REVIEW ARTICLE

Role of Mitochondrial Heat-shock Proteins and Immunophilins in Neuro Degenerative Diseases

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Abstract: Pathophysiologic conditions of neurodegenerative diseases are unquestionably related to protein misfolding. The accumulation of misfolded proteins into relatively ordered structures such as fibrillar intracellular and extracellular amyloids results in tissue lesions that lead to neuronal loss and brain damage. In these pathologies, the occurrence of protein aggregates suggests certain inefficient or insufficient cellular responses of those molecular chaperones that should properly assist the folding of the client proteins. In this regard, most experimental models for neurodegenerative diseases have demonstrated that the overexpression of molecular chaperones provides effective neuroprotection. A subset of these molecular chaperones corresponds to a group of proteins that exhibit peptidylprolyl isomerase enzymatic activity, the immunophilins. Most of the family members of the latter group were first described as being responsible for the immunosuppressive response or they were reported as members of the chaperone complex associated with HSP90 in steroid receptor oligomers. In this article, we review some aspects of the liaison between molecular chaperones and neurodegenerative diseases, in particular heat-shock proteins and immunophilins with demonstrated influence on the proper function of mitochondria. This article is intended to address a field that represents a yet critical unmet clinical need for the development of neuroprotective molecules focused on potentially novel molecular targets.

1. INTRODUCTION

One of the most crucial properties achieved for the living matter is the compartmentalization of the cell work in organelles. The generation of energy from the cellular metabolism is one of the most relevant duties reserved to a major ancient endomembrane factory, the mitochondria. This type of organelle arose almost two billion years ago, most likely from the engulfment of an α-proteobacterium within the body of an ancestor of the modern eukaryotic cell [1, 2]. In addition to being the powerhouse of the cell, mitochondria also perform other essential activities that are closely related to the cellular metabolism, such as synthesis of steroid hormones, the synthesis of heme, calcium storing for its later release, *i.e.* acting as a cytosolic buffer for Ca^{2+}-dependent signaling, and is also responsible for specific pathways leading to cell death decisions [3]. Also, mitochondria are the primary source of endogenous reactive oxygen species, which are regarded to be mainly responsible for the unavoidable process of cell aging [4].

Failures in the mitochondrial function generate diseases. This is particularly notable for the case of neurodegenerative diseases, notwithstanding the normal aging processes themselves [5]. Most of these pathologies associate with protein instability and the formation of protein aggregates. As a result, neuronal malfunction is produced due to the devastating effects related to cell death and miscommunications between brain cells. Therefore, the affected individual shows severe problems to control physical movements as well as other deficiencies related to learning ability, memory capacity, speech skills, *etc*. It is noteworthy that the specific causes are so complex that they are mostly unknown or poorly understood [6], and most therapies are applied to alleviate or retard the symptoms. Table **1** summarizes the most important neurodegenerative diseases and the proteins involved in the pathology.

Table 1. Most frequent neurodegenerative diseases due to protein misfolding and aggregation.

Disease	Proteins Involved	References
Alzheimer's Disease (AD)	β-Amyloid and Tau	135, 171
Parkinson's Disease (PD)	α-Synuclein and Tau	26, 62
Huntington's Disease (HD)	Huntingtin	218, 222
Prion	PrP	128, 202
Tauopathies	Tau	44, 127
Lewy's Bodies Dementia	(LBD) α-Synuclein and ubiquitin	200, 201

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Molecular chaperones are a family of proteins that play a critical role in both the regulation of mitochondrial functions and neurodegenerative diseases. The term 'chaperone' refers to proteins that assist others in their proper folding and biological functions. Classically, chaperones protect client-proteins from misfolding, aggregation and denaturation, thus preserving the protein homeostasis of the cell (or proteostasis) [7]. The expression level of the subfamily of the chaperone family is highly induced by temperature changes, in which case they are named 'heat-shock proteins' (HSPs). This implies that even though all HSPs are members of the chaperone family, not all chaperones are necessarily HSPs. Nonetheless, all of them share the same functional characteristics. These proteins play a critical role in preserving and/or reverting the protein misfolding and aggregation that results from mitochondrial dysfunction or cell exposure to harmful stimuli (Fig. **1**). This imbalance of protein stability usually leads HSPs to join the damaged protein to block or hinder the aggregation process of misfolding. Also, they may have a role in promoting bonding to ubiquitin and proteasomal degradation.
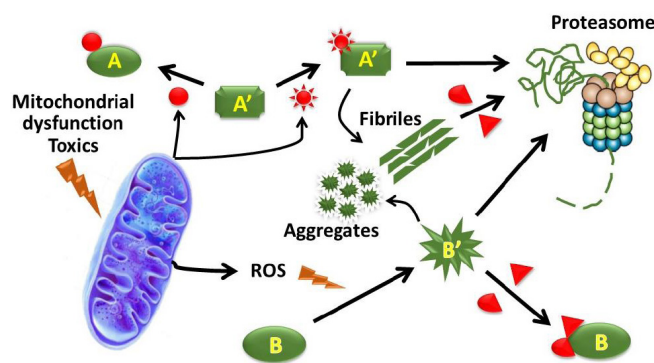

Fig. (1). The schematic interplay between mitochondrial dysfunction and chaperone function. High levels of reactive oxygen species (ROS) lead to modifications of native proteins A and B, which become misfolded (**A**' and **B**'). This may occur because of failures in the protein folding machinery as a consequence of harmful stimuli or due to genetic reasons. Molecular chaperones (shown in red) may stabilize the damaged protein (cases **A** and **B**), preventing and/or reverting protein aggregation. In some cases, the proper chaperone is damaged (case **A**') and cannot play its role, such that the misfolded protein A' is targeted to proteasomal degradation, which happens in the best case. If this would not occur, the misfolded proteins can precipitate or form aggregates and fibril structures that cannot be efficiently reversed by molecular chaperones. Nonetheless, chaperones can also facilitate proteasomal degradation of misfolded proteins. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

2. MITOCHONDRIAL HEAT-SHOCK PROTEINS

Even though a few numbers of mitochondrial proteins are encoded on the mitochondrial genome, most of the proteins belonging to this organelle are encoded by genes that reside in the nuclear genome of the cell. Therefore, there exists a complex biogenesis pathway for mitochondrial proteins that must be synthesized in the cytosol and is required to be imported into the organelle. There is an extra complica-

tion related to the limited dimensions of the mitochondrial translocation channels, such that the protein must traverse the double system of membranes in an unfolded state [8]. The proper recognition of mitochondrial preproteins requires the accessibility of diverse N-terminal sequences or internal translocation signal sequences by mitochondrial surface receptors. In most cases, this fact precludes the acquisition of the final active conformation of the protein, a phenomenon that requires the assistance of chaperones. There are four important groups of HSPs implicated in mitochondrial protein homeostasis that are involved in protein translocation of the client-factor HSP90, HSP70, HSP60, and HSP27. Except for the small HSP, the other chaperones possess intrinsic ATPase activity, and both HSP70 and HSP90 have specific mitochondrial homologs named respectively *Mortalin* (mtHSP70) [9] and *tumor necrosis factor receptor-associated protein*-1 (TRAP1) [10].

2.1. HSP60

HSP60 proteins form a subfamily of chaperones whose genes encode for heat-inducible 60-kDa proteins. Actually, they are classified as chaperonins, *i.e.* oligomeric high-molecular weight chaperones capable of folding proteins that cannot be folded by simpler chaperone systems [11]. It is regarded that approximately 80% of HSP60 is scattered throughout the mitochondria, where it catalyses the proper folding of mitochondrial matrix proteins [12]. The remaining pool of HSP60 resides in the endoplasmic reticulum, the cell surface, peroxisomes and/or cytosol. The non-mitochondrial HSP60 retains the mitochondrial localization signal and is also called naïve HSP60 [13]. The targeting sequence is cleaved by proteases when HSP60 is imported to mitochondria yielding the so-called 'mature' HSP60 protein.

HSP60 shows a barrel-shaped structure of two stacked rings of 7 subunits, each limiting a cavity with a lining of largely hydrophobic amino acid residues. This cavity is capable of accommodating unfolded peptides up to a size of ~50-kDa. Other small chaperonin termed HSP10 covers the opening of the 7-subunits ring by binding to the apical areas of them. The inner lining of the cavity undergoes an ATP-dependent conformational change becoming more hydrophilic and generating a space where the 'analysed' foreign polypeptide folds without the interference of external protein contacts. Then, HSP10 opens and the substrate is released for processing and assembly events that ultimately lead to the final active folded protein. Functionally impaired or damaged HSP60/HSP10 complexes lead to mitochondrial dysfunction and deficient physiologic functions that are deemed to be related to the onset of several diseases such as diabetes, Hashimoto's thyroiditis, juvenile rheumatoid arthritis, myasthenia gravis, and chronic obstructive pulmonary diseases [14]. Importantly, it is also related to neurodegenerative diseases such as SPG13 (*Hereditary Spastic Paraplegia*) [15] and BHLD (*Brain Hypomyelination Leukodystrophy*) [16].

Interestingly, it has been proposed that the depletion of soluble HSP60 is a major fact in the neuronal degeneration associated with amyotrophic lateral sclerosis [17]. In turn,

the accumulation of intracellular β-amyloid in Alzheimer Disease models was not significantly affected due to the high expression levels of HSP60, but a dramatic reduction of its aggregates was observed by the combined action of high expression level of HSP60 along with HSP70 and HSP90 [18]. Accordingly, β-amyloid aggregation could be inhibited *in vitro* by the addition of HSP60. An encouraging observation was the good induction of specific anti-β-amyloid antibodies after the injection of a β-amyloid-HSP60 peptide-conjugate vaccine, a response that was associated with a significant reduction of cerebral amyloid accumulation in mouse models of Alzheimer's disease [19]. Proteomic analysis of hippocampi of *amyloid precursor protein* (APP)-transgenic mice showed high levels of β-amyloid oligomers during the early age of the animal, but no plaques were detected in old animals, which showed altered levels of HSPs, in particular decreased HSP60. Moreover, it was reported that HSP60 favours the translocation of APP to the mitochondria, which leads to organelle dysfunction. Consequently, the precise role of HSP60 in Alzheimer's disease is still controversial and further investigations are required to determine if the chaperone is either a 'friend' or a 'foe' for this disease.

2.2. HSP70

HSP70 proteins comprise another large subfamily of chaperones with ATPase activity that are characterized by its ubiquity, structural conservation and pleiotropic biological involvement. Eukaryotes express more than a dozen of different isotypes of HSP70s that are localized in all major compartments of the cell [20]. Mitochondrial HSP70 is an essential chaperone that is absolutely required for cellular survival and the vectorial transport of mitochondrial preproteins from the cytosol into the matrix of the organelle through the translocase complexes located in the mitochondrial membranes [21]. HSP70 functions are normally associated with HSP40, a co-chaperone belonging to the J- domain proteins or DNA-J like proteins, which assists HSP70 in binding the substrate protein and stimulating ATPase activity. The mitochondrial isoform of HSP40 is MDJ1. This HSP70•MDJ1 complex encounters the completely unfolded preprotein when it is crossing the membrane [22], a property that mimics the function of the cytosolic isoforms of HSP70 when they assist the proper folding of a nascent peptide emerging from the ribosome tunnel [23]. Even though HSP70•MDJ1 plays a cardinal role in the mitochondrial matrix compartment during the folding of imported proteins, both HSP60 and HSP90 also cooperate actively and are a key requirement for this process.

It is regarded that high levels of expression of HSP70 are a desirable condition to protect neuronal cells against proteolytic and mitochondrial stress in both normal conditions and neurodegenerative diseases such as Alzheimer's, where the conjunct overexpression of the chaperone and the E3-ligase Parkin enhances the protection of cells in cases of β-amyloid-induced mitochondrial dysfunctions [24]. In Parkinson's disease, the overexpression of HSP70 protects cells against proteolytic and mitochondrial stress in a similar manner to that brought about by Parkin overexpression [25]. Interestingly, rising the cytoplasmic expression of α-synuclein at the nM range induces the expression of HSP70, which in turn restricts the accumulation of α-synuclein and its cytotoxic effects [26]. HSP70 also reduces poly(Q)-mediated cell death by protecting against ROS harmful effects and by inhibiting the activity of cytochrome-c and, therefore, apoptosis [27]. Accordingly, the overexpression of HSP70 in Huntington disease mice models also inhibits polyQ accumulation [28]. On the other hand, reduced HSP70 expression has been found in the spinal cord tissues of patients with amyotrophic lateral sclerosis (ALS) [29]. Also, the knock-down of HSP70 in neuroblastoma cells favours the cytoplasmic accumulation of TDP-43 [30], the major pathological marker of ALS, suggesting a role of HSP70 in suppressing the generation of toxic forms of this primarily nuclear protein belonging to the hnRNP family.

2.3. TRAP1

Mitochondrial HSP90 is known as TRAP1 and HSP75. It is localized in the mitochondrial matrix [31], although some degree of extra-mitochondrial localization cannot be ruled out. TRAP1 exerts protective effects on mitochondria preventing oxidative stress-induced cell death thanks to the inhibition of the permeability transition pore opening [32], an effect that occurs by inhibition of CyPD (*cyclophilin D*) and indirectly due to the modulation of the ROS levels. Even though the homology of TRAP1 with cytosolic HSP90 is significant, both chaperones seem to differ in their functional properties and TRAP1 was incapable to functionally replace HSP90 when it was expressed in the cytosol [31]. However, TRAP1 mitigates the proapoptotic toxicity of α-synuclein and prevents the formation of fibrils, and both proteins colocalize in mitochondria [33]. In Parkinson's disease models, it was reported [34] that the overexpression of TRAP1 fully rescues mitochondrial impairments associated with PINK1 (*phosphatase and tensin homolog (PTEN)-induced kinase-1*) loss of function and also mechanisms related to Parkin. Interestingly, TRAP1 is released from mitochondria into the cytosol of dopaminergic neurons following a 6-hydroxy-dopamine stimulation, a translocation that cannot be emulated by apoptotic inducers such as etoposide or staurosporine [35].

More recently, it was proposed that *S*-nitrosylation of the Cys^{501} residue of TRAP1 favors its loss of activity and the chaperone degradation [36]. Also, this fact may have relevance in aging and age-related diseases such as neurodegeneration [37], processes that are closely related to pathological states due to mitochondrial dysfunctions. Whether or not β−amyloid is imported into mitochondria remains uncertain. Thus, it was reported that the Tom complex can transport β-amyloid into the mitochondrial matrix [38], but another study showed that the β-amyloid interferes with the mitochondrial import of nuclear-encoded mitochondrial proteins [39]. One possible explanation for this controversy would be the possible mitochondrial import of the β-amyloid before it forms aggregates.
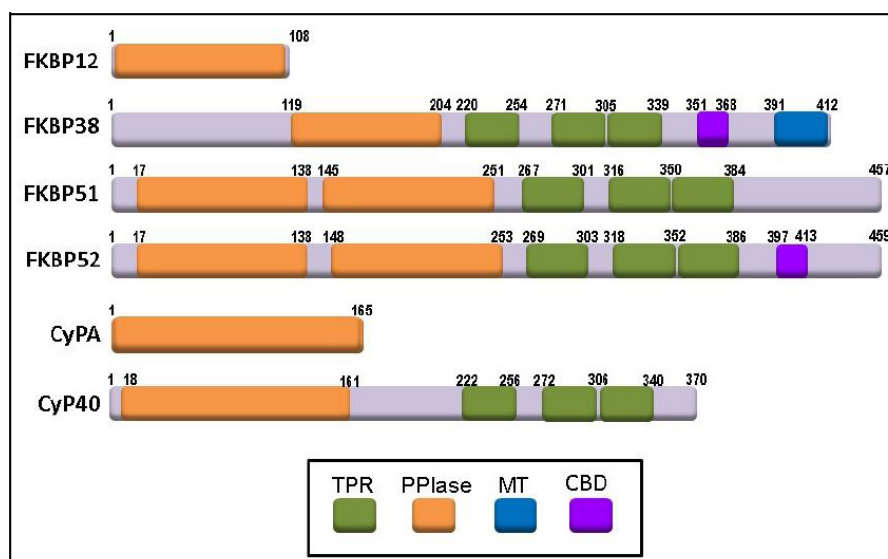
Fig. (2). Structural domains of the most abundant immunophilins expressed in the nervous system. The signature domain of the family is the PPIase domain (orange box). HSP90-binding members show TPR domains (green box), a property that is not shared by the two smallest members of the family, FKBP12 and CyPA/CyP17, which are responsible for immunosuppressive action when they are bound to the proper ligand. FKBP38 is a constitutive mitochondrial immunophilin, thanks to the MT targeting sequence shown at the N-terminal end (blue box). It has a poorly characterized calmodulin-binding domain (CBD, purple box), which is also present at the C-terminal end of FKBP52. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

2.4. HSP27

The so-called small HSPs have a molecular weight ranging from 12-kDa to 43-kDa for their monomeric forms, and are structurally characterized by the presence of the so-called α-crystallin domain, a conserved sequence of the homonymous chaperone protein expressed in the intact lens preventing aggregation of other proteins. Among the members of this subfamily, HSP27 is one of the most iconic small HSP and is responsible for increasing cell viability, anti-apoptotic actions, antioxidant effects, and microfilament remodeling [40]. Upon phosphorylation, HSP27 promotes actin polymerization contributing to microfilament network maintenance by preventing filament degeneration, which in turn provides cell stability to proapoptotic stimuli [41]. On the other hand, in its unphosphorylated form, HSP27 prevents actin assembly of wild-type proteins by actin capping [42]. Its overexpression protects cells from oxidative stress since HSP27 hampers the upstream production of ROS [43]. There are some studies limited to the therapeutic capabilities of HSP27 on Alzheimer's disease showing restoration in the amyloid plaque and tangle formation, HSP27-dependent degradation of hyperphosphorylated Tau and prevention of fibril formation [44-46] It has also been postulated that in cases of Parkinson's disease, the kinetics of α-synuclein aggregation is prevented by HSP27, the chaperone being less effective at a faster rate of aggregation [47].

3. IMMUNOPHILINS

Immunophilins are a group of molecular chaperones characterized by the presence of a PPIase domain (Fig. **2**), *i.e.* a relatively conserved sequence of amino acids that usu-

ally shows the enzymatic activity of PPIase (*peptidylprolyl-cis/trans-isomerase*) and also binds immunosuppressive ligands, which in turn inhibit the enzymatic activity [48]. According to the type of ligand they recognize, immunophilins are classified into two subfamilies, CyPs (*cyclophilins*) when they bind the cyclic undecapeptide cyclosporine A, and FKBPs (*FK506-binding proteins*) when they bind the macrolide FK506.

The so called high molecular weight immunophilins are characterized by the additional presence of TPR domains (*tetratricopeptide-repeats*), α-helix pair repeats that usually fold together to produce a linear solenoid domain through which they usually bind to HSP90. *Via* this chaperone, the TPR-domain immunophilins contribute to the regulation of the biological functions of several client-proteins [49, 50]. In contrast to low molecular weight immunophilins, which are incapable to interact with HSP90, these larger TPR-domain proteins are not related to immunosuppression. Actually, only the smallest members of each subfamily of immunophilins, CyPA and FKBP12, are responsible for the immune-suppressive effect when they are respectively activated by cyclosporine A or FK506. Thus, the immunophilin•drug complex inhibits calcineurin activity [51].

3.1. CyPD

The oldest known mitochondrial immunophilin described in the literature was CyPD [52]. It must not be confused with the TPR-domain immunophilin CyP40 (40-kDa), since at times, both proteins are named indistinctly. Human CypD is a cytoplasm-translated globular protein of 206 residues and ~22 -kDa. Upon its transport to the mitochondria,

its mitochondrial targeting sequence is cleaved, thus resulting in a mature protein with a theoretical MW of 18.9-kDa [53].

CyPD is a protein related to the regulation of the mitochondrial permeability transition pore, whose opening normally leads to cell death by apoptotic mechanisms and has also been implicated in the ischemia-reperfusion phenomenon that provokes severe injuries in multiple organs, muscular dystrophies and neurodegenerative disorders [54]. CypD is highly expressed in several nervous cell types such as astrocytes, microglia, and neurons [55], where it plays a significant role in excitotoxicity and cell death, especially in cases of multiple sclerosis [56].

The mitochondrial permeability transition leads to mitochondrial swelling, outer membrane rupture and the release of apoptotic mediators. Mice lacking CyPD expression are protected from ischaemia/reperfusion-induced cell death *in vivo*, whereas CyPD-overexpressing mice show mitochondrial swelling and spontaneous cell death. Mitochondria isolated from brains of transition pore null mice are resistant to mitochondrial swelling and permeability transition *in vitro* [57]. On the other hand, CyPD knock-out mice show a less serious phenotype in models of autoimmune encephalomyelitis when they are compared with wild type animals [58]. Similar benefits have also been observed in CypD knock-out mouse models of Alzheimer's disease [59], amyloid lateral sclerosis [60], traumatic brain injury [61], Parkinson's disease [62], and Huntington's disease [63]. CyPD also regulates the expression of mitochondrial genes, affecting cell proliferation and differentiation [64].

3.2. CyPA

CyPA is the archetype cyclophilin member and is involved in multiple cellular processes such as protein folding, intracellular trafficking, signal transduction, transcriptional regulation, *etc*. CyPA is ubiquitously expressed in the cell, although it can also be secreted into the medium in response to inflammatory stimuli such as hypoxia, infection, and oxidative stress, among others [65]. Importantly, the secreted form shows autocrine and paracrine properties by binding to the CD147 cell surface receptor [66], also called basigin and EMMPRIN (*extracellular matrix metalloproteinase inducer*). This receptor seems to be expressed in neurons but not in glial cells [67].CyPA shows pleiotropic biological actions in addition to protein folding and trafficking, such as it is also related to cell activation, cardiovascular diseases, diabetes, chemotaxis, atherosclerosis, viral infections, drug resistance, cancer, neurodegenerative diseases, aging, *etc* [65, 68-70].

Regarding their roles in the nervous system, CyPA has been implicated in essential neuronal functions such as axonal transport, synaptic vesicle assembly, neuroprotective roles against abnormal protein aggregation [71], as an auxiliary factor for BDNF neuroprotective actions [72, 73], *etc*. CyPA also performs neuroprotective responsibilities against both oxidative stress [74] and ischemic events [67]. In line with these observations, the direct injection of purified CyPA exerts protective roles after brain injury [75], and it was also reported that fibril formation in a cell-free system [76] and β-amyloid toxicity in PC12 cells [77] were prevented by incubation with recombinant CyPA. In the case of the cells, the most likely reason for these effects is because CyPA acts as a scavenger of reactive oxygen species, thus attenuating oxidative stress [77]. Clearly, these observations have implications in cases of Alzheimer's disease and other neurogenerative diseases. Strikingly, it has recently been demonstrated that CyPA colocalizes with the Parkinson's disease (PD)-associated protein α-synuclein and is also capable of interacting with α-synuclein oligomers [78].

3.3. FKBP12

FKBP12 is involved in a high level of aggregation of α-synuclein and, therefore, in Parkinson's disease [79]. The PPIase catalytic activity is required since site-directed mutagenesis of Pro to Ala makes FKBP12 incapable to accelerate the aggregation process in dendrites [80]. Accordingly, the pharmacologic inhibition of FKBP12 with a non-immunosuppressive synthetic ligand (ElteN378) overturns the formation of those dendritic fibrillar structures and leads to the formation of poorly branched molecular assemblies of small size [81], which is consistent with the above-mentioned effect on the aggregation of α-synuclein. On the other hand, the nature of the putative FKBP12-dependent mechanism that ultimately leads to Alzheimer's disease tauopathies and Lewy Body Dementia still remains uncertain. Thus, even though the dysregulation of the expression level of FKBP12 may lead to aberrant aggregation of proline containing peptides, the consequent dysregulation of any cellular pathway where FKBP12 may participate can also take place in parallel. Nonetheless, it appears that FKBP12 is indeed related to these diseases and emerges as a promising biomarker and potential target for inhibitors in ongoing clinical trials [79, 82]. It is accepted that Alzeimer's disease is the consequence of the activity imbalance of various different proteins [83, 84]. In this regard, a disrupted expression of FKBP12 has been reported in Alzheimer's disease brain samples, where a reduced expression of this immunophilin has been detected [85].

3.4. Pin1

Another member of the immunophilin family that is related to neurodegenerative diseases is Pin1 (*Peptidylprolyl isomerase Interacting with Nima-1*). It is a unique PPIase from the perspective that binds to specific phosphorylated proline-directed serine or threonine motifs (pS/T-P) [86]. Pin1 is highly abundant in the nervous system [87] and has been related to Tau and β-amyloid stability [88, 89]. Accordingly, mice lacking the expression of Pin1 develop tauopathies and experience a high rate of the loss of neurons [90]. Pin1 binds Thr^{231}-phosphorylated Tau and catalyzes the transformation of *cis*-Tau to *trans*-Tau, allowing its binding to microtubules [91]. Nevertheless, it has also been shown that β-amyloid oligomers affect Tau regulation by Pin1 stimulating Tau dephosphorylation at Thr^{231} [92]. Moreover, Pin1 can modulate GSK3β leading to downstream regula-

tion of Tau and β-amyloid. GSK3β is usually hyperactivated in Alzheimer's disease brains [93]. Therefore, it is not surprising the association of deficient Pin1 activity with high levels of Tau, leading to decreased degradation, elevated levels of β-amyloid, and decreased GSK-3β inhibition. Interestingly, it is thought that this phenomenon could be sufficient to initiate a process leading to Alzheimer's disease [59, 88, 89].

3.5. High molecular weight immunophilins

It is regarded that the biological actions of this group of immunophilins are coupled to their capability to interact with HSP90 *via* TPR domains [94], such that the association of both proteins forms a functional unit [48]. This may be the case in Alzheimer's disease where FKBP52, FKBP51, FKBP38, FKBP37/Xap2, and CyP40 (see Fig. **2**) are involved in its biology *via* a molecular mechanism that also involves the HSP90/HSP70 heterocomplex. In addition to the mandatory presence of the PPIase domain in this family and the HSP90-binding TPR-domain, high molecular weight immunophilins may exhibit additional domains. The most frequent of them (especially in plant immunophilins) is the CBD domain (*calmodulin-binding domain*). In mammals, the CBD is present in FKBP38 and FKBP52. Even though it is clear that the CBD domain interacts with Ca^{2+}/calmodulin and shows the capability to bind microtubules, its true biological significance still remains unknown. It was first thought that it can affect tubulin polymerization, but all microtubule polymerization assays with FKBP52 were carried out in the presence of Ca^{2+}-chelator such as EGTA, which rules out calmodulin as the candidate molecule required for this process [95, 96].

3.5.1. FKBP52

Some members of the TPR-domain subfamily have liaison with both Tau and β-amyloid proteins, in particular FKBP52 [88, 97, 98]. This immunophilin has been shown to be highly expressed in normal neurons of the hippocampus, cortex, and basal ganglia, but is abnormally low in Alzheimer's disease brains [99]. This was particularly evident in the frontal cortex of all 17 studied brains as compared to control brains. Interestingly, this low level of FKBP52 expression is accompanied by normal amounts of its specific mRNA level. Therefore, the involvement of FKBP52 in pathological Tau expression and function is likely. In this regard, it has been demonstrated that FKBP52 binds directly to Tau and is capable of regulating microtubule dynamics [100]. In this regard, it has also been reported that FKBP52 expression is inversely related to β-amyloid toxicity in a Drosophila model [97], but the inverse effects were also shown [101] for the effect of FKBP52 on the *in vitro* oligomerization of a pathological P301L mutant of Tau responsible for human tauopathy.

We have shown that FKBP52 is upregulated during neuro-differentiation and also in regenerating neurons [102, 103]. This indicates a protective and a regenerative role of this immunophilin. In an Alzheimer's disease model in *Dro-sophila*, mutations in the orthologue dFKBP59 exacerbated both the expression levels and also the toxicity of β-amyloid in transgenic flies overexpressing β-amyloid peptides [97]. It is interesting to emphasize that the authors demonstrated that the overexpression of the orthologue dFKBP52 suppressed the β-amyloid-induced short lifespan and reduced levels of β-amyloid in the nervous system of the flies. In the same study [97], cells stably transfected with APP (HEK-APP cells) were assayed, and a similar reduction of β-amyloid peptides was observed. These observations validate those made in the *Drosophila* model.

As stated above, human Alzheimer's disease is probably similar to most of the polygenic diseases, *i.e.* possibly resulting from an imbalanced expression of many proteins. FKBP52 may be included within this model since its expression level in brain tissue from people who had died of Alzheimer's disease is low when compared to normal brains or non-neurological disease brains [98]. Decrease in FKBP52 expression may additionally have multiple consequences in tauopathies, such as defects of axonal guidance [104] related to the loss of its regulatory capacity on the TPRC1 calcium channel, as well as destabilization of the microtubule network, which may lead to synaptic dysfunction and neuronal death [95]. Another FKBP52 interacting protein is APP (*Amyloid Precursor Protein*), whose C-terminal end also binds FKBP12 [105]. It has been demonstrated that endogenous APP co-immunoprecipitates with FKBP52 in a manner that is competed by FK506 [97], suggesting that the PPIase domain of this immunophilin is required for the interaction. At present, whether the binding of FKBP52 to APP disrupts the amyloidogenic management is still unclear and needs to be resolved.

3.5.2. FKBP51

FKBP51 (encoded by *FKBP5* gene) is a closely related homolog of FKBP52 (encoded by *FKBP4* gene) that is also highly expressed in neurons, although it has been primarily characterized as a member of the GR•HSP90 heterocomplex [48, 94]. Actually, the relationship of FKBP51 with GR is negative in the sense that the immunophilin is an inhibitor of steroid binding, GR transport towards the nucleus and steroid-dependent transcriptional activity. Such a short feedback loop negatively regulates GR activity. FKBP51 is highly expressed in rodents' brain structures, especially in the hippocampus, amygdala, and the hypothalamic paraventricular nucleus, especially after stress stimuli or challenge with glucocorticoids [106]. Furthermore, FKBP51 has also been shown to be prominently upregulated in neurons of the dorsal horn in mice models of inflammatory pain.

The aggregation of Tau protein in the brain has been associated with a family of neurodegenerative diseases known as tauopathies. FKBP51 forms mature chaperone complexes with HSP90 that exert a strong effect on Tau degradation. Consistently, Tau levels are reduced throughout the brains of *FKBP5*^{−/−} mice. Recombinant FKBP51 and Hsp90 synergize to block Tau clearance through the proteasome, resulting in Tau oligomerization. Overexpression of FKBP51 in a

Tau transgenic mouse model revealed that FKBP51 preserves the Tau stability, a phenomenon that worsens Alzheimer's disease pathogenesis. It also interacts with β-amyloid formation [107, 108], but the functional role of such interaction has not been elucidated yet. FKBP51 has also been characterized for its role in the regulation of Tau biology [109]. Thus, while FKBP51 overexpression preserves Tau stability, FKBP51-KO mice show reduced levels of endogenous Tau [107].

3.5.3. FKBP38

FKBP38 is a peculiar member of the immunophilin family because, even though it possesses a diffuse sequence of amino acids compatible with a PPIase domain, the constitutive enzymatic activity is loosely conserved, although it can be substantially recovered in a Ca^{2+}/calmodulin-dependent manner [110]. FKBP38 does not bind the immunosuppressive drug FK506 either [111]. It shows three TPR domains through which FKBP38 interacts with HSP90. It is localized in mitochondria and inhibits apoptosis by recruiting the anti-apoptotic proteins Bcl-2 and Bcl-xL to the organelle. Although FKBP38 is expressed in all tissues, it is especially abundant in the brain and can be found in both neurons and in glial cells. It has been observed that FKBP38 deficient mice die soon after birth due to defects in neural tube closure, which is the consequence of unrestrained apoptosis. As much as neuroectoderm organization fails during embryogenesis, mice not only die soon after birth, but they also show prominent malformations in the nervous system [112]. Moreover, the animals also show malformations of the cerebrum, cerebellum, and dorsal root ganglia.

In Parkinson's disease, PINK1-regulated mitophagy events have been linked to the loss of dopaminergic neurons in the substantia nigra, and it has been observed that the susceptibility to neuronal apoptosis during mitophagy is markedly increased in FKBP38-deficient mice, suggesting a protective role of this immunophilin in the development of that neurodegenerative disease [112]. When FKBP38 is associated with the small-like GTPase Rheb protein, the mTOR signaling cascade is inhibited [113], which is regarded to be a favorable defensive mechanism against Alzheimer's disease [88, 114]. Thus, various stimuli that favor the development and progression of the disease, for example, constant augmented oxidative stress, can activate the mTOR pathway enhancing the formation of β-amyloid aggregates. This is mostly due to the blockage of autophagy. In line with this, the inhibition of mTOR cascade by rapamycin decreases the accumulation of β-amyloid and ameliorates the cognitive function in mouse models of Alzheimer's disease [115], this being an alternative and unconventional treatment.

3.5.4. CyP40

Cyp40 is a cyclosporine A binding immunophilin of 40-kDa that has a PPIase domain and three TPR-domains. As such, it is an HSP90-interacting protein that was first described as a co-chaperone bound to steroid receptor complexes [116]. This TPR-domain immunophilin was shown to compete with FKBP52 for binding to HSP90, especially in estrogen receptor and progesterone receptor heterocomplexes [117]. In contrast to its smaller partners CyPA and CyPD, it is not a major mitochondrial factor strongly involved in immunosuppressive effects or in the activity of the mitochondrial permeability transport pore. Like CyPA [118], it has been observed that CyP40 can also be involved in anti-apoptotic mechanisms [119].

CyP40 is an immunophilin abundantly expressed in the CNS, whose specific biological roles have begun to be elucidated very recently. Interestingly, it has been reported that CyP40 binds β-amyloid and regulates its import into mitochondria [120]. Accordingly, the inhibition of Cyp40 was found to be protective against the β-amyloid toxicity in both whole mitochondria and neurons. Transduction of CyP40 in a tauopathic brain reduced Tau oligomers and tangles, yielding significant improvements in the overall neuronal health, and mice also preserved cognitive functions. CyP40 decreases both Tau fibril and oligomer accumulation in a transgenic mouse tauopathy model and delivery of CyP40 to neurons early in the pathogenic progression of the mouse model results in significant improvements in learning and memory as assessed by radial arm water maze and fear conditioning paradigms.

These observations suggest that CyP40 may be a potential therapeutic pharmacologic target for the treatment of tauopathies and other amyloidogenic disorders [121]. Because it has been reported that upon cellular stress, HSP90 dissociates from CyP40 complexes [122], it may be speculated that the generation of certain situation of stress could increase the pool of more catalytically active CyP40, a possible therapeutic alternative to activate this immunophilin and inhibit the potential toxic effects of amyloid build-up.

3.5.5. Other Immunophilins

In addition to the better-studied group of immunophilins described above, there are several other immunophilins that show a relatively good expression in the CNS, such as FKBP133, FKBP65, FKBP63, FKBP25, FKBP23, FKBP19, FKBP13, FKBP12.6 and FKBPL. Even though they are not prolifically investigated in this tissue, some of these members have been linked to neurodegenerative diseases, especially Alzheimer's disease, such as FKBP133, FKBP65, and PTPA [88]. It is known that FKBP133 (also named WAFL) is expressed in the hippocampus, cerebral cortex, and peripheral ganglia, and is predominantly localized to axonal shafts, and also associated with F-actin in growth cones [123]. Little is known about the properties of this PPIase, and to date, it has not been related in a direct manner to neurological diseases. Nonetheless, it has been observed that FKBP133 deficient cells show delayed transport of endosomal cargoes, which was observed in a model whereby this immunophilin was found to be implicated in the transport of early endosomes at the level of transition between microfilament-based and microtubule-based movement [124], playing an important role in endocytosis and subsequent membrane trafficking [125].

FKBP63 (also named FKBP60 and FKBP9) has been suggested to play a role in prion spreading and degradation [126]. Because β-amyloid and tau can spread in a prion fashion [127], this may imply that FKBP63 could potentially play a role in their propagation, particularly if it would be considered that prions are thought to be initiating factors of Alzheimer's disease [128]. Recently, it has been suggested that this immunophilin promotes malignant behaviour of glioblastoma cells and confers resistance to endoplasmic reticulum stress inducers [129].

PTPA (*Phospho-Tyrosyl Phosphatase Activator*) is a distinctive PPIase that enhances the enzymatic activity of protein phosphatase-2A [130]. This is relevant for the phosphorylation status of Tau since it is regarded that this protein-phosphatase is mainly responsible for Tau dephosphorylation [131]. In Alzheimer's disease, brain PTPA is downregulated, thus leading to the subsequent decreased activity of protein-phosphates 2A and the elevated levels of Tau species [132].

4. HEAT-SHOCK PROTEIN OF 90-kDa

4.1. Overview

The reader can find most of the properties of HSP90 on protein aggregates in the sections where every involved protein is described. This is not surprising because HSP90 is the gravity centre for most of the biological responses to the harmful effects of protein misfolding. Nonetheless, in this section, we will summarize some general features of this cardinal chaperone.

This chaperone is the most abundant soluble protein in the cell. In resting cells, HSP90 accounts for ~2% of the total amount of soluble proteins; it represents ~5% in several cancer cell types and can reach up to 10% in cells or unicellular organisms under stress [133]. It shows intrinsic ATPase enzymatic activity and functions as a hub protein capable of interacting with several proteins in oligomeric heterocomplexes. Perhaps one of the most distinctive features compared to other chaperones is the fact that, even though HSP90 can rescue aggregated and denatured proteins or prevent protein denaturation, it functions as a refined sensor of protein function. This means that HSP90 facilitates the biological activity of properly folded client proteins that already have a preserved tertiary structure. Thus, HSP90 relates to various elemental cell functions such as the regulation of the biological activity of key signaling proteins (steroid receptors, protein kinases, ubiquitin ligases, cell cycle regulators, transcription factors, *etc.*), the cytoplasmic transport of soluble proteins, the translocation of client proteins to organelles, and it can even act as an extracellular factor with autocrine/paracrine-like properties [134].

4.2. The HSP90• Tau association

Compared to the chaperones described above, HSP90 shows high homology and structural characteristics with the previously described mitochondrial protein TRAP1. Like the other HSPs, HSP90 has a profound protective role in most

neurodegenerative diseases. It can interact and rescue aggregates of amyloid, Tau, huntingtin, synuclein and prion proteins. It forms complexes with other chaperones (detailed in each individual section), but it forms a special partnership with HSP70. A good example of this functional association is the fate of Tau, which is defined by the HSP70/HSP90 complex;HSP70 participates during the early folding pathway and associates with misfolded Tau and transfers it to HSP90 for its further processing. Failure of this mechanism leads to Tau degradation either by the ubiquitin-proteasome system or by autophagy [135].

The region of the chaperone involved in the formation of complexes with Tau shows a profound dip topography between amino acids 210 and 380, which comprises of a repeat region of HSP90 [136]. In turn, the area of Tau involved in the binding to HSP90 shows a large number of aromatic and hydrophobic side-chains when compared to the N-terminal and C-terminal domains. HSP90 shows a large binding site for Tau equivalent to 106-Å long and 840-Å, which permits several low-affinity contacts between the chaperone and the client protein. The substrate-binding site on HSP90 shows negatively charged amino acids that interact with the positively charged amino acids of Tau [137].

The functional coordination with other chaperones also plays a key role in the interaction of HSP90 with Tau (and also other clients). Thus, co-chaperones such as CHIP and HOP (*Hsp70 and Hsp90 organizing protein*) act in a coordinated fashion with both HSP90 and HSP70 [138], as well as Aha1 (*Activator of HSP90 ATPase-1*), the Ser/Thr-phosphatase PP5, Cdc37 (*Cell Division Cycle 37-kDa protein*), p23, *etc.*, among the other HSP90 cochaperones that help in the proper folding mechanism of the client protein or in their degradation mechanism [135, 139]. The consequences of these associations follow two possible ways: (a) reducing the transition time for HSP90•ADP, a chaperone isoform that enhances the client protein release, and (b) stabilizing the HSP90•ATP isoform attached to the client protein. The latter is the case for HSP90•Tau complexes that recruit PP5 to dephosphorylate the highly phosphorylated forms of Tau, thus favoring its proper folding. However, when HSP90•Tau complex associates other TPR-domain factors such as CHIP, the Tau fate ends in its ubiquitination followed by proteasomal degradation [138].

Because both terminal domains of HSP90 are involved in the intrinsic ATPase activity of the chaperone, several small molecules have been designed and assayed as inhibitors of the protein folding cycle [140], and they are the subject of pharmacological studies to affect Tau aggregates by targeting HSP90. The inhibition of the ATPase activity of HSP90 with the ansamycin geldanamycin resulted in a significant increase in levels of soluble Tau and also microtubule-associated Tau but decreased levels of Tau aggregates [141]. The N-terminal domain inhibitor EC102 was administered to transgenic mice causing HSP90 inhibition and the subsequent degradation of aberrant phosphorylated Tau species [142]. In contrast to the ATPase inhibitors that bind the C-terminal end of HSP90, which are not capable of af-

fecting HSF1 activity, those that associate with the N-terminal end favour the activity of HSF1, and therefore, the expression of other chaperones is also induced. In turn, higher expression of chaperones is effective for decreasing the levels of aggregated proteins. In this regard, it is our opinion that controlling HSP90 function itself is indeed a challenging issue too rife with liabilities to pursue in the clinic due to the pleiotropic actions of this chaperone. Perhaps, an alternative approach to controlling co-chaperones may have greater potential to confer specificity to a particular disease target through HSP90. This is because co-chaperones modulate significantly fewer processes than the parent chaperone and it becomes more probable to avoid undesirable side-effects. In other words, HSP90 co-chaperones hold promise for targeting β-amyloid, α-synuclein and/or Tau more specifically than through HSP90 alone.

5. FKBPs AND RECEPTOR TRAFFICKING

5.1. The transportosome model

Both TPR-domain immunophilins, FKBP51 and FKBP52, were first characterized as members of the steroid receptor•HSP90 heterocomplex [143, 144]. The subsequent discovery that the dynein/dynactin motor protein complex associates with FKBP52 [145] and also with other TPR-domain proteins belonging to the HSP90-based complex such as CyP40 and PP5 [146] has led to analyse the composition of the steroid receptor complex [147-150] and other soluble factors [151-154]. The evidence showed that the dynein-based motor complex binds to FKBP52 *via* the PPIase domain [145, 146, 155], a property that is not shared by FKBP51 [156]. Importantly, FKBP51 is mostly found to be associated with the receptor in the ligand-free state and is functionally replaced by FKBP52 upon steroid binding [157-159].

As a consequence of those studies, a novel model for the mechanism of action of the receptor•hormone complex was proposed [160] and is summarized in Fig. (**3**). The receptor is actively transported towards the nucleus on cytoskeletal tracks by a chaperone machine named 'transportosome', which is assembled by a dimer of HSP90 and one molecule of HSP70, one molecule of p23, and one TPR-domain immunophilin [161]. This concept radically modified the classic model posed decades ago for the mechanism of activation of steroid receptors, which stated that HSP90 must be released from the complex upon steroid binding to "detach" the receptor from its cytoplasmic anchorage sites.

It should be pointed out that, regardless of their primary subcellular localization, these receptors and almost most soluble proteins are not necessarily confined to a particular cell compartment in a static manner, but they continuously shuttle between cytoplasm and nucleus [159, 160, 162, 163]. Thus, the heuristic classic dogma was replaced by a model where the receptor•(Hsp90)$_2$•FKBP52•dynein complex mediates the cytoplasmic transport and also translocates GR through the nuclear pore. Therefore, the GR•chaperone hete-

rocomplex is just dissociated in the nucleoplasmic compartment rather than in the cytoplasm, such that the receptor dimerizes and is activated to function as a transcription factor. Importantly, all these mechanistic steps were experimentally tested for each individual step [155, 160, 164-166].

5.2. GR Nuclear Translocation and Alzheimer's Disease

Because hypercortisolemia is a common feature in many neurological disorders, the modulation of the GR nuclear translocation in neurons by FKBP51 and FKBP52 has been linked to the development of depressive disorders [167] and is considered a risk factor to develop Alzheimer's disease [168]. Glucocorticoid hormones are synergized by excitatory amino acids (for example, glutamate) favouring the disruption of the hypothalamic-pituitary-adrenal (HPA) axis. This over-stimulation and/or modifications of the GR properties are neurotoxic, a phenomenon particularly notorious in limbic structures such as amygdala, prefrontal cortex, and hippocampus [169]. It is accepted that chronic stress and subsequent repeated situations of stress affect the dendrites of neurons located in the CA3 region of the hippocampus leading to neuronal atrophy and suppression of neurogenesis in dentate gyrus neurons [170]. This loss of synaptic plasticity represents a cardinal situation of the Alzheimer's disease syndrome and can be related to cognitive decline that is characteristic of these patients [171].

As mentioned above, depressive disorders are linked to mechanisms that develop Alzheimer's disease, although the actual switch is still poorly understood. Nevertheless, some evidence indicates that one of the possible reasons may be the dysregulation of the HPA axis that accompanies the high plasma levels of glucocorticoid steroids and impairment of the GR-dependent signaling response. One common and old evidence of such dysregulation is the functional failure for cortisol suppression following a dexamethasone challenge, which reflects the inability of the HPA axis to preserve the hormonal homeostasis [172, 173]. Interestingly, the activity of GR can be indirectly regulated by other factors that may be used for therapeutic purposes. For example, it was reported that in murine models of spinal cord injury, the activation ADORA2A, also known as adenosine A2A receptor, mimicked the effects of GR activation in attenuating neuronal damage [174], and its pharmacologic inhibition reversed memory deficits by the reestablishment of the HPA axis feedback [175]. It is regarded that A2A receptor activation enhances susceptibility to glucocorticoids by favoring GR nuclear accumulation and consequently GR down-regulation. The inhibition of A2A receptor impacts GR nuclear translocation and transcription and represents a novel therapeutic strategy to ameliorate cognitive deficits in neuropsychiatric disorders by precluding GR action [168]. As a matter of fact, A2A receptor has been found upregulated in the forebrain of Alzheimer's disease patients [176], and glucocorticoids have been shown to up-regulate both Tau and β-amyloid pathology, which may represent a secondary mechanism by which immunophilins such as FKBP52 are known to be involved in Alzheimer's disease mouse models [177].
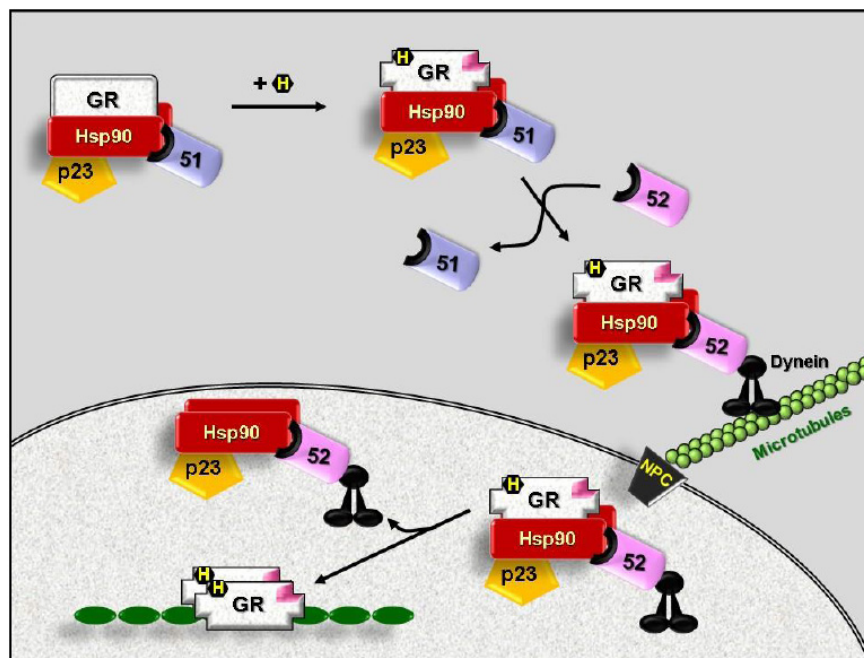
Fig. (3). Active retrotransport of GR is mediated by the HSP90•FKBP52•Dynein complex, a functional unit also referred to as "transportosome". Unliganded GR forms cytosolic complexes with a dimer of HSP90 and one molecule of HSP70, the cochaperone p23, and FKBP51. Steroid (H) binding favors the exchange of FKBP51 by FKBP52, an immunophilin that interacts with the dynein/dynactin motor complex that powers GR retrotransport on cytoskeletal tracks. Note that the entire heterocomplex passes through the nuclear pore complex (NPC) and is dissociated in the nuclear compartment, where GR dimerizes. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Another unexpected regulator of the GR function is melatonin (N-acetyl-5-methoxytryptamin), an endogenous hormone produced in the brain by the pineal gland. Its production decreases during aging and also in patients with Alzheimer's disease [178]. Treatments with melatonin showed effective protection of neuronal cells from β-amyloid toxicity and attenuated Tau hyperphosphorylation. However, the exact mechanism is not known yet, but it is likely to assume that its antioxidant and anti-amyloid properties may be involved. This hormone not only impairs amyloid generation but also arrests the formation of amyloid fibrils by interaction with the structure of the β-amyloid. An effect on the GR-dependent mechanism cannot be ruled out since it has also been documented that melatonin has antagonistic action on GR-mediated effects, a mechanism that involves the inhibition of the dissociation of HSP90 from the receptor, disruption of the transportosome machinery and the consequent retention of the GR in the cytoplasm [179].

5.3. Transportosome Inhibition Leads to GR Aggregation in Axons

The HSP90 inhibitor geldanamycin prevents the retrotransport of agonist-preloaded GR due to the disruption of the chaperone function [180]. As it was shown in fibroblast cells, the treatment of neurons with geldanamycin slowed down but did not entirely block the retrograde movement of GR in the cell body, *i.e.* with time (more than one hour *versus* 10 min in normal conditions), GR becomes nuclear anyway. However, in neurites, the GR transport towards the nucleus is blocked by the HSP90 inhibitor [181]. Interestingly, the receptor collects in globules located periodically along the neurites (Fig.**4**). When geldanamycin is withdrawn, the GR exits these globules and movement towards the nucleus continues. If geldanamycin is maintained in the medium, the GR is targeted to degradation *via* the proteasome. This was evidenced because CHIP (*C-terminus of HSC70-interacting protein*), the E3-ubiquitin ligase for the GR [182], also moves into those globules by a glucocorticoid-dependent mechanism when cells are treated with geldanamycin (Fig.4). Consequently, in the neurites of cells exposed continuously to the HSP90 inhibitor, the ubiquitin ligase that initiates the process of GR degradation by proteasome moves with the receptor into centres where protein degradation takes place [181]. HSP70, which is also required for GR proteasomal degradation, is also recruited to the same structures. All this process is inhibited by MG132, a proteasome inhibitor. A possible explanation for the periodic location of these 'GR globules' along the neurites may lie in the fact that the receptor accumulates in protein-quality control centres containing the machinery (for example, CHIP and HSP70) required for proteasomal degradation, and it localizes periodically along the neurite. Because HSP90 is also capable of interacting with cytoskeletal proteins [183], it can also be possible that GR aggregates due to an alteration in the cytoskeletal network.
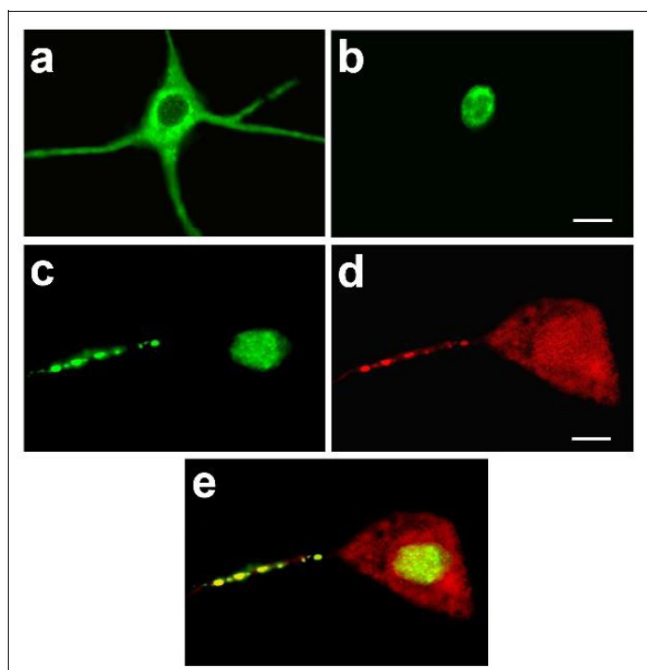
Fig. (4). HSP90 inhibitors aggregate GR in neurites. GFP-GR localizes in the cell body and neurites of neurons not exposed to steroid (**a**), whereas it was fully accumulated in the nucleus 30 min after the addition of 100 nM dexamethasone (**b**). When the cells were preloaded on ice with a steroid (to permit steroid binding, but not the nuclear translocation), and then incubated at 37°C in the presence of 0.1 μM geldanamycin, the GFP-GR pool of the cell body rapidly moved into the nucleus, but not the receptor present in long neurites (**c**). Here, GFP-GR formed aggregates that co-localized with CHIP (**d**) the E3-ligase of GR, and also HSP70 (not shown). Panel € shows the colocalization of GFP-GR (green) and CHIP (red). Bar= μ10 m. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

5.4. CHIP, HSPs and Dynein Motors

The excessive formation of protein aggregates and/or their fibrillar structures is generally observed in at least thirty different human diseases, most of them being neurodegenerative diseases [184, 185]. In highly polarized cells such as neurons, the axonal transport of organelles, vesicles, mRNAs, signaling proteins and transcription factors to and from the neuronal cell body is a critical issue that requires the co-ordinated action of motor proteins. Therefore, it is not surprising that impairing axonal transport adds to both the initiation and progression of several neurodegenerative diseases [186, 187].

As commented in the previous section, CHIP is a key neuronal E3-ligase responsible for proteasome substrate recognition in the case of damaged or aberrantly unfolded proteins [138]. Similar to the case of the GR aggregates described in Fig.4, poly-Q isoforms of the androgen receptor (AR) are also targeted to proteasomal degradation *via* CHIP [188]. The glutamine tract encoded by the AR gene comprises between 9 and 37 residues, but there are pathological expansions to 38 or more glutamines. This causes SBMA (*Spi-*

nal and Bulbar Muscular Atrophy), also known as Kennedy's disease, a progressive neuromuscular disorder that affects only men [189]. It is characterized by AR aggregation, especially in spinal cord motoneurons and skeletal muscles, induced by the presence of androgens. Therefore, the immunoadsorption of poly-Q AR is accompanied by co-immunoadsorption of HSP90, p23, and the HSP90-binding immunophilins FKBP52 and PP5 and the dynein/dynactin motor complex [188], consistent with the entry of poly-Q AR into aggregates as trafficking complexes. In agreement with this observation and like the case above described for GR, HSP90 inhibitors promote proteasomal degradation of the AR [190, 191] and ameliorate poly-Q-mediated motor neuron impairment in mouse models [191, 192]. Like the case of the GR, HSP70 also co-stains with ubiquitin and proteasome components.

Notably, HSP90 and HSP70 play opposing roles in the triage of misfolded proteins. Thus, HSP90 stabilizes proteins in a near-native state, protecting them from degradation. In contrast, when the protein is greatly misfolded to be stabilized by HSP90, HSP70 facilitates its ubiquitination by chaperone-dependent E3 ubiquitin ligases, such as CHIP. Interestingly, the chaperone BAG3 interacts with HSP70 in complexes with CHIP and these polyubiquitinated substrates [193]. When this heterocomplex commands aggresome complexes, the direct retrograde transport of misfolded proteins occurs on microtubules towards the MTOC, and those aggregated complexes that were sequestered in these misfolded structures become cleared by a different system rather than by the proteasome, *i.e.* the CHIP•HSP70•BAG3 complex targets poly-Q AR to degrade the lysosome by chaperone-assisted selective autophagy [194, 195]. Both HSP90 inhibitors and HSP70 ligands such as VER-155008 [196] enhance this activity. Taken together, the evidence provides strong encouragement for the sustained development of small--molecule modulators of the HSP90/HSP70 chaperone machinery as a potential therapeutic approach.

In cases of human Alzheimer's disease, the level of CHIP expression in the brain is inversely proportional to the degree of Tau protein aggregation [197]. In a transgenic mouse model of Alzheimer's disease, it was also shown that the accumulation of β-amyloid reduced the expression of CHIP, whereas the level of Tau protein increased simultaneously [198]. Conversely, the restoration of CHIP expression could rescue the normal level of Tau. Moreover, CHIP is also able to interact with APP and, in certain contexts, it can accelerate the removal of β-amyloid and therefore protect cells against proteotoxicity [199], following a mechanism where the effects of CHIP, HSP70 and HSP90 are cooperative. All these observations highlight the critical role of CHIP and HSPs in Alzheimer's disease, Parkinson's disease, Lewy's Body Disease, prion or huntingtin pathologies. Table **2** summarizes the properties of all HSPs, immunophilins, and other molecular chaperones discussed here that are involved in the biology of aggregated proteins responsible for neurodegenerative diseases [107, 135, 195, 200-202].

Table 2. Chaperones and co-chaperones related to neurodegenerative diseases.

Protein	Biological functions	Main Localization	Diseases*	References
HSP90	Protein folding, affords functional activity to clients, degrades P-Tau, increases Tau solubility, amyloid fibril formation, α-synuclein vesicle binding	Ubiquitous, mostly cytoplasmic; Extra-C cellular	AD, HD, ALS, KD	[109, 135, 139, 188, 199]
TRAP1	Mitigates toxicity of α-synuclein, Prevents the formation of fibrils, Regulates CyPD	Mitochondrial matrix, Partially cytosolic	PD, AD?	[33, 34, 38, 39]
HSP70	Mitochondrial import of proteins, Tau turn-over (increases degradation), Protein folding	Ubiquitous, mostly cytoplasmic, Extracellular	AD, PD, HD	[24, 26-29]
HSP60	Folding of mitochondrial matrix proteins, Hypomyelination	80%: Mitochondrial 20%: Cytosolic, ER, Peroxisomes; Extra-cellular	ALS, BHLD, AD, SPG13	[12, 15-18]
HSP27	Averts filament degeneration, Increases dephosphorylated Tau levels, Restoration in the amyloid plaque and tangle formation, Prevention of fibril formation and α-synuclein aggregation.	Cytoskeleton, Synaptic and outer mitochondrial membranes, Extra-cellular	AD, PD	[44-47]
CyPA	Prevents abnormal protein aggregation, fibril formation, amyloid toxicity, and ROS damage; Stabilizes a-synuclein	Cytoplasm, mito- chondria, nucleus, Extracellular	AD, PD	[71, 74, 77, 78]
CyPD	Regulation of mitochondrial permeability transition pore, Apoptosis, Excitotoxicity	Mitochondria	AD, HD, ALS, KD	[59-63]
Pin1	Influences Tau and β-amyloid stability, Can restore the functional activity of P-Tau	Nucleoplasm, cytosol	AD, Tauopathies	[88-91]
FKBP12	High level of aggregation of α-synuclein	Cytoplasm	PD, AD, Lewy Body Dementia	[79-81]
FKBP38	Inhibits apoptosis by recruitment of Bcl2 to mitochondria, Decreases β-amyloid levels	Mitochondria	PD, AD	[112, 115]
FKBP51	Prevents Tau degradation enhancing neuro-toxicity, Interacts with β-amyloid (function?)	Nucleus, cytosol and mitochondria	AD, Taupathies	[108, 109]
FKBP52	Promotes Tau oligomerization; protects against β-amyloid toxicity	Nucleus, cytosol	AD	[88, 97, 98]
FKBP63	Prion spreading and degradation	ER, mitochondria	Prion Disease, AD?	[126, 128]
CyP40	Protects against β-amyloid toxicity, Reduces Tau oligomers and tangles	Cytosol, nucleus	AD	[120, 121]
CHIP	Targets poly-Q AR for degradation, Prevents Tau aggregation	Cytoplasm, nucleus	SBMA, KD, AD	[189, 191, 193, 196]
PTPA	Protects against β-amyloid toxicity	Nucleus, cytoplasm	AD	[131, 132]

(*) AD: Alzheimer's Disease, **PD;** Parkinson's Disease; **HD:** Huntington's Disease; **KD:** Kennedy's Disease; **ALS:** Amyotrophic Lateral Sclerosis; **SBMA:** Spinal and Bulbar Muscular Atrophy; **BHLD:** Brain Hypomyelination Leukodystrophy; **SPG13:** Hereditary Spastic Paraplegia; **?:** Uncertain/To be demonstrated.

6. MITOCHONDRIAL TRAFFICKING OF TPR-DOMAIN IMMUNOPHILINS

The presence of immunophilins in mitochondria is a field recently developed. The biological functions of these proteins in the organelle are poorly understood, and mostly, they are subject to speculations and hypothesis based on what is known for 'regular' immunophilins. Nonetheless, the most common feature described for all of them in mitochondria relates to their participation in mechanisms of apoptosis.

6.1. Mitochondrial FKBP38

FKBP38, FKBP51 and CyPA have been described in the mitochondria of neurons, but only FKBP38 shows a known mitochondrial localization signal that justifies this location [203]. The mitochondrial localization of FKBP38 has been associated with anti-apoptotic actions due to its capability to recruit the antiapoptotic factor Bcl2 to the organelle. This immunophilin also shows the capability to translocate to the endoplasmic reticulum. Thus, when the human neuronal cell line SH-SY5Y is exposed to a mitochondrial uncoupler such as carbonylcyanide-*m*-chlorophenylhydrazone, mitochondrial membrane depolarization is triggered, and the relative

abundance of most mitochondrial proteins decreases in parallel to the progression of mitophagy [204]. However, the amounts of FKBP38 and Bcl-2 are not down-regulated, demonstrating that not all mitochondrial proteins are necessarily degraded during mitophagy. Actually, FKBP38 leaves mitochondria and resides in the endoplasmic reticulum. The physiological relevance of such translocation during mitophagy lies in the fact that it seems to be a requirement to trigger anti-apoptotic mechanisms rather than being responsible for mitophagy itself. This is supported by the fact that mitophagy also occurs in FKBP38-deficient cells [112, 204]. Neuronal FKBP38 has a Ca^{2+}/calmodulin-stimulated PPIase activity that results in being essential for FKBP38–Bcl-2 interaction to occur, Bcl-2 being a regulator of the transcriptional activity of several other factors such as NF-κB, AP1, CRE and NFAT [205]. It has also been associated with calcineurin and p53, possibly modulating their function [206]. In short, FKBP38 indirectly regulates the activity of those factors involved in the apoptotic response and represents one of the first examples of a cofactor-regulated PPIase. This activity participates in Bcl-2-mediated apoptosis control and might provide the cellular mediator of neurotrophic effects of neuroimmunophilin inhibitors.

6.2. Mitochondrial FKBP51

FKBP51 has always been considered a cytosolic soluble protein. Recently, it was unexpectedly detected in mitochondria [207]. This localization is not dependent on the cell type since it was observed in neuroblastoma cells, hippocampal neurons, glial cells, adipocytes, fibroblasts, *etc*. Associated with this subcellular localization (which represents more than 50% of the cellular pool), FKBP51 shows antiapoptotic actions. Thus, its overexpression stabilizes the mitochondrial membrane depolarization, whereas its knock-down makes mitochondria more sensitive to harmful stimuli [207]. The mitochondrial localization of FKBP51 in normal resting cells becomes nuclear upon the onset of stress situations. Thus, FKBP51 translocates rapidly (15–30 min) to the nucleus, where it is thought to play anti-apoptotic roles. Such nuclear localization is rapidly reversed when the stimulus ceases. It has also been documented that during fibroblast differentiation into adipocytes, FKBP51 abandons mitochondria and migrates to the nucleus with a PKA-dependent mechanism [208].

Interestingly, mitochondrial FKBP51 was found in the GR•HSP90 mitochondrial complex, its biological effect being unknown to date [207]. However, it is accepted that mitochondrial GR drives the expression of mitochondrial genes [209, 210]. Therefore, FKBP51 may play a similar inhibitory role as that described for the nuclear receptor, which should lead to antiapoptotic actions. When cells were treated with dexamethasone, Bax accumulated in mitochondria and became associated with Bak, Bim, Bcl-xL [211]. Moreover, cytochrome c and active caspases were detected, indicating that during the early steps of glucocorticoid-induced apoptosis, the mitochondrial GR plays a crucial role.

These observations should be evaluated within the context of the role of glucocorticoids in the dysregulation of the HPA axis, the classic inhibitory action of FKBP51 on GR-dependent response, and the consequent development of neurodegenerative diseases. Importantly, the translocation of FKBP51 to nuclei concentrates almost the entire cellular pool of the immunophilin in the nuclear compartment, and colocalizes with GR. In cortical neurons, the mitochondrial translocation of GR is followed by a series of events that exacerbate mitochondrial oxidations in a time- and dose-dependent fashion [212, 213]. The biological relevance relates to the generation of ROS and subsequent neurodegeneration observed after chronic exposure to glucocorticoids. In other words, an inappropriate response to these hormones may contribute to the pathogenesis of Alzheimer's disease and Parkinson's disease.

6.3. Mitochondrial CyPA

In contrast to the group of TPR-domain immunophilins, CyPA (also named CyP17), the small archetype of the cyclophilin subfamily, does not interact with HSP90. CyPA lacks TPR-domains (Fig.2). Actually, its full structure is limited to the PPIase domain. We have recently evidenced by confocal microscopy and biochemical fractionation that CyPA is also a mitochondrial factor [214]. Comparable to

FKBP51, CyPA also abandons mitochondria upon the onset of stress stimuli and concentrates in the cell nucleus in a reversible manner, although its nuclear translocation rate is relatively slower than that of FKBP51 ($t_{0.5}$ of □2 h *versus* 15-30 min). Standard assays showed that the overexpression of CyPA in N2a neuroblastoma cells favoured cell survival when N2a cells were exposed to harmful stimuli, which normally leads to apoptosis. Interestingly, it has also been documented that CyPA directly interacts with p23 [158], a small acidic Hsp90-cochaperone that has already been evidenced to show antiapoptotic action per se [215]. The association of both factors, CyPA and p23, enhances the antiapoptotic effect when they are assembled in a functional unit whose high level of expression plays a significant role in cell survival [214]. This observation may explain the observed effects *in vivo* and *in vitro* against oxidative stress and ischemia-like situations, and the putative beneficial action of the specific p23 ligand genduin, which has recently been proposed as a non-conventional therapeutic agent for Parkinson's disease [216].

7. HSF1 AND MITOCHONDRIAL RESPONSE

The expression of both HSPs and immunophilins is under the command of the Heat-Shock Factor (HSF), a primarily cytoplasmic transcription factor bound to a similar HSP90-based heterocomplex as that described for steroid receptors. There are various isoforms of HSFs (namely HSF1, HSF2, HSF3, HSF4, HSF5, HSFXs and HSFYs,), HSF1 being the best characterized and commonly expressed among vertebrates [217], whereas invertebrates express only a single HSF [218]. Among the mammalian HSFs, HSF1 is the master regulator of HSP expression, although HSF2 can also hetero-trimerize with HSF1. HSF1 is cytoplasmic in its monomeric form, which is kept inactive in the cytoplasm by the HSP90 protein complex [217]. Upon exposure to protein-damaging stress, it is thought that the HSPs are diverted to the newly misfolded proteins, allowing the HSF to translocate to the nucleus as homotrimers. It binds to *Heat Shock Element* sequences in the promoters of genes encoding HSPs to turn on transcription [217].

There is consensus to affirm that the HSF1shows protective action against neuronal death in diverse models of proteinopathic neurodegenerative diseases. Accordingly, the HSF1 knock-down favours the neuropathological effects of toxic misfolded proteins [219], whereas its overexpression shows protective effects [220]. In line with these observations, the degradation of HSF1 in neurons contributes to mitochondrial dysfunction and synaptic deficits [221, 222]. Accordingly, it has been reported that in Huntington's disease, HSF1 is abnormally degraded by the sequential action of inappropriately up-regulated CK2α' (Protein kinase CK2 alpha prime) and Fbxw7, an E3 ligase [222]. In turn, this leads to mitochondrial dysfunction due to a deficient response to stress of molecular chaperones and immunophilins. Actually, the major role of HSF1 in mitochondrial activity was reported in cardiomyocytes of HSF1^{-/-} mice, which showed increased overloading of calcium and exacerbated production of ROS that cause mitochondrial permeability transition

pore to open [223]. Such mitochondrial dysfunction contributes to creating an imbalance of potential redox homeostasis leading to oxidative damage, not only in Huntington´s disease, but also in Alzheimer's and Parkinson's disease patients [224]. In the brain, this oxidative stress causes damage that contributes to neuronal loss and formation of protein aggregates. Thus, similar mechanisms have been proposed for other neurodegenerative diseases such as Kennedy's disease and Prion disease, where the disruption of the normal HSF-HSP functional axis also leads to the accumulation of harmful protein aggregates that interfere with intracellular trafficking.

Among all the neuro-degenerative diseases, Huntington's disease is perhaps the most sensitive to mitochondrial dysfunction due to regulation of HSF1 by CK2α' and Fbxw7 E3 ligase described above. The decreased HSF1 levels and the inability to resolve protein aggregates are exacerbated, thereby contributing to increased proteotoxicity, neuronal dysfunction and death. Moreover, axonal trafficking is greatly affected due to the particular scaffolding nature of the protein huntingtin that interacts with both kinesin-1 and dynein motors, as well as over four hundred other proteins, many of which are active in microtubule-based or actin-based transport [225]. Thus, the transport of key vesicles is affected carrying BDNF (Brain-Derived Neurotrophic Factor), GABA receptors, precursors of synaptic vesicles, the amyloid precursor protein, VAMP7 (involved in the fusion of transport vesicles to their target membranes), Rab proteins, protein-RNA complexes, autophagosomes, lysosomes and endosomes [187]. Among all these cargoes, BDNF is perhaps the most critical due to its role in the health of the cortico-striatal neuronal circuit, the primary site of degeneration in the disease []. Striatal neurons are greatly dependent on the trophic stimulation of corticostriatal afferents. Thus, the inefficient stimulation by BDNF causes neurodegeneration.

CONCLUSION AND FUTURE PERSPECTIVES

Mitochondrial HSPs and immunophilins are vital players in mitochondrial function and consequently neuron function and survival. They regulate cardinal events ranging from protein synthesis, protein folding, protein transport, ATP production, reactive oxygen species production and cell homeostasis. Failure in their key roles is likely an essential component that worsens other deficiencies of the cell. Their expression and function are vital to participate in the natural aging process and progression of neurodegenerative and metabolic diseases that affect the 'mitostasis'. Although there are several studies on the role of the GR in regulating the stress response, little is known about its potential participation in mitochondrial responses. Several studies have advanced our understanding of both the structural and functional regulation of this receptor by HSP90-based oligomeric complexes. Nonetheless, there is still much to learn about the *in vivo* regulation of GR signaling by HSP90 cochaperones and how the intracellular feedback loops and the major HPA axis of the whole body are interconnected. This is particularly true for PPIases, which are a unique family of protein chaper-

ones that began to be considered in this aspect just a short time ago. Therefore, modulating the activity of these proteins through specific drugs may restore the normal processing of, for example, β-amyloid fibrils or Tau aggregation to non-pathogenic states, or even better, prevent such pathogenic processing that leads to neurodegeneration.

In addition to their natural roles in assisting protein folding, HSPs have other functions like the regulation of protein degradation and signalling pathways, especially those dependent on the assistance of HSP90. Therefore, the potential use of drugs targeting these chaperones is a likely pharmaco-therapeutic alternative. For example, it was shown *in vivo* in a rat model where the animals were injected with a β-amyloid peptide in the CA1 area of the hippocampus, and then treated orally with 17-(allylamino)-17-demethoxy-geldanamycin (17-AAG) [226]. The encouraging results demonstrated that immediate neuronal damage generated by the accumulation of β-amyloid aggregation was depurated by the treatment, which showed a rapid induction of endogenous HSP90 and HSP70 and great improvement in the cognitive capabilities of the animals. The inhibition of HSP90 could be a useful pharmacological tool in cases of Alzheimer's disease to counteract the aggregation of hyper-phosphorylated Tau. The disadvantage is that geldanamycin itself cannot cross the blood-brain barrier [227], although more permeable and less toxic derivatives such as 17-AAG and 17-DMAG could be an alternative; they are difficult to formulate, have limited oral availability, or have caused varying degrees of hepatotoxicity in clinical cancer trials [228]. The search of HSP90 inhibitors in neurodegenerative diseases could benefit from clinical trial studies regarding anti-cancer treatments.

Because chaperones are highly associated with the cancer field and neurodegenerative diseases, an alternative therapeutic approach could be the thermal treatments against cancer. Thermotherapy is a relatively novel treatment that uses heat in a targeted way to generate hyperthermia in the tumour. This makes more effective conventional treatments such as radiotherapy, presumably due to the positive influence of the induced chaperones [229, 230], target more efficiently tumor areas which are poorly perfused, hypoxic or have a low tissue pH [231]. Not only HSPs are induced with this procedure, but also the HSF1 becomes activated, enhancing all the mechanisms to clear protein aggregates.

A more direct approach can also be assayed, *i.e.* using peptide inhibitors. For example, Nemirovsky *et al*. [19] used a β-amyloid-HSP60 peptide conjugate vaccine to treat mice. This immunization led to the induction of specific antibodies that produced a significant reduction in cerebral amyloid accumulation. This proves that the external application of proteins could be an alternate approach, which could be explored properly to broaden the search for an efficient therapy.

The potential role of immunophilin ligands in neurodegenerative diseases needs to be investigated. It is clear that the expression balance of the immunophilins FKBP52 and FKBP51 plays a critical role in the neurodifferentiation

[103, 232] and neuroregeneration [102, 233] process triggered by the macrolide FK506, but it was not assayed in those pathologies. However, FK506 appears to target glial cells in the brain and impairs the inflammatory reactions mediated by astrocytes and microglia [234], which could be of help for the inflammatory reaction that usually accompanies neurodegenerative diseases. However, FK506 could potentially reduce calcineurin activity (which dephosphorylates Tau [235]) *via* FKBP12 inhibition and, therefore, promotes greater Tau phosphorylation. On the other hand, it has been shown that FKBP51 and Tau proteins interact, and that in cell culture, the overexpression of this immunophilin significantly increases the phosphorylation of Tau and total Tau proteins [109]. Inversely, PP5 dephosphorylates Tau and can restore microtubule-binding function [236]. This is relevant since both FKBP51 and PP5 are competing immunophilins to bind GR•HSP90 complexes, and glucocorticoids increase FKBP51 expression and are responsible for major depressive disorders.

The studies published to date indicate that central and peripheral nervous systems are enriched in only five out of the 16 FKBPs encoded by the human genome, *i.e.* FKBP12, FKBP38, FKBP51, and FKBP52 [204], and a poorly characterized FKBP of 65-kDa localized in the endoplasmic reticulum that is predicted to play a role in the folding and trafficking of secretory proteins [205]. Among the members of the CyP subfamily, the best studied is CyPA, and only in the very recent times, CyP40 has been identified as being enriched in the basolateral amygdala of normal mice, and it is in reduced levels in mice showing impairments in extinction learning capability [206]. Interestingly, these neurons show that CyP40 colocalizes with GR, and that the extinction regulating effects are inhibited by GR antagonists. This suggests a potential role of CyP40 in post-traumatic stress disorders. Much work needs to be done to identify unique neuro-immunophilins, understand their signalling pathways, the proper regulatory networks, and assess their biological responses to injury. This will greatly enhance our understanding of the mechanisms required to promote efficient and healthy cellular neuroprotection.

Finally, new therapeutic approaches are being incipiently explored. One alternative is based on the preclusion of the abnormal targeting of proteins to mitochondria, *i.e.*, it favours protection of normal mitochondrial functions increasing neuronal survival, and at the end, ameliorating symptoms of neurodegenerative disorders. In line with this notion, inhibitors of the molecular association between Hsp90/Hsp70 and the mitochondrial protein import receptor Tom70 and TPR domain co-chaperones have been recently designed and tested [237, 238]. One of these novel drugs is GMP-1 (2-(methoxy-methyl)-pyrimido-[1,2-a]enzimidazole-4-ol, which was found to compete with HSP90 for Tom70 binding because it interacts with the TPR domains of the translocase that participates in the recognition, unfolding, and translocation of preproteins into the mitochondria, and shows a low affinity for other TPR proteins such as PP5, FKBP51 and Tom34. GMP-1-treated animals show lower astrogliosis and activation of microglia due to reduced neuroinflammation [238], a phenomenon that is linked to the reduced brain β-amyloid aggregation. Therefore, new therapeutic strategies based on protecting mitochondrial function *via* modulation of molecular chaperone network are quite possible and open a new front to battle against neurodegenerative diseases. Today, it is clear that the association of Hsp70 and Hsp90 with co-chaperones determines the fate of protein aggregates by clearing aberrant forms from the cell. In such a scenario, the development of small molecule modulators that can harmonize the interaction of chaperones, co-chaperones and misfolded proteins is an endeavour of great interest and necessity.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors have no conflicts of interest, financial or otherwise.

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