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Impaired mitochondrial energy production and ABC transporter function – a crucial interconnection in dementing proteopathies of the brain

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Abstract

Ageing is the main risk factor for the development of dementing neurodegenerative diseases (NDs) and it is accompanied by the accumulation of variations in mitochondrial DNA. The resulting tissue-specific alterations in ATP production and availability cause deteriorations of cerebral clearance mechanisms that are important for the removal of toxic peptides and its aggregates. ABC transporters were shown to be the most important exporter superfamily for toxic peptides, e.g. -amyloid and -synuclein. Their activity is highly dependent on the availability of ATP and forms a directed energy-exporter network, linking decreased mitochondrial function with highly impaired ABC transporter activity and disease progression. In this paper, we describe a network based on interactions between ageing, energy metabolism, regeneration, accumulation of toxic peptides and the development of proteopathies of the brain with a focus on Alzheimer's disease (AD). Additionally, we provide new experimental evidence for interactions within this network in regenerative processes in AD.

Keywords

ageing; ABC transporters; mitochondria; Alzheimer's disease; Parkinson's disease; energy metabolism; dementia; neurodegeneration; ABCB1; ABCC1; ABCA7; ABCA1; Aqp4

Introduction

Neurodegenerative diseases (NDs) and dementias in particular have become a serious and global challenge. In 2010, an estimated number of 35 million people suffered from dementia. According to the most recent dementia report from the World Health Organization, the world population aged 60 years and older will reach 2 billion by the year

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2050 (WHO, 2012). Because of the ageing Western and Asian societies, the prevalence of NDs is rising continuously, because age is still the main and only risk factor thus far widely acknowledged. In addition to the physiological and psychological burden for the affected and their relatives, a high economic burden, with worldwide expenses of US\$604 billion, was estimated in 2010 (WHO, 2012). Therefore, the rapid development of novel strategies is critical to match the increasing prevalence of these disorders. The pathogenesis of most NDs is commonly hallmarked by the accumulation of insoluble neurotoxic peptides, e.g. - amyloid (A β) in Alzheimer's disease (AD) or -synuclein (α -Syn) in Parkinson's disease (PD) and Dementia with Lewy-bodies (DLB), and a consequent decline of neuronal and synaptic function (Johnson, 2000). Although these peptides are physiologically produced during the whole life and have distinct functions in the brain, their concentration gradually reaches toxic levels in specific brain regions of the elderly, leading to specific clinical disease hallmarks. In sporadic cases, the distinct localizations do not indicate localized overproduction, but rather insufficiencies in clearance processes such as degradation by proteases, proteasomes and/or autophagy or active export across the blood-brain barrier and the perivascular drainage channels (Mawuenyega et al., 2010; Pahnke et al., 2009b). Since the precise mechanisms underlying the accumulation of harmful levels of soluble peptides/ oligomers and non-soluble aggregates in the brain remain are still unknown, current treatment strategies focus on proposed pathogenesis-related markers, such as peptide production by cleavage enzymes from precursor proteins, peptide deposits and neuronal functional deficiencies (Selkoe, 2001). However, neither of these strategies (e.g. active or passive immunization, and secretase inhibition in AD) could accomplish sufficient clinical effects to be introduced in routine treatment. Most of the studies were halted in early phases (e.g. phase 2 trial of bapineuzumab), or even late in phase 3 (e.g. phase 3 trials of solanezumab, a mixture of two humanized anti-A β -monoclonal antibodies) due to the lack of observed benefit for the patients (Imbimbo et al., 2012; Salloway et al., 2009). Hence, a desperate need has driven the search for new approaches apart from the current 'overproduction and aggregation' hypotheses.

New strategies may aim toward *i*) normalization of the soluble peptide equilibrium/flow between brain tissue and vasculature/serum and simultaneously, and *ii*) the replacement of the lost or impaired neurons. The removal of insoluble aggregates from the brain was thought to be a promising strategy, especially because A β plaques have been recognized as one of the first histological applicable structures during neurodegeneration in AD (Alzheimer, 1907). However currently, the opinions have changed tremendously: the most toxic effect on neurons is assumed to be facilitated by small peptide-oligomers, rather than by large fibrillar species (reviewed in (Pahnke et al., 2009b)). Mechanisms influencing their clearance from the brain are widely accepted as new targets for fighting NDs. In this context, two major brain barriers have recently been in the focus of research. A accumulation in the epithelial cells of the choroid plexus and in cerebrovascular walls has been correlated with disruption and dysfunction in the blood-cerebrospinal fluid barrier (BCSFB) as well as in the blood-brain barrier (BBB) (Liu, 1991). Both barriers regulate the exchange of toxic peptides, compounds and metabolites by the specificity of their cellular structures. Beside structural specificity of cells, drainage of small molecules to the blood, e.g. A β , is age-dependent and correlates with changes in capillary density (Hawkes et al., 2011).

The BCSFB is defined by having a fenestrated basal membrane and highly a specialized choroid plexus epithelial layer, which are located in the ventricles. The capillary BBB is a structure composed of a monolayer of brain endothelial cells and encompasses pericytes and astrocytes' endfeet separated from the capillary endothelium by a tight basal lamina. It is unique in that it lacks fenestration and the presence of tight junctions, which support the maintenance of the brain's microenvironment (reviewed in (Pahnke et al., 2009b; Zlokovic,

2008)). Tight junctions are located between the endothelia and allow only small, nonpolar molecules to passively diffuse through the barrier (Pardridge, 1999). The active transport of nutrients to the brain and the efflux of toxic compounds via the BCSFB and BBB are facilitated by specified membrane receptors and transporters (Weiss et al., 2009). Many of these membrane transporter proteins are encoded by a superfamily of genes that can be found in both prokaryotes and eukaryotes: the ATP-binding-cassette (ABC) transporters (Saurin et al., 1999).

Together, 49 human ABC transporters are known and they are divided into seven subfamilies (ABCA to ABCG). They are characterized by having broad substrate specificity and two conserved ATP-binding sites that generate the energy needed for transport processes. Most human ABC transporters are expressed in a strict pattern of polarization, which leads to an asymmetrical arrangement, not only at barriers of the brain, and ensures a very restricted influx of substrates through the blood-brain barrier (Pahnke et al., 2009b; Pahnke et al., 2008). Consequently, ABC transporters have been identified as a crucial protein superfamily representing potential targets in the prevention and treatment of various diseases. They share responsibility for development of multidrug resistance in cancer and of cerebral proteopathies (reviewed in (Bartels et al., 2009; Kanwar et al., 2012)).

Neurodegeneration is defined by the reduction or even total loss of distinct groups of neurons in specified locations that lead to specific clinical symptoms, e.g. short-term memory deficits in mild cognitive impairment (MCI)/AD, motor and cognitive deficits in DLB and PD. Hence, the continuous energy-dependent renewal and reconstruction of the neuronal network is crucial to maintain normal function. It is widely acknowledged that alterations in the mitochondrial genome occur during the ageing process, which is referred to as ‘the free radical theory of aging’, and which have also been found in NDs (reviewed in (Coskun et al., 2012; Harman, 2003; Lin and Beal, 2006; Wallace, 1992)). Regenerative mechanisms are insufficient or become insufficient during age progression and disease development. We hypothesize that the dysfunction of mitochondria that leads to alterations in ATP production has an important impact on active transport at the BBB and BCSFB. This article summarizes recent literature describing various energy-dependent mechanisms involving ABC transporters and highlights how these findings support the hypothesis that each of these contributes to the pathogenesis of age-related NDs with a focus on AD as the most common cause of neurodegeneration and dementia.

ABC transporter function in ageing-related diseases

Barriers of the brain provide effective protection against the influx of harmful and dangerous substances from the blood. However, substances and metabolites produced in the brain must also cross these barriers to reach the circulatory system. Both directions of active transport are tightly regulated and facilitated by specific transport molecules. Unfortunately, the brain lacks a lymphatic circulation that could support gross clearance processes. Thus, the metabolites/substances have to fulfill specific requirements related to their size and charge to be excreted or imported by the transporters. If these requirements are not met, bioavailability in the brain is low or accumulation in the brain tissue may occur. This not only accounts for small molecules, but also for peptides that are produced at physiologic levels in the brain throughout the whole life, e.g. A .

Several studies have described an association between decreased ABC transporter activity and increased incidence of neurodegenerative disease, showing that these transporters are important for the export of toxic peptide species from the brain. One of the first *in vivo* pieces of evidence was provided by Bartels and colleagues in an investigation of ABC transporter function in patients with neurodegenerative syndromes: PD, progressive

supranuclear palsy (PSP), and multi-system atrophy (MSA), which are characterized by accumulation of α -Syn or Tau (Bartels et al., 2008b). These disorders were examined by positron-emission tomography (PET) using an ABC transporter-specific probe, [^{11}C]-verapamil, that is exported exclusively by ABCB1 (Bartels et al., 2008b). They demonstrated a specific accumulation of the radio-probe in brain regions where these diseases primarily start, e.g. Substantia nigra in PD, and described a decrease of ABCB1 function precisely in these locations. Moreover, using Parkinson's patients with frontal basal brain involvement, mimicking DLB, these regions were also noted to accumulate [^{11}C]-verapamil. This method was applied to the third disease with α -Syn accumulation, MSA, that primarily affects central basal ganglia to detect this primary pathogenic locus. Assema and colleagues gathered similar results for AD. They showed decreased ABCB1 function in AD patients with mild to moderate disease status using [^{11}C]-verapamil PET (Assema et al., 2012). Reduced binding potential values were also found in brain regions affected late in AD, such as the occipital cortex, but not in unrelated areas.

Does an impairment of ABC transporters in distinct brain regions lead to a disturbed detoxification of these areas, which results in the development of toxic peptide aggregates (Bartels et al., 2008a; Pahnke et al., 2009a)?

Mawuenyega and colleagues proved an impairment of the detoxification mechanisms/or processes by measuring both the production of $\text{A}_{40}/\text{A}_{42}$ and the clearance rates from the CNS of elderly patients suffering from AD and age-matched controls. They showed that the clearance rates of A_{40} and A_{42} were impaired in the affected group, as compared to rates of the control group. In fact, A_{42} clearance rates decreased by approximately 30% in the AD group and, thus, the authors considered inhibition/reduction of clearance rates to be essential in the development of AD (Mawuenyega et al., 2010). Recent investigations by our group have revealed a mechanism that may underlie the effects found by Mawuenyega *et al.* (Krohn et al., 2011). We observed that decreased ABC transporter function of ABCB1 and ABCC1 leads to a highly increased accumulation and aggregation of A_{42} *in vivo*. Investigations of ABCC1-deficient mice illustrated that the accumulation of A_{42} is 12- to 14-fold higher than in non-deficient control animals (Krohn et al., 2011). Using a mathematical model, we were also able to show that a decline of export function by only 11% accounts for a 4-fold increase of A_{42} in the brain of mice. In keeping with these observations, we hypothesized that a chronic decline of export activity of ABCC1 and ABCB1 caused by nutrition and drugs can lead to a reduction of continuous removal of toxic peptide species (Krohn et al., 2011; Pahnke et al., 2009b).

Furthermore, Cirrito *et al.* showed a decreased clearance of [^{125}I] A_{40} and [^{125}I] A_{42} microinjected into the CNS of ABCB1-deficient mice, and increased A_{42} levels within the brain interstitial fluid after APP-transgenic mice were dosed with an ABCB1 inhibitor (Cirrito et al., 2005). Consistently, Hartz *et al.* demonstrated a reduced ABCB1 expression and transport activity *ex vivo* in brain capillaries as compared with wild-type controls. Additionally, they showed that compared to control mice, brain A_{42} levels were significantly reduced after the restoration of ABCB1 expression and transport activity in brain capillaries (Hartz et al., 2010). This data further supports our hypothesis that reduced ABC transporter function in AD is a cause rather than a consequence of A_{42} accumulation. Very recently, one important piece was added to the puzzle: how A_{42} arrives at the vessels and perivascular drainage channels (PVDC) to be excreted by ABC transporters. Iliff and colleagues revealed that a substantial amount of A_{42} is transported by an intercellular 'water flow' that is driven by aquaporin-4 water channels (Iliff et al., 2012). Aquaporin-4 is expressed highly polarized in perivascular endfeet of astrocytes and is proposed to facilitate various functions in maintaining convective currents that drive the clearance of interstitial solutes from the brain parenchyma to the CSF (Iliff et al., 2012; Noell et al., 2012). Because ABC transporters

(esp. ABCA1) are also highly expressed at the choroid plexus (CP), both mechanisms may contribute to the establishment a constant physiological route for A β drainage. Other ABC transporters that interact with Apolipoprotein E variants (ABCA1) (Fitz et al., 2012) and membrane receptors such as LRP1/RAGE (low-density lipoprotein receptor-related protein/receptor for advanced glycation end products) (Deane et al., 2003; Shibata et al., 2000) may also contribute to the 'A β excretion highway'.

ABC transporters in general play a key role in the pathology and treatment of several diseases, and therefore, are denoted as 'multidrug-resistance transporters'. More importantly, drugs and their metabolites are able to modulate the binding affinity for substrates that often results in a change in their transport kinetics. Several drugs that are prescribed to reduce blood pressure (α -blockers, calcium-antagonists) are known to decrease ABC transporter function (reviewed in (Schinkel and Jonker, 2003) and (Lee, 2010)). In this context, it would be interesting to evaluate the risk for ND in patients being treated with such drugs. To our knowledge, this has not yet been done. With advancing age, such drugs and age-related, structural changes in the vasculature (media thickening, lipid storage, and calcifications) could lead to an impaired clearance of toxic peptides from the brain. Lipid metabolism seems to play an important role in the development of AD. ABCA1, ABCA2, and ABCA7 are representatives of the A-subfamily of ABC transporters that mediate the transport of a broad range of physiologic lipid compounds across membrane barriers, including the BBB (reviewed in (Piehler et al., 2012)). Their effects on the development of AD, however, as well as their modes of interaction differ. ABCA1 is highly expressed in neurons, microglia, astrocytes, and oligodendrocytes and also found in brain capillary endothelial cells (Kim et al., 2006; Koldamova et al., 2003; Panzenboeck et al., 2002). Studies have shown that ABCA1 enhances amyloid formation indirectly via facilitation of apoE lipidation; specifically, the binding of apoE-lipid particles with A β facilitates the cellular uptake and clearance of A β via the ApoE-receptor LRP1 (Bell et al., 2007; Hirsch-Reinshagen et al., 2009; Hirsch-Reinshagen et al., 2007; Wahrle et al., 2008). Fitz and colleagues recently showed that the human ApoE4 gene A β deposition and, consequently, cognitive impairment are exacerbated in ABCA1-deficient mice (Fitz et al., 2012). In animals, the loss of one ABCA1 allele seems to be compensated with the ApoE3 gene. With regard to this knowledge, further research is necessary to examine interactions between the ABCA1 and ApoE isoforms. Current opinions suggest that ABCA1 acts as a suppressor of A β production and deposition. Recent experiments involving ABCA1 and liver X receptor agonists have shown promising, anti-amyloidogenic effects and, thus, highlight the importance of ABCA1 as a drug target (Koldamova et al., 2003).

Other members of the A-family, e.g. ABCA2 and ABCA7, also affect A β production *per se*. ABCA2 depletion leads to a shift from α - to β -secretase dependent cleavage of APP, resulting in increased levels of APPs β and a decrease in APPs α production (Davis, 2010; Michaki et al., 2012). ABCA7 prevents A β accumulation by inhibiting A β production and promoting Fc γ -receptor-independent phagocytosis (Bacskai et al., 2002; Chan et al., 2008). ABCA7 transporters are highly expressed in microglia and play an active role in the phagocytic uptake of debris and plaques generated in NDs (Bacskai et al., 2002; Das et al., 2003; Kim et al., 2006; Stolzing and Grune, 2004).

Several genome-wide association studies (GWASs) found associations between the A-subfamily of ABC transporters and AD in large cohorts (Hollingworth et al., 2011; Naj et al., 2011). For example, variants of ABCA7 were identified in several joint- and meta-analyses positively correlated with an increased risk for AD. Allen and colleagues revealed a correspondence between small nucleotide polymorphisms (SNPs) and an increased expression of ABCA7 and Apolipoprotein J, which is associated with cell debris and apoptosis (Allen et al., 2012). Both proteins, ABCA7 and Apolipoprotein J, are proposed to

have protective effects. Further analyses of SNPs in ABCA2, with regard to the development of AD, were ethnicity-dependent and thus not conclusive (Wollmer et al., 2006). Reviewing the results of the previous investigations, the use of ABC transporters as diagnostic markers seems promising, but has to be confirmed in further studies. The previous GWASs examined only specific haplotypes. As a consequence of the promising results from molecular and GWASs, whole-exon-sequencing, including the promoter and regulatory regions, will be of high interest in the near future.

Impact of mitochondrial alterations on ageing and neurodegeneration

The fact that the central nervous system already consumes 20% of the bodies' energy indicates not only that mitochondria play an essential role in the maintenance of neuronal and synaptic function, but also in important cell signaling pathways (Di Filippo et al., 2010). In addition to their role in ATP production, these organelles are highly important for Ca^{2+} homeostasis, apoptosis, synthesis of iron-sulfur clusters, and steroids (reviewed in (Martin, 2012)). They have also been investigated for their contribution to ageing. A widely acknowledged hypothesis implies a causative role of accumulated mitochondrial DNA (mtDNA) mutations acquired during life and the resulting excessive production of reactive oxygen species (ROS) in the pathogenesis of NDs, like AD and PD (reviewed in (Harman, 2003; Lin and Beal, 2006; Wallace, 2005, 2011). ROS production occurs endogenously as a natural process during oxidative phosphorylation and is normally compensated for by the presence of antioxidants, including glutathione, carotenoids, and antioxidant enzymes (reviewed in (Naik and Dixit, 2011)). The hypothesis further states that the produced ROS mainly targets mitochondria and cause further damage to the cells and mitochondria itself. Since mitochondrial DNA is not protected by histones, ROS leads to mutations in the mitochondrial genome and can promote mitochondrial dysfunction even more (Keil et al., 2004). The vicious cycle thus created leads to cellular dysfunction and altered ATP production. In PD, it has been recognized for many years that mitochondrial changes are correlated with pathogenesis. In cells of the affected regions (e.g. *Substantia nigra pars compacta*), complex I activity of the mitochondrial respiratory chain were reduced and inhibitors of this complex, like the toxin 1,2,3,6-methyl-phenyl-tetrahydropyridine (MPTP), caused damage to disease-related (dopaminergic) neurons in an animal model (reviewed in (Martin, 2012; Olanow and Tatton, 1999)).

The first experimental evidence supporting the hypothesis that mutated mtDNA contributes to deleterious neurodegenerative effects during the process of ageing was presented by Trifunovic and colleagues in 2004 using a knock-in mouse model with a mutated mtDNA-polymerase A (Trifunovic et al., 2004). Because of a deficiency in the proof-reading function, the number of mtDNA mutations increased, resulting in a decreased life span for these mice due to the early onset of various ageing-related phenotypes. Several subsequent studies revealed that mitochondrial dysfunction is, at least in part, also a consequence of pathological changes occurring during neurodegeneration. With regard to AD, A β was shown to influence key enzymes, inhibit respiration, and cause imbalances in mitochondrial function, e.g. cytochrome c oxidase (COX), α -ketoglutarate dehydrogenase and pyruvate dehydrogenase (Casley et al., 2002; Crouch et al., 2005; Devi et al., 2006; Hernandez-Zimbron et al., 2012; Manczak et al., 2006; Rui et al., 2006). Until now, knowledge of this interaction has permitted only a few distinct statements to be made, because of the complexity of the relationships between energy-producing enzymes. For example, on one hand A β was recognized to induce inhibition of cytochrome c oxidase by binding the amino-terminal region of subunit one of the enzyme (Hernandez-Zimbron et al., 2012) or directly induce cytochrome c oxidase release and mitochondrial swelling in neurons followed by activation of caspase-3, finally leading to apoptotic death (Kim et al., 2002). On the other hand, cytochrome c oxidase-deficiency itself resulted in decreased ROS production and

increased amyloid burden in an animal model, while the expression of the amyloid precursor protein (APP) remained unchanged. These conflicting data points prevented researchers from drawing the conclusion that COX impairment plays an initiative role in the disease development and is an indicator for a potential disturbance in APP processing (Fukui et al., 2007). Thus, the role of cytochrome c oxidase in the pathology of NDs remains elusive.

Several other examples regarding the influence of A β on mitochondrial key enzymes have been identified. The A β -binding alcohol dehydrogenase (ABAD) is located in neuronal mitochondria and is involved in mitochondrial functional alterations during neurodegeneration. ABAD binds A β and, thereby, causes mitochondrial dysfunction (Lustbader et al., 2004; Takuma et al., 2005). Inhibition of this interaction leads to reduced A β accumulation and improved mitochondrial function (Yao et al., 2011). Other groups reported that A β directly participated in mitochondrial processes like NO and ATP production. A β mediates increased NO levels that lead to a reversible inhibition of cytochrome c oxidase and, in turn, to decreased ATP levels. If NO persists at high levels, RNS (reactive nitrogen species) are generated that may irreversibly inactivate respiratory chain complexes and ATP synthase (Keil et al., 2004; Radi et al., 2002). Further evidence for the mitochondrial link in α -synucleinopathies was recently presented by Rhinn and colleagues, who described a specific transcript variant of Syn, referred to as SynL, which showed a shift in the preferred accumulation site from synaptic terminals towards mitochondria. These observations, consistent with PD pathology, were supported by the increase of SynL transcript expression in the presence of PD risk factors like age, toxin exposure and genetic variants of Syn, indicating a possible role in the initiation of the disease pathology (Rhinn et al., 2012).

Even though direct toxic effects of neurodegeneration-related peptides on mitochondria that lead to dysfunction in complexes of the respiratory chain have been demonstrated several times, indicating that mtDNA mutations may not play an initial role in the development of NDs, this important issue remains highly controversial. Recent data acquired using AD mice show that higher ATP levels caused by polymorphic mtDNA is accompanied by lower A β plaque number and size, as well as lower soluble A β levels (Scheffler et al., 2012). Additionally, evidence exists that these alterations increase the phagocytic activity of microglia. An ageing-related switch of microglial function from neuroprotective to neurotoxic was observed in a mouse model of AD, demonstrating an age-dependent release of cytotoxic factors (e.g. TNF α) that is followed by an increase in neuronal death (Jimenez et al., 2008).

According to the observed alterations in mitochondrial function, we hypothesize that variations in ATP levels have a great impact on the progression of NDs. Reasons may include the revealed connection between mtDNA mutations and alterations in microglial phenotype, but more likely involve the critical role of ATP in various vital mechanisms for peptide degradation/efflux, e.g. the ubiquitin proteasome complex. The main function of the ubiquitin proteasome complex is the degradation of aggregated or misfolded macromolecules. Consequences of its dysfunction were shown in the context of PD. Parkin (part of the ubiquitin proteasome complex)-knock-out mice showed a loss of function in dopaminergic neurons in the striatum and a decrease in expression levels of proteins involved in the mitochondrial oxidative phosphorylation and, thereby, respiration. These accumulated changes lead to a further decrease in ATP levels (reviewed in (Martin, 2012)).

Furthermore, proteases for A β degradation, e.g. the insulin-degrading enzyme (IDE) or Neprilysin (NEP), are influenced by fluctuations in the ATP levels. Although findings using IDE could thus far only confirm an increase in small peptide degradation upon an increase

of ATP production (Song et al., 2004), an evaluation of the effects on A β monomers degradation remains elusive.

Yet another important mechanism for peptide removal, which highly depends on the availability of ATP, is active transport across the blood-brain barrier by ABC transporters. As described above, these transporters facilitate peptide efflux, and this activity has a strong therapeutic relevance. While decreased ATP levels reduced transporter activity and accumulation of toxic A β (Scheffler et al., 2012), the pharmaceutical increase of transporter activity was accompanied by lower plaque burden, plaque number and size in a mouse model of AD (Krohn et al., 2011). Neuroregeneration provided by neuronal stem/progenitor cells (NSPCs) was decreased in mice due to the loss of specific ABC transporter function (Schumacher et al., 2012) and, thereby, could be determined to be highly dependent on ATP availability, too.

ABC transporter function in neuroregeneration

While the involvement of ABC transporter dysfunction in AD has been recently demonstrated (Krohn et al., 2011), previous studies had previously indicated that ABC transporters might also participate in neuroregenerative processes because they were found to be abundantly and transiently expressed in neurosphere-forming stem and progenitor cells (NSPCs). In those studies, robust expression rates of ABCB1 and ABCG2 were reported and the high abundance of these transporters was noted to decrease during lineage commitment (Islam et al., 2005a; Islam et al., 2005b). Both ABCB1 and ABCG2 were proposed to play a functional role in maintaining the stem cell status (Lin et al., 2006). Accordingly, our most recent study on the role of ABC transporters in neuroregeneration demonstrated how ABC transporter dysfunction contributed to adult neuroregeneration in mice (Schumacher et al., 2012). Interestingly, the impairments in neuroregeneration seem not to be related to cell-intrinsic dysfunctions of NSPCs, since *in vitro* experiments on proliferation and differentiation capacity did not reveal significant impairments as a result of ABC transporter-deficiency. Instead, the data suggested that the loss of ABC transporter function alters the export kinetics at both the blood-brain and cerebrospinal fluid- brain barriers and, thereby, might significantly compromise the homeostasis of the brain's stem cell niche.

The concept that a so-called stem cell niche is a specific extracellular compartment that enables stem cells to maintain their undifferentiated and proliferating state was introduced in the late 1970's (Schofield, 1978). Since then, researchers identified this niche in various tissue types in various organisms (Li and Xie, 2005). All stem cell niches thus far studied share a variety of anatomical features, such as diffusible signaling molecules and cell-to-cell and cell-to-extracellular matrix interactions, which allow the maintenance of the specific microenvironment needed for maintaining the stem cell pool. A common feature of these niches is that they always have a close interaction with the vasculature. The vasculature not only provides a scaffold for stem cell migration (Palmer et al., 2000), but also facilitates the local and long distance transport of signaling molecules (Jones and Wagers, 2008). Even signaling pathways like Notch 1, which is mostly responsible for local signaling between neighboring cells using the ligands Delta and Jagged, are to a certain degree interacting via diffusible ligands. It has been shown that diffusible components of the extracellular matrix can also activate the Notch pathway via α -integrin receptors (Campos et al., 2006).

Keeping in mind that ABC transporters convey many biological and metabolic substrates, (Ferreira and Sa-Nogueira, 2010; Gisin et al., 2010; Linton, 2007) while distinct cell types (e.g. endothelial cells) are able to release soluble factors that directly affect NSPC functions (Shen et al., 2004), we postulate that loss of ABC transporter function could severely change the brain's homeostasis, leading to the observed results. Data from further regeneration-

inducing experiments support this hypothesis and show strong implications for the importance of ABC transporters in maintaining the homeostasis of the stem cell niche. The location of the stem cell niche between the vascular and the ventricular system indicates that impairments in ABC transporter-mediated export of metabolites could directly affect NSPC fate. NSPCs may even interact with both systems (Shen et al., 2008), and the assumption that NSPC fate depends on ABC transporter functions is theoretically valid. In the absence of specific ABC transporters, distinct metabolites could reach functional or even toxic concentrations within the stem cell niche and, thereby, affect NSPC maturation. Additionally, many natural and pharmacological ABC transporter ligands are known to alter ABC transport kinetics (Lee, 2010; Shukla et al., 2008). Thus, these ligands could easily contribute to altered neuroregeneration, which is relevant at advanced ages or during chronic medication.

Neuroregeneration in AD mouse models depends on ABC transporter expression

ABC transporters have been recently acknowledged to play a prominent role in A β clearance across barriers of the brain (Cirrito et al., 2005; Koldamova et al., 2005; Krohn et al., 2011; Rodriguez-Rodriguez et al., 2007; Vogelgesang et al., 2004) and in regular stem cell differentiation and neuroregeneration (Islam et al., 2005a; Schumacher et al., 2012). It is of great importance to understand how alterations in ABC transporter function contribute to peptide clearance and also to altered neuroregeneration during the pathogenesis of AD.

A β peptides are mostly deemed to be neurotoxic in low molecular weight oligomeric states (Cleary et al., 2005; Lacor et al., 2004), but evidence also exists that they can have a neuroprotective role. Whereas the ability of A β ₁₋₂₈ monomers to enhance survival of hippocampal neurons *in vitro* was first observed more than a decade ago (Whitson et al., 1989), other A β species have recently been demonstrated to have some neuroprotective traits when present in their monomeric form. A β ₁₋₄₂ monomers were shown to rescue developing neurons, even under trophic-factor deprivation. The IGF-1 pathway is seemingly required for the A β 's neuroprotective effect, because A β was able to phosphorylate IRS-1 (insulin receptor substrate 1) (Giuffrida et al., 2009) and locally induce insulin production (Townsend et al., 2007) or bind the insulin receptor directly (Xie et al., 2002). Evidence for a direct function in neural stem cell differentiation has also been presented. The two amyloidogenic A β species, A β ₁₋₄₀ and A β ₁₋₄₂, thus contrarily affect the differentiation fate of NSPCs. While A β ₁₋₄₀ promotes pro-neuronal NSPC differentiation, A β ₁₋₄₂ has the opposite effect, leading towards promoting astroglial differentiation. In contrast to A β ₁₋₄₂, which seemed to act directly on the NSPCs, A β ₁₋₄₀ appeared to indirectly support the progenial differentiation by inducing cytokine release in active astrocytes, which are toxic to developing neurons and inhibit axonal growth (Chen and Dong, 2009).

Nonetheless, the toxic effects of A β deposition during AD pathogenesis still outweigh its possible minor positive effects toward neuroregeneration.

Studies on neuroregeneration during AD pathogenesis are mostly based on animal models, examining A β deposition by the use of mutated human APP, with or without additional presenilin transgenes, as well as the activity of different promoters driving their expression. Therefore, the observed effects on neurogenic functions differ substantially. While some studies suggest that in general neurogenesis increased (Jin et al., 2004), at least at distinct time points (Ermini et al., 2008), most studies reported impairing effects on neuroregeneration (Feng et al., 2001; Haughey et al., 2002a; Haughey et al., 2002b).

In the next section, we highlight as-yet unpublished information using the combined Thy1-APPKM670/671NL - Thy1-PS1L166P (APP/PPS1) amyloidosis mouse model (Radde et al., 2006). While A β deposition leads to a robust increase in neuroregenerative function in transgenic mice in comparison to non-transgenic littermates, the pro-neurogenic effect is strongly influenced by ABC transporter expression (Figure 1), which fits with the knowledge that this expression strongly influences the equilibrium of soluble and aggregated forms of A β (Krohn et al., 2011). Comparative data on the neuroregenerative capacity of ABC transporter-deficient and control mice were recently published (Schumacher et al., 2012). The data imply that dysfunctions in ABC transporters may affect neuroregeneration at least at two different levels: *i*) impairment of the microenvironment in the stem cell niche, and *ii*) shift in the concentration and composition of different A β species/aggregates that specifically influence NSPC maturation. The latter is particularly supported by the presented datasets (Figure 1), which show that loss of ABC transporter function not only increases the concentration of intracerebral A β species, but also triggers adult neuronal differentiation. The effect of A β on neurogenesis does not seem to be altered simply in an A β concentration-dependent manner; compared to their non-transgenic counterparts, neurogenesis was most significantly increased in APP/PS1xABCG2^{0/0} mice. A β levels in those mice were comparable to APP/PS1 controls, but APP/PS1 mice showed much significantly lower A β - deposition levels as compared to ABCC1^{0/0} transgenic mice. Both showed comparable levels of neurogenesis induction compared to their respective non-transgenic controls (see also (Krohn et al., 2011)). At the age analyzed for neurogenesis, quantification of soluble and insoluble A β revealed decreased concentrations of soluble A β_{42} in ABCG2^{0/0} transgenic mice as compared to ABCC1^{0/0} and control transgenic mice, while the insoluble A β_{42} concentration was between that of the ABCC1^{0/0} and the control AD mice (see also (Krohn et al., 2011)). These subtle ratio differences of soluble and insoluble A β suggest that A β in distinct states of oligomerization displays different binding affinities to the analyzed ABC transporters and NSPCs. Where distinct transporters are lacking, alterations in the overall concentration of intracortical A β as well as the homeostasis of oligomeric states of the β -amyloids may occur, leading to the observed effects on adult neurogenesis.

Interestingly, precisely the same ABC transporters that are known to clear A β peptides across cellular membranes are also expressed in NSPCs. How do dysfunctions of these transporters contribute to the cytotoxic effects of oligomeric A β species on NSPCs *in vitro*? Various protocols have been established to generate solutions containing distinct A β oligomer species (Dahlgren et al., 2002). Studies with these species have revealed different traits, mostly concerning their respective level of cytotoxicity, but also their potential influence on stem cell functions (Dahlgren et al., 2002; Shruster et al., 2011). Most researchers have used the original A β preparation protocol of Dahlgren *et al.*, but their results are not easily comparable. Oligomeric A β_{42} was shown to impair neuronal differentiation in neural stem cells at low micromolar concentrations by one study (Chen and Dong, 2009), but the opposite effect was demonstrated by others (Heo et al., 2007; Shruster et al., 2011). With regard to the different effects of distinct oligomeric A β species (Shruster et al., 2011), minor and involuntary changes in the A β preparation protocol could lead to unpredictable changes in the configuration of the comprising A β oligomer species and, thereby, lead to the conflicting results. Similarly, our experiments using control and ABC transporter-deficient NSPCs (ABCB1^{0/0}, ABCC1^{0/0}, and ABCG2^{0/0}) showed that NSPC proliferation was not affected by A β administration per se (data not shown). The increase of pro-neuronal cell differentiation (Tuj1⁺ cells) was statistically significant only in ABCG2^{0/0} cells after treatment with oligomeric A β_{42} *in vitro*, indicating that the expression of ABC transporters in NSPCs may be of importance for protection against A β . ABC transporter dysfunction, however, affects brain homeostasis directly and, thereby, only indirectly affects NSPC function. Studies have shown that changes in the A β deposition characteristics during AD pathogenesis influence adult neuroregeneration significantly (Heo

et al., 2007, 2007). This data taken together indicate that the observed inconsistency in results from *in situ* analyses of neuroregeneration in mice can be explained by the combined effects of the disturbed stem cell microenvironment and the specific concentrations and compositions of A β species in different mouse strains (i.e. variability in numerous experimental parameters)

The ‘Ageing-Energy-Export’ network – linking physiologic ageing and pathologic protein accumulation

Ageing itself is thus far the only consistent risk factor for most sporadic, neurodegenerative and dementing disorders, and therefore, the mechanisms involved in and altered by this exceptional biological condition are vitally important. Recent data have provided numerous insights into a network of age-related processes, in which rates of accumulation of mitochondrial mutations and efflux/export of toxic peptides play a central role (Figure 2). Strong, albeit debatable, evidence exists that randomly occurring, age-dependent mitochondrial mtDNA changes result in subtle functional changes, with substantial, long-term metabolic effects (reviewed in (Lin and Beal, 2006; Wallace, 2005, 2011)). Although the precise location of specific changes varies, the biochemical effect unexceptionally leads to dysfunction or alterations in mitochondrial respiratory chain complexes and, consequently, to changes in the availability of ATP (Casley et al., 2002; Crouch et al., 2005; Devi et al., 2006; Hernandez-Zimbron et al., 2012; Manczak et al., 2006; Rui et al., 2006). Deficiency in chemical energy production induces a wide range of negative effects on the cellular or tissue levels. Concomitant decrease in the export function of the BBB and BCSFB, respectively, due to the reduced activity of transporter molecules, gradually leads to accumulation of peptides near vessels, in cells, or in organelles, causing long-term toxic effects that result in dysfunction. Aquaporin-4, a highly expressed water channel at the endfeet of astrocytes, however, can limit the accumulation of peptides to a non-toxic level (Iliiff et al., 2012). This channel transfers A β peptides by a paravascular ‘water flow’ that reaches CSF spaces and the choroid plexus and finally results in a clearance of the brain. Besides AQP4, the ATP-dependent ABC transporters play an important role in the maintenance of the brain’s microenvironment. The deregulation of metabolic exchange via the brain’s barriers drives the pathogenesis of diseases, resulting in the aggregation of toxic peptides (Graf et al., 2004; Krishnamurthy et al., 2006).

ABC transporters are also expressed in different cell types and organelles, e.g. microglia, astrocytes and mitochondria (reviewed in (Kim et al., 2006; Zutz et al., 2009)). The consequences of disturbances in energy production and ABC transporter function affect these cells and organelles. Defects in the phagocytotic function of microglia, decreased protease activity, and reduced export rates from mitochondria lead to further toxic effects and enhanced ROS production, processes that are widely acknowledged in ND pathology (Gibson et al., 2012; Graf et al., 2004; Krishnamurthy et al., 2006; Song et al., 2004). The resulting accumulation of toxic peptides (e.g. A β , Syn) within the brain culminates in the formation of poorly soluble deposits (e.g. senile plaques and Lewy bodies). The presence of these deposits and their peptide predecessors induces a decline in neuronal and synaptic function and leads to the clinical symptoms seen in patients and animal models (Johnson, 2000). The progressing atrophy of the parenchyma, however, may be suspended by the replacement of dead neurons through neuroregeneration. With decreased ABC transporter activity, this process is also impaired, because the homeostasis of the stem cell niche and the differentiation of NSPC into neurons highly depends on the number and function of ABC transporters and is, thereby, also linked to the energy level (ATP) provided by mitochondria (Schumacher et al., 2012).

This ‘Ageing-Energy-Export’ network is not only endogenously influenced by metabolites, but more importantly is influenced by a genetic predisposition, such as we know from AD. Studies support that the risk of developing AD is increased when the patient’s mother and grandmother were also sufferers, an observation that directly correlates with the maternal inheritance of mitochondria (Honea et al., 2010; Mosconi et al., 2010).

The described complex coherencies between ageing, energy production and export function offer new opportunities for the development of new diagnostic tools and treatment strategies. The risk of being affected may be determined by screening the mitochondrial genome and assessing the mitochondrial function of the elderly. Whether skin fibroblasts or white blood cells will be most appropriate for such a screening approach has yet to be determined.

Additionally, the improvement of the ABCC1 and ABCB1 transporter function using specific compounds may be a novel treatment strategy, since both transporters contribute to A⁺ clearance via the BBB and BCSFB (Krohn et al., 2011). The results of improvement of the maintenance of the stem cell niche, seems to be promising, but are still highly speculative and the contribution of ABC transporters herein has to be determined in more detail.

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Highlights

- The paper describes the ‘ageing-energy-export’ network.
- This network is impaired in neurodegenerative diseases.
- Energy production is facilitated by mitochondria, and fails due to mtDNA mutations.
- ABC transporters need ATP and facilitate Abeta export from brain.

Figure 1. A β deposition triggers neurogenesis dependent on ABC transporter expression. ABC transporter dysfunction and A β proteopathy impair the neuroregeneration

Graphs were established from quantification of immunofluorescence staining. Procedures were the same as in (Schumacher et al., 2012).

(A) A β deposition does not significantly alter the quantity of Sox2⁺ (transcription factor, active only in stem and progenitor cells) stem cells in comparison to non-transgenic littermates. However, ABC transporter-deficiency increases the relative number in APPtg mice (black bars, ABCB1^{0/0} +16%, ABCG2^{0/0} +19%, ABCC1^{0/0} +12%).

(B) The pool of DCX⁺ (doublecortin, a microtubule associated protein which is transiently expressed only in neuronal progenitor cells) neuroblasts is increased in APPtg animals (ctrls +52%, black bars), ABCB1^{0/0} (+71%), ABCG2^{0/0} (+172%), and ABCC1^{0/0} (+52%, not significant) mice versus non-transgenic littermates. A significant difference between APPtg and APPtg/ABC^{0/0} strains is only observable in the ABCB1^{0/0} strain (−28%). ABC transporter-deficiency leads to a loss of DCX⁺ cells even in non-transgenic (non-tg) mice (ABCB1^{0/0} −36%; ABCG2^{0/0} −24%).

(C) In case of newly generated Calretinin⁺ neurons, the increase in cell numbers reaches statistical significance in all APPtg mice as compared to non-transgenic littermates (ctrls +164%, ABCB1^{0/0} +59%, ABCG2^{0/0} +357%, ABCC1^{0/0} +109%). In the APPtg lines a significant effect is only observable for the ABCB1^{0/0} strain which is decreased by −62%. In non-tg mice only the deficiency of ABCB1^{0/0} leads to a significant decline in Calretinin⁺ cell number (−38%).

(D) The incorporation rate of BrdU (bromodeoxyuridine a halogenated thymidine analogue) during proliferation showed significant effects only in APPtg controls (+68%) and APPtg/ABCG2^{0/0} (+175%) mice compared to non-tg littermates.

Summarizing, ABC transporter dysfunction and A β proteopathy impair the neuroregeneration. Numbers of cells are presented relatively to the previously published data on non-tg littermates (white bars, (Schumacher et al., 2012)).

Diagrams indicate means $\pm$ SEM;

t-Test: APPtg ctrls vs. APPtg/ABC^{0/0} strains: * 0.05; ** 0.01; n 4 (males)

t-Test: APPtg vs. non-transgenic littermates: + 0.05; ++ 0.01; +++ 0.001; n 4; (males)

t-Test: non-transgenic ctrls vs non-transgenic ABC^{0/0} strains: # 0.05; ## 0.01; n 4 (males)

Figure 2.

A hypothetical outline of interactions within a complex ageing network involving ABC transporters and mitochondria: i) continuous accumulation of mutations in the mitochondrial DNA and ii) decreased ATP-binding-cassette (ABC) transporter function in all cell types (neurons, microglia, astrocytes, neurosphere-forming stem and progenitor cells) closely interact.

Increasing numbers of mitochondrial DNA mutations result in mitochondrial dysfunction that lead to increased ROS production and decreased ATP production and availability. Due to the loss of ABC transporter function, neuroregenerative processes are disturbed and the replacement of lost neurons is reduced. Increasing amounts of highly aggregated A β shift the microglia phenotype from neuroprotective to neurotoxic, further promoting neurodegeneration and cognitive decline.