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Mortalin – a multipotent chaperone regulating cellular processes ranging from viral infection to neurodegeneration

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Summary. – Heat shock 70kDa protein 9 (HSPA9)/mortalin is a heat-uninducible member of the heat shock 70 protein family. This protein has been attributed many cellular functions, including energy generation, stress response, carcinogenesis and involvement in neurodegenerative diseases, which is well documented by many names it has been given (CSA, MOT, MOT2, GRP75, PBP74, GRP-75, HSPA9B, MGC4500, MTHSP75, and mortalin). As an immortalization marker (hence the name "mortalin") in mouse embryonic fibroblasts cybrids it preferentially segregated with loss of immortality in passaged cells. Mortalin regulates the functions of the tumor suppressor protein p53 and plays important roles in stress response and maintenance of the mitochondria and endoplasmic reticulum. Furthermore, mortalin appears to have roles in membrane trafficking and viral release regulation, since it interacts with Nef protein it is necessary for secretion of exosomal negative factor (Nef) and HIV-1 virus release. Recently, mortalin has been described as a significant player in neurodegenerative diseases. Mutations in HSPA9 gene have been found in Parkinson´s disease patients; mortalin isoform expression differs in hippocampus of patients with Alzheimer´s disease and could regulate the β-amyloid toxicity pathway. In this review we summarize the functions of mortalin, its pathological implications in neuronal dysfunction and possible roles in neurodegenerative diseases.

Keywords: HSPA9/mortalin/GRP75; mitochondria; cancer; Alzheimer´s disease

Contents:

1. Introduction

Proteins are crucial to the existence of every cell by fulfilling the fundamental functions in energy production and metabolism, structural stability and flexibility, preservation and transmission of genetic information. To fulfil all these functions, an average cell of a multicellular organism usually expresses around 10,000 different proteins, whose numbers are further multiplied by post-translational modifications. Proteins can perform all the necessary cellular functions due to their exceptional structural versatility and complexity. However, the high structural versatility of proteins comes with a drawback – the cell has to ensure that the proteins are properly folded to their functional structure and has to maintain their conformational integrity throughout their lifespan. The complex task of maintaining the homeostasis of the cellular proteome ("proteostasis") is performed by a sophisticated network of dedicated protein chaperones (Hsps), which help with proper folding (and re-folding) of nascent protein chains, and ubiquitin-proteasome and autophagy systems, which are responsible for the removal of misfolded proteins (Hartl *et al.*, 2011; Schwartz and Ciechanover, 2009; Sridhar *et al.*, 2012). The functional pathways of chaperone, proteasomal and autophagy systems form

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Abbreviations: Aβ = beta-amyloid; AD = Alzheimer´s disease; PD = Parkinson´s disease; HSPA9 = heat shock 70 kDa protein 9; Hsp = chaperone; MAC = membrane attack complex; Net = negative factor

a complex intertwined network of shared components and/or mechanisms (e.g. ubiquitination, chaperone function) (Cuervo, 2011; Gamerdinger *et al.*, 2011; Shaid *et al.*, 2012). Failure of these systems to remove misfolded proteins often results in conformational (or protein misfolding) diseases, which include cancer, cystic fibrosis and neurodegenerative disorders like Alzheimer′s disease (AD), Parkinson′s disease (PD), Huntington′s disease and amyotrophic lateral sclerosis.

Chaperones constitute the first line of proteostasis by assisting not only in the proper protein folding but also in the formation of multisubunit complexes and transport of proteins into organelles (Hartl *et al.*, 2011). The crucial role of chaperones in practically all cellular processes and pathways has recently been recognized and broad scientific interest sprouted in exploitation of selected chaperones to treat various diseases including atherosclerosis (Xu *et al.*, 2012), cancer (Mahalingam *et al.*, 2009), neurodegenerative diseases (Koren *et al.*, 2009), cardiovascular diseases (Ghayour-Mobarhan *et al.*, 2009), motor neuron diseases (Adachi *et al.*, 2007) and viral infections (Beck and Nassal, 2007; Brodsky and Chiosis, 2006).

In this review we focus on HSPA9, a heat-uninducible member of the heat shock 70 kDa protein family of chaperones, whose pleiotropic roles range from cell proliferation, organellar proteostasis, apoptosis, vesicular transport of proteins and neurodegenerative diseases (Deocaris *et al.*, 2009).

Mortalin, also known as mtHsp70/PBP74/Grp75/HSPA9, was first identified as a member of the Hsp70 protein family and was detected in the cytoplasmic fractions of normal CD1-ICR mouse fibroblasts. (Bhattacharyya *et al.*, 1995b; Domanico *et al.*, 1993; Kaul *et al.*, 1993; Wadhwa *et al.*, 1993a). Mortalin is a house-keeping mitochondrial protein, coded by the nuclear gene HSPA9B (GeneID, 3313) on chromosome 5q31.1. (Bhattacharyya *et al.*, 1995a). It is a 679 amino acid protein that has been found in multiple subcellular localizations such as the endoplasmic reticulum, mitochondria, Golgi apparatus, cytoplasmic vesicles and the cytosol (Ran *et al.*, 2000; Wadhwa *et al.*, 1995). According to its subcellular localisation it has multiple binding partners including p53, FGF-1, IL-1 receptor type1, GRP94, VDAC, NADH dehydrogenase, MPD, Mge1 Tim44 and Tim23, and is involved in diverse molecular pathways (Mizukoshi *et al.*, 1999; Sacht *et al.*, 1999; Schwarzer *et al.*, 2002; Takano *et al.*, 2001; Wadhwa *et al.*, 1998, 2003). The protein levels of mortalin correlate with muscle activity and mitochondrial biogenesis and the protein is inducible by ionizing radiation, ozone, glucose deprivation (thereby identified as Grp75), calcium and thyroid hormone (Craig *et al.*, 1998; Resendez *et al.*, 1985; Sadekova *et al.*, 1997).

2. Mortalin and mitochondria

Mitochondria represent the powerhouse of cells. They are responsible for ATP production and oxidative phosphorylation, they are involved in cell survival, have a central role in ageing, participate in buffering of calcium ions, lipid metabolism and synthesis of iron-sulphur clusters (Murgia *et al.*, 2009). A great majority of the mitochondrial proteins are responsible for the energy production synthesized in cytosol, so they have to be imported into mitochondria (Harsman *et al.*, 2011).

Mortalin/HSPA9/mtHsp70 is one of the proteins that actively participate in the import of mitochondrial proteins through the mitochondrial membrane into the mitochondrial matrix. The majority of cellular mortalin is located within the mitochondrial matrix (Burbulla *et al.*, 2010). The protein reaches this location after its import via the translocases of the mitochondrial outer and inner membranes (Rehling *et al.*, 2004; Webster *et al.*, 1994). Studies focused on explanation of the molecular mechanism of the mitochondrial transport system in yeast revealed that mortalin homologue SSC1p is an essential mitochondrial protein (Strub *et al.*, 2000). It is bound to the mitochondrial translocation canal on the matrix side of the mitochondrial membrane as a core of the presequence translocase-associated motor (D′Silva *et al.*, 2004; Chacinska *et al.*, 2009). Two energy sources are required for import of precursor proteins across the mitochondrial inner membrane into the matrix (Jensen and Johnson, 1999; Neupert, 1997; Pfanner *et a.l*, 1997). One is the electrical potential gradient across the inner membrane, which induces translocation of the amino-terminal signal sequences (presequences) of the preproteins across the membrane, and ATP utilized by mortalin to promote further translocation of the preprotein in transit and its re-folding in the mitochondrial matrix (Bukau and Horwich, 1998; Ellis and van der Vies, 1991; Geissler *et al.*, 2001; Kang *et al.*, 1990). To facilitate translocation of the proteins, mortalin cooperates with Tim44, a peripheral subunit of the translocase of the inner membrane (Kronidou *et al.*, 1994; Schneider *et al.*, 1996) and Mge1, a nucleotide-exchange cofactor (Schneider *et al.*, 1996; von Ahsen *et al.*, 1995). The mitochondrial precursor proteins are translocated into the mitochondrial matrix by mortalin, using an ATP-dependent mechanism with the assistance of co-chaperones (Scherer *et al.*, 1992; Voos and Rottgers, 2002). The matured proteins are subsequently transferred to Hsp60, which allows proteins to refold back, assemble, sort and finally perform their functions (Wadhwa *et al.*, 2005).

3. The role of mortalin in cancer

Cancer is a collective name for a group of diseases characterized by unregulated division of cells, which form

tumors and invade various parts of the body. Chaperones play a significant role in cancer. They possess the ability to rescue cells under chaotic cellular situations and are responsible for protein homeostasis where they interact with unfolded (nascent) or misfolded (denatured) proteins while preventing their aggregation (Gosslau *et al.*, 2001). Those reparation mechanisms ensure the normal cell environment (Lu *et al.*, 2011). Recently it was shown that mortalin is involved in tumor processes, but the molecular mechanism remains unclear. Immunostaining analysis of normal and immortal cells with a specific mortalin antibody revealed that mouse mortalin is distributed in the cytoplasm of normal cells and in the perinuclear region in immortal mouse cells (Kaul *et al.*, 2003). It turned out that mortalin cDNA encodes two isoforms of mortalin, mot-1 is localised in the cytoplasm and mot-2 is localized in the perinuclear region (Wadhwa *et al.*, 1993d). These isoforms differ in two amino acids (Val618 and Arg624 in mot-1 are replaced by Met and Gly in mot-2, respectively) and have contrasting biological activities. The mot-1 cDNA, encoding the pancytoplasmic form of mouse mortalin, induces cellular senescence-like phenotype in NIH 3T3 cells (Wadhwa *et al.*, 1993d). In contrast, overexpression of mot-2, the perinuclear protein, resulted in malignant transformation of NIH 3T3 cells (Kaul *et al.*, 1998). Analysis of the mortalin expression in rat tissues revealed that the non-dividing cell populations such as neurons, nerve fibres and heart muscle cells have a higher expression of mortalin compared to glial cells, endothelial cells and ovarian follicles (Kaul *et al.*, 1997). Elevated levels were also detected in cells with an immortal divisional phenotype, in tumors (Chen *et al.*, 2011). Different types of tumor tissue, the tumor-derived or *in vitro* immortalized cells exhibit higher expression levels of mortalin compared to normal primary cells (Wadhwa *et al.*, 2006). Recently, it has been demonstrated that mortalin translocates into the nucleus, where it interacts with the retinoic acid receptor to augment retinoic acid -elicited neuronal differentiation (Shih *et al.*, 2011). Interestingly, mortalin is upregulated in retinoic acid-treated neuroblastoma cells and in patients suffering from neuroblastoma (Hsu *et al.*, 2008). Experimental studies confirmed that mortalin interacts with the cellular protein p53 (Wadhwa *et al.*, 1998; Mizukoshi *et al.*, 2001; Wadhwa *et al.*, 2003). p53 is a tumor suppressor protein (Isobe *et al.*, 1986; Matlashewski *et al.*, 1984), it is synthesized in the cytoplasm and becomes translocated to the nucleus to exert its sequence-specific transcription factor and cell cycle regulatory functions (May and May, 1999; Vousden and Woude, 2000), including activation of DNA repair (Hupp and Lane, 1995), induction of growth arrest at the G_1/S regulation point upon DNA damage and initiation of apoptosis (Bates *et al.*, 1998). Mutation in the p53 gene results not only in the loss of p53 function but also in gain of oncogenic functions (Dittmer *et al.*, 1993). Recently, it was observed that p53 contributes to the regulation of the mitochondrial membrane potential by interactions with the mitochondrial proteins Bcl2 and mortalin (Leu *et al.*, 2004; Mihara *et al.*, 2003; Murphy *et al.*, 2004; Perfettini *et al.*, 2004). The co-localisation of mortalin and p53 was detected in the perinuclear region in many types of cancer cells (human colorectal adenocarcinomas, glioblastomas and hepatocellular carcinomas) such as NIH 3T3 (murine fibroblasts, wt p53), Balb/3T3 (immortalized cell line), HeLa (cervical carcinoma, wt p53), A2182 (bladder carcinoma, wt p53), U2OS (osteosarcoma, wt p53), A172 (glioblastoma, wt p53), NT-2 (teratocarcinoma, wt p53), SY-5Y and YKG-1 (neuroblastoma, wt p53), COS7 (monkey kidney), MCF7 (breast carcinoma) (Wadhwa *et al.*, 2003) and human adenocarcinoma cell lines (Sadekova *et al.*, 1997). The interaction between mortalin and p53 is provided through the mortalin N-terminal region and the carboxy terminus (aa 312-352) region of p53 protein (Kaul *et al.*, 2001; Wadhwa *et al.*, 1998, 2002b). This interaction leads to the cytoplasmic sequestration of p53 (Kaul *et al.*, 2005; Lu *et al.*, 2011) resulting in p53 functional inactivation, inhibition of the transcriptional activation and cell immortalisation (Wadhwa *et al.*, 2002a). Sequestration of p53 in the cytoplasm enhances its degradation by the MDM2-mediated proteasome degradation pathway (Kaul *et al.*, 2005). They showed that peptide containing amino acids 323–352 of p53 displaced p53 from the cytoplasmic complexes with mortalin and increased its nuclear localisation and induced growth arrest of human osteosarcoma and breast carcinoma cells. They confirmed the co-localisation of those peptides with mortalin. Similar results were obtained using mortalin inhibitor, MKT-077 (Walker *et al.*, 2006). Treatment with MKT-077, a cationic rhodocyanine dye, induced translocation of p53 back to the nucleus (Walker *et al.*, 2006). Widodo and co-workers reported that the treatment of cancer cells with an extract of the Indian shrub ashwagandha, which was reported to have anticancer activity, induced death of cancer cells in a p53-dependent manner (Widodo *et al.*, 2007). Detailed studies showed that withanone, a compound isolated from the ashwagandha shrub, induced the dissociation of the mortalin-p53 complex, nuclear translocation of p53 and functional reactivation of p53 in human cancer cells (Grover *et al.*, 2012). The function of mortalin in malignant cell division was confirmed by silencing experiments using mortalin-specific small interfering RNA (siRNA) expressed from adeno-oncolytic viruses (Yoo *et al.*, 2010). Yoo and co-workers showed the potency of mortalin-specific siRNA to enhance apoptosis and suppress angiogenesis, which was caused by reactivation of p53 functions by releasing it from the complex with mortalin (Yoo *et al.*, 2010).

The key role of mortalin in cancer severity and poor prognosis has been recently showed by proteomic analysis of early-recurring hepatocellular carcinoma tissues (Yi *et al.*, 2008). The study found mortalin overexpression in

hepatocellular carcinoma and that this increased expression was closely associated with advanced tumor stages and venous infiltration, connected to increased malignancy and aggressive behaviour.

Thus, cytoplasmic mortalin inactivates tumor suppressor p53 protein by direct binding, which results in cell immortalisation and tumorigenesis. Prevention of the sequestration of p53 in cytoplasm by peptides or mortalin inhibitors provides a potential therapeutic opportunity in treatment of a number of aggressive and drug-resistant cancers (Deocaris *et al.*, 2009). Furthermore, mortalin might also serve as a diagnostic biomarker for the cancer surveillance after surgery.

4. Role of mortalin in endocytosis

Endocytosis is used by cells to compartmentalize components of the plasma membrane and extracellular space into intracellular vesicles that are further distributed into cell compartments (Lakadamyali *et al.*, 2006; Mayor and Pagano, 2007). Endocytosis regulates signalling pathways responsible for cell motility and cell fate determination and is currently exploited for the delivery of therapeutic molecules. Interestingly, the same process is often used by microbial and viral intruders for infection (Luo, 2012; Schelhaas *et a.l*, 2012). Endocytosis pathways can be subdivided into four categories: clathrin-mediated endocytosis, caveolae, macropinocytosis and phagocytosis (Mukherjee *et al.*, 1997; Parton and Simons, 2007). Recently, it was shown that mortalin has a role in endocytosis mediated by heparan sulphate proteoglycans (HSPGs) (Wittrup *et al.*, 2010). HSPGs represent a protein family substituted with polysulfated heparan sulphate polysaccharides, and have a key role in the endocytic uptake of macromolecular drugs, growth factors and morphogens (Belting, 2003; Belting *et al.*, 2002, 2005; Mislick and Baldeschwieler, 1996). Wittrup and co-workers used anti-heparan sulphate antibody-coated magnetic nanoparticles to isolate endocytic vesicles in order to identify proteins associated with this endocytic pathway. Proteomic analysis of the vesicular fraction showed enrichment of mortalin suggesting its role in the pathway, which was confirmed by microscopic observations (Wittrup *et al.*, 2010). Functional analysis revealed that RNAi-mediated downregulation of mortalin expression or its inhibition with anti-mortalin antibody resulted in severe reduction in the internalization of the magnetic nanoparticles. Furthermore, anti-mortalin antibody also inhibited HIV TAT-peptide mediated DNA delivery to cells. Finally, mortalin was observed on the surface of cells and inside of endocytic vesicles. Thus, mitochondrial chaperone mortalin plays an important (yet unknown) role in nonclassical endocytic pathway involving macromolecular uptake through cell-surface heparan sulphate proteoglycans (Wittrup *et al.*, 2010). Since mortalin is not the only intracellular chaperone that appears on the cell surface (Robert *et al.*, 1999), it is supposed that the role of chaperones in endocytosis involves facilitating protein-protein interactions in cholesterol-rich membrane regions resulting in membrane deformation, in the recruitment of other participating proteins or by providing a scaffold during endocytosis.

5. Mortalin in exocytosis

Exocytosis provides for the release of enzymes and other proteins that act in other areas of the cell or body, or the release of molecules that help cells communicate with each other (Bacsi *et al.*, 2001). The membrane-bound vesicles can be generated inside endosomes (exosomes) or bud directly from the plasma membrane (ectosomes) (Fevrier and Raposo, 2004; Schneider and Simons, 2012). Multivesicular bodies, which are formed inside endosomes by budding from the limiting membrane into the lumen of endosomes, can fuse with lysosomes and enter the degradation pathway (Pelkmans and Helenius, 2003) or fuse with the plasma membrane where the internal vesicles are released from multivesicular bodies into the extracellular space as exosomes (Culp and Christensen, 2004). These membrane-bound vesicles contain soluble proteins and nucleic acids, which need to be secreted to the extracellular environment or transported into target cells, as well as membrane proteins and lipids that are sent to become components of the cell membrane (Schneider and Simons, 2012).

Shelton and co-workers identified mortalin as a protein functionally involved in exocytosis (Shelton *et al.*, 2012). They analyzed proteins involved in exocytosis of viral protein Nef, a 27-kDa protein produced in the early stages of HIV infection (Kim *et al.*, 1989). The protein is myristoylated and its interactions with membranes and host cell proteins are central to its many effects in cells (Shelton *et al.*, 2012). Nef is secreted out of the cell (Fujii *et al.*, 1996) and is implicated in viral pathogenesis and is one of the candidate proteins that might induce apoptosis in bystander $CD4^+$ T-cells (Annunziata, 2003; Calenda *et al.*, 1994; Campbell *et al.*, 2008). Secreted Nef can induce apoptosis via the CXCR4 receptor on the cell surface (James *et al.*, 2004). Shelton and coworkers identified proteins involved in Nef secretion that bind to the secretion modification region of Nef. Beside the fact that Nef induces its own secretion in exosomes (Fevrier and Raposo, 2004), the authors identified mortalin as a specific cellular protein interacting with Nef (Shelton *et al.*, 2012). It is known that mortalin binds directly to several proteins and regulates their intracellular trafficking (Iosefson and Azem, 2010; Kaul *et al.*, 2005). The interaction of mortalin with Nef is required for Nef secretion, since both reduction

of mortalin protein levels and inhibition of Nef-mortalin interaction either by anti-mortalin antibody or by secretion modification region-derived peptides drastically reduced Nef secretion (Shelton *et al.*, 2012).

Independent of these studies, mortalin was found to mediate the resistance of cells to membrane attack complex (MAC), the effector of innate and acquired immune responses (Pilzer *et al.*, 2005). The resistance is achieved either by internalization of the membranes with MAC in endosomes and their degradation or by ectosomal release of membrane particles containing MAC. It has been proposed that mortalin is involved in the ectocytic release of MAC-containing complexes (Pilzer *et al.*, 2005). Since mortalin/PBP74 is able to present antigens to T cells (Kim *et al.*, 1995; Vanbuskirk *et al.*, 1989) and membrane vesicles released after sublytic complement attack may contain mortalin-protein/peptide complexes, the authors proposed that, like MHC-loaded exosomes, mortalin-loaded membrane vesicles may play a role in the regulation of normal and pathological immune responses (Pilzer *et al.*, 2005).

Thus, mortalin appears to play multiple roles in membrane-mediated macromolecular transport, endocytosis, and exocytosis and perhaps in ectocytosis. Mortalin might serve as a promising target for anti-HIV therapy by reducing the release of Nef (and perhaps other viral proteins), for the modulation of immune response via ectosomes, and further possible roles in coagulation, vascular functions, angiogenesis, wound healing, and development (Martinez *et al.*, 2005; Morel *et al.*, 2004; Pilzer *et al.*, 2005; Shelton *et al.*, 2012; Wittrup *et al.*, 2010).

6. Mortalin and neurodegenerative diseases

Neurodegeneration is a progressive loss of structure or function of neurons, often resulting in death of neurons. Neurodegenerative diseases such as AD and other tauopathies, PD, Huntington disease, frontotemporal lobar degeneration and amyotrophic lateral sclerosis are characterized by accumulation of misfolded proteins in the form of pathological deposits and selective neuronal vulnerability resulting in degeneration in specific brain regions. These diseases are therefore called protein misfolding disorders. AD is the most common form of dementia. Histopathologically it is characterized by accumulation of misfolded proteins in the form of insoluble fibrous material: extracellular senile plaques and intracellular neurofibrillary deposits. Both result from aberrant folding of proteins, senile plaques composed of beta-amyloid (Aβ) (Glenner and Wong, 1984) and neurofibrillary deposits (or tangles, NFT) composed of the tau protein (Grundke-Iqbal *et al.*, 1986; Wischik *et al.*, 1988). The interplay between tau and Aβ, the cleavage product of amyloid precursor protein, is still not clear. Both pathological proteins exhibit toxic properties *in vitro* and *in vivo* (Eckermann *et al.*, 2007; Rapoport *et al.*, 2002; Roberson *et al.*, 2007; Spillantini *et al.*, 1998; Spillantini and Goedert, 1998; Zilka *et al.*, 2006).

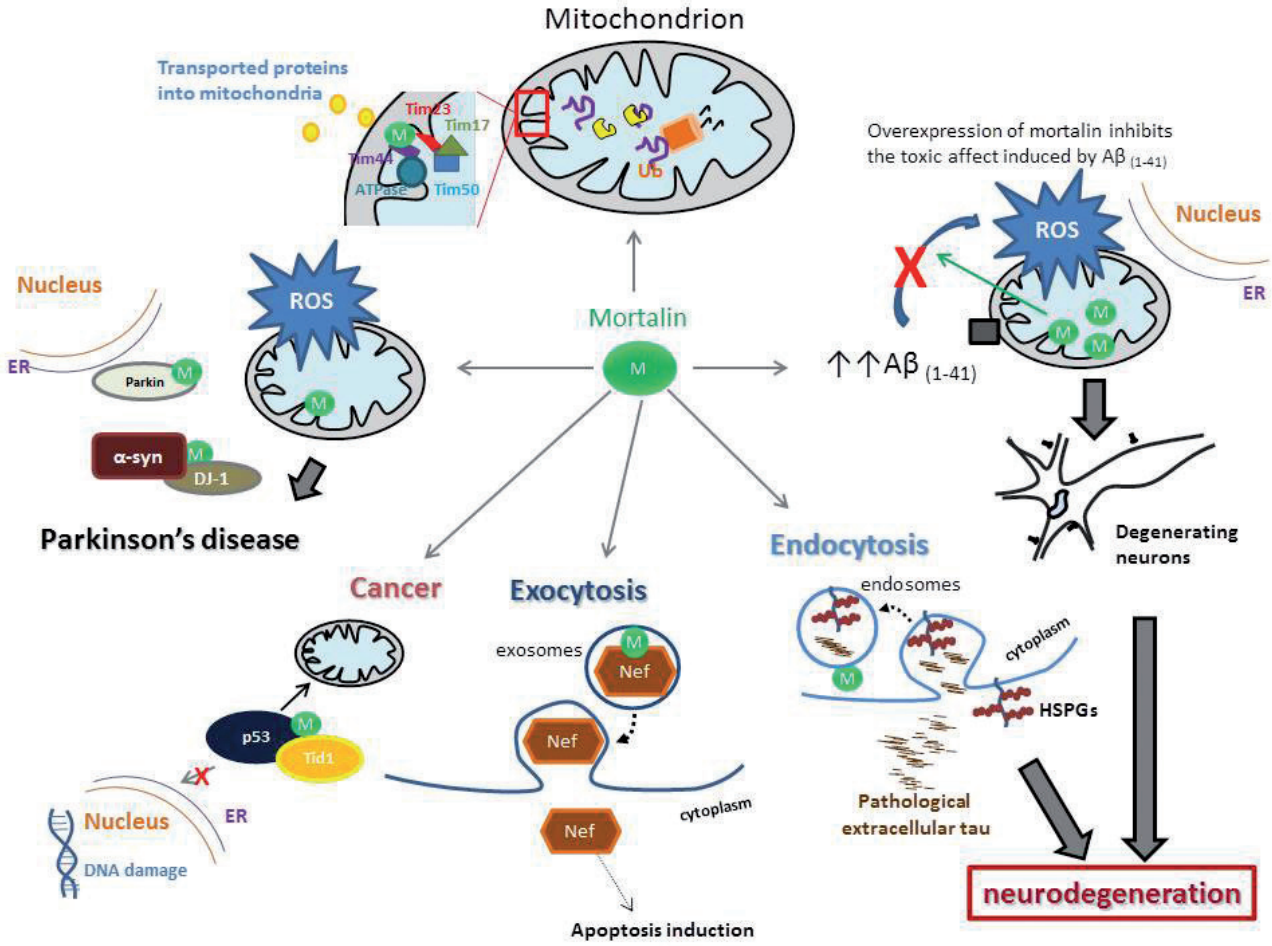
Recently, mortalin was suggested to have a protective function against neurodegeneration (Burbulla *et al.*, 2010; Wadhwa *et al.*, 2002a). Mortalin is primarily localised in mitochondria. Mitochondria are dynamic organelles that actively move within the axons to ensure adequate energy supply in energy-hungry neurons (Trushina *et al.*, 2012). It is supposed that impaired mitochondrial biogenesis contributes to the development of neurodegenerative diseases. Damages in mitochondria were found in all brain regions of AD patients, as well as in Aβ transgenic mouse models, cell lines expressing Aβ or cells treated with Aβ (Hirai *et al.*, 2001) and in a rat model of tauopathy (Cente *et al.*, 2009; Cente *et al.*, 2006; Filipcik *et al.*, 2009; Zilka *et al.*, 2006). Mitochondrial dysfunction was associated with increased levels of reactive oxygen species (Mancuso *et al.*, 2010). This intracellular mitochondrial oxidative stress contributed to tau hyperphosphorylation in the transgenic model expressing human mutant tau and Tg2576:sod2 mice (Melov *et al.*, 2007). Proteomic analysis of protein oxidation in different brain regions of ApoE-knockout animals showed that total protein oxidation in the hippocampus of the transgenic animals was approximately 2-fold higher than in control animals (Choi *et al.*, 2004). Mortalin was identified as one of the six oxidation-sensitive proteins by using two-dimensional electrophoresis coupled with immunostaining for protein carbonylation (Choi *et al.*, 2004). Differential protein expression analysis of human AD brain samples revealed differentially expressed mortalin isoforms (Osorio *et al.*, 2007). One of the mortalin isoforms was increased within AD hippocampi compared to the normal tissue. For further analysis the authors concentrated on the effect of ApoE alleles ApoE3 and ApoE4 on gene expression. These alleles are known to be either associated with significantly increased risk of Alzheimer´s disease in human population (ApoE4) or to have a rather protective role (ApoE3) (Keene *et al.*, 2011). The authors generated a transgenic mouse models by replacing the endogenous mouse ApoE with either human ApoE4 or ApoE3 allele (Osorio *et al.*, 2007). Mortalin was the only protein that was found to be differentially expressed in ApoE4 transgenic mice hippocampus compared to ApoE3 mice. Moreover, different phospho-isoforms of mortalin have been found as well (Osorio *et al.*, 2007). In another study a significant upregulation of mortalin gene expression was observed in PC12 cells overexpressing amyloid precursor protein (Kogel *et al.*, 2005). Significantly, overexpression of mortalin in the neuroblastoma cell line SH-SY5Y conferred protection against $A\beta_{(1-42)}$ - induced neurotoxicity (Qu *et al.*, 2011). Exposure to sub-lethal levels of $A\beta_{(1-42)}$ led to defects in the

import of mortalin and other components of the import machinery into mitochondria, which resulted in decreased mitochondrial membrane potential, increase in the levels of reactive oxygen species (ROS), increased vulnerability to oxygen-glucose deprivation and altered mitochondrial morphology (Sirk *et al.*, 2007). Increased levels of mortalin were shown to protect cells against $A\beta_{(1-42)}$-induced depolarization of mitochondrial membrane potential, reversed the reduction in cytochrome c oxidase activity and suppression of mitochondrial apoptotic cascade, and suppressed the $A\beta_{(1-42)}$-induced reactive oxygen species accumulation and lipid peroxidation (Qu *et al.*, 2011, 2012).

Changes in the levels of mortalin were related with the toxic effect of rotenone on dopaminergic neurons in PD (Jin *et al.*, 2006). PD belongs to the group of neurodegenerative disorders and is characterised by the degeneration of dopaminergic neurons in the substantia nigra pars compacta and the presence of Lewy bodies in the remaining nigral neurons (Braak *et al.*, 2003; Samii *et al.*, 2004). Decreased levels of mortalin were found in brains of PD patients as well as in a cellular model of PD in the isolated mitochondrial fraction (Jin *et al.*, 2006). Moreover, it was confirmed that mortalin interacts with the PD-related proteins DJ-1 and α-synuclein in cultured cells (Jin *et al.*, 2007; Liu *et al.*, 2005).

The role of mortalin in the etiology of PD was further supported by identification of three alleles of the mortalin gene associated with PD: two missense (R126W and P509S) and 17 bp insertion in intron 8 (De Mena *et al.*, 2009). The fourth mortalin variant (A476T) was later identified in German PD patients (Burbulla *et al.*, 2010). To define the function of these PD-associated mortalin variants, the authors overexpressed all four in neuronal and non-neuronal cellular models. The disease-associated variants exhibited normal import into mitochondria, but caused a mitochondrial phenotype manifested by an increase of ROS levels in cells producing mortalin variants, as well as reduced mitochondrial membrane potential compared to control cells overexpressing wt mortalin.

Chiasserini and coworkers have analyzed mortalin expression in a Parkinson´s disease rat model generated by inhibiting mitochondrial complex I by injecting 6-hydroxy-



dopamine into the medial forebrain bundle (Chiasserini *et al.*, 2011). Using different proteomic approaches they investigated the role of mortalin in both the physiological and the parkinsonian states and confirmed down regulation of mortalin in the treated rats in comparison with sham-operated animals (Chiasserini *et al.*, 2011). MKT-077, a mortalin inhibitor, caused electrophysiological changes in the striatal medium neurons and confirmed the role of mortalin in neuronal homeostasis. Finally, mortalin was found to be a target of covalent modification by oxidized dopamine (Van Laar *et al.*, 2008, 2009).

7. Conclusion

Chaperones are the most highly conserved protein family and perform essential functions in cells (Lindquist and Craig, 1988). They help in protein homeostasis, stress response and degradation of aggregated and misfolded proteins, but they also take part in normal cellular processes (Hartl *et al.*, 2011; Schwartz and Ciechanover, 2009; Sridhar *et al.*, 2012).

Multifunctional heat shock protein mortalin (Wadhwa *et al.*, 1993b) is involved in a plethora of pathways in cells (Fig. 1). Mortalin is localised predominantly in the mitochondria, where it is a part of the ATP-dependent mitochondrial protein import machinery (D´Silva *et al.*, 2004), but its presence was detected in the endoplasmatic reticulum, Golgi network, exosomes and on the surface of the plasma membrane (Deocaris *et al.*, 2007; Pilzer *et al.*, 2005; Shelton *et al.*, 2012; Wadhwa *et al.*, 1993c).

Discoveries that mortalin plays a role in exocytosis and release of viral proteins open several novel connections to neurodegenerative diseases. For example, recently, it was found that neuronal protein tau is released from living neurons in exosomes (Lee *et al.*, 2012; Saman *et al.*, 2012), and this secretion is assumed to help spread tau pathology throughout the Alzheimer´s disease brain (Clavaguera *et al.*, 2009; Frost *et al.*, 2009). Since mortalin isoform expression is altered in AD brains (Osorio *et al.*, 2007), it could influence the composition of exosomal vesicles and contribute to the exosomal release of pathological tau proteins.

In sporadic AD, the herpes simplex virus 1 (HSV-1) is suspected to play a role in the disease (Itzhaki and Wozniak, 2008). After a primary infection, the virus becomes latent mainly in the ganglia but viral DNA can be found in the neurons of several areas of the central nervous system (Cabrera *et al.*, 1980; Drummond *et al.*, 1994). The reactivation of HSV-1 in the brain by stress factors (Drummond *et al.*, 1994; Kastrukoff *et al.*, 1981; Whitley, 1996) might contribute to neurodegenerative development. Itzhaki and coworkers suggest that HSV-1 in the brain and the presence of the apolipoprotein E allele 4 (the recognized risk factor for AD) together confer high risk for AD (Lin *et al.*, 2002). Studies on neuropathological features of HSV-1 demonstrated that the viral infection of human neuronal cells in culture causes an increase in intracellular levels of both Aβ (Piacentini *et al.*, 2011; Santana *et al.*, 2012; Wozniak *et al.*, 2007) and phosphorylated tau (Lerchundi *et al.*, 2011; Wozniak *et al.*, 2009; Zambrano *et al.*, 2008). Furthermore, HSV-1 triggers AD-like caspase-3 activation and tau cleavage (Lerchundi *et al.*, 2011).

Where is the connection to mortalin? Cellular antioxidant chaperone Hsp27 enhances replication of the herpesvirus, most likely due to the increased oxidative stress in cells caused by viral infection (Mathew *et al.*, 2009, 2010). The oxidative stress, one of the hallmarks of neurodegenerative diseases like AD and PD, is connected to mitochondrial dysfunction (Mancuso *et al.*, 2010). In a cellular model oxidative stress can be prevented by increased levels of mortalin (Qu *et al.*, 2011, 2012). Thus, interplay between herpesvirus re-activation and secondary infections, oxidative stress, mitochondrial dysfunction and altered levels of mortalin in AD provide a new paradigm for identification of pathomechanisms leading to AD and also to other neurodegenerative disorders.

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