere dysfunction of lymphocytes in patients with Alzheimer disease. Cogn. Behav. Neurol*., 16*: 170-176.

ZHOU, X. and J. JIA (2010): P53-mediated G1/S checkpoint dysfunction in lymphocytes from Alzheimer's disease patients. Neurosci. Lett., *468*: 320-325.

ZIVKOVIC, L., B. SPREMO-POTPAREVIC, N. DJELIC and V. BAJIC (2006): Analysis of premature centromere division (PCD) of the chromosome 18 in peripheral blood lymphocytes in Alzheimer disease patients. Mech. Ageing Dev., *127*: 892–896.

ZIVKOVIC, L., B. SPREMO-POTPAREVIC, B. PLECAS-SOLAROVIC, N. DJELIC, G. OCIC, P. SMILJKOVIC, S.L. SIEDLAK, M.A. SMITH and V. BAJIC (2010): Premature centromere division of metaphase chromosomes in peripheral blood lymphocytes of Alzheimer's disease patients: relation to gender and age. J. Gerontol. A: Biol. Sci. Med. Sci., *65A*: 1269-1274.

ZIVKOVIC, L., V.P. BAJIC, D. ZUKOVEC, A. CABARKAPA and B. SPREMO-POTPAREVIC (2013a): Alterations of acrocentric chromosomes in peripheral blood lymphocytes in patients with Alzheimer`s disease. Arch. Biol. Sci., *65*: 439-445.

ZIVKOVIĆ, L., B. SPREMO-POTPAREVIĆ, S.L. SIEDLAK, G. PERRY, B. PLEĆAŠ-SOLAROVIĆ, Z. MILIĆEVIĆ and V.P. BAJIĆ (2013b): DNA damage in Alzheimer disease lymphocytes and its relation to premature centromere division. Neurodegener Dis., *12*: 156-163.

ZLOKOVIC, B.V. (2005): Neurovascular mechanisms of Alzheimer's neurodegeneration. Trends Neurosci*., 28*: 202-208.

CITOGENETIČKE PROMENE U PERIFERNIM ĆELIJAMA PACIJENATA SA ALCHAJMEROVOM BOLEŠĆU

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Izvod

Alchajmerova bolest (AB) je najučestaliji neurodegenerativni poremećaj starije populacije, praćen ireverzibilnim slabljenjem kognitivnih sposobnosti i demencijom. Kod 90% do 95% pacijenata bolest se javlja posle 65. godine života, kao sporadična forma (SAB). Uprkos istraživanjima koja traju više od jednog veka, etiologija i patogeneza, naročito SAB, nije objašnjena. Postoji nekoliko hipoteza o uzrocima neurodegeneracije kod AB; prema jednoj, glavni uzrok je genetska nestabilnost neurona određenih područja mozga i njihov ulazak u ponovni ćelijski ciklus, koji se posle određenog vremena rezultuje apoptozom. Iako AB prvenstveno oštećuje mozak, u literaturi su opisane brojne promene u perifernim tkivima ukazujući na to da je AB generalizovana sistemska bolest. One uključuju poremećaje ćeliskog ciklusa i hromozomsku nestabilnost, promene u proliferaciji i apoptozi, metabolizmu prekursora amiloidnog proteina i amiloidnog proteina β i brojnih drugih ćelijskih procesa. Ispitivanje lako dostupnih perifernih ćelija (ćelije krvi, fibroblasti kože, ćelije bukalne sluzokoža) ima značajnu ulogu u intenzivnoj potrazi za specifičnim i pouzdanim biomarkerima rane faze bolesti, tj., pre ispoljavanja kliničkih simptoma. U ovom radu ćemo sumirati naše i rezultate drugih autora koji se odnose na genetske, odnosno hromozomske poremećaje perifernih ćelija AB pacijenata i razmotrićemo njihovu moguću ulogu u patogenezi bolesti, kao i značaj daljih istraživanja u tom pravcu.