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Review Article

# Mortalin as a Biomarker Disease and Therapeutic Target -

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## Abstract

Heat Shock Proteins (HSPs) are specific proteins that act in stressful situations, such as those caused by many diseases. Mortalin, one of the most important HPS, is a mitochondrial molecular chaperone usually found in multiple subcellular locations, being directly related to the processes of cellular stress. Given its importance as a disease biomarker, therapeutic target and therapeutic agent, the aim of this review is to specify mortalin's functions and its relationship with diseases already presented in the literature, such as in neurodegenerative (Parkinson's and Alzheimer's disease), immunological (human immunodeficiency virus), and endocrine diseases (diabetes), as well as in different kinds of cancers (ovarian, urogenital, brain, colorectal, leukemia, among others), providing information about this important thermal protein for future studies.

**Keywords:** Alzheimer; Cancer; Diabetes; HIV; Heat shock protein; Parkinson

## INTRODUCTION

Heat Shock Proteins (HSPs) are chaperone proteins vital to the cell providing protection against a variety of cellular stressors, being their nomenclature derived from the discovery proteins responded to heat stress as well as their molecular size [1]. These thermal proteins are involved in many processes to maintain cellular homeostasis, as they help newly synthesized proteins to adopt their correct conformation, restore the structural folding of deformed proteins, and act in the degradation of proteins with incorrect and irreversible folding. In addition, HSPs are also important in the regulation of caspase-dependent and -independent apoptotic pathways and in the modulation of the immune system, as they act in the formation of antibodies, the presentation of antigens and their recognition by T lymphocytes and natural cell killers [2].

HSPs are present in various cellular compartments such as the nucleus, cytosol, and endoplasmic reticulum, being the cytosolic the most abundant and expressed in cells, including the HSP90 family [3]. However, much of these proteins are also found in the mitochondrial region (HSP60, HSP70 and TRAP -1), either as result of local production or formed in the cytoplasm and transported to mitochondria. These organelles play an important role in the cells' survival, as loss of mitochondrial function or integrity can activate various death pathways, leading to the release of apoptotic proteins in the cytoplasmic matrix [4,5].

Mortalin, belonging to HSP70 family, encoded by HSPA9 and also called GRP75/PBP74, has been shown to possess unique functional properties in several subcellular loci, and its functional roles can be divided into two broad categories according to the subcellular localization. The first one comprehends those that take place in the mitochondria, such as acting in the import of nuclear-encoded, cytoplasmically delivered proteins, folding of nascent proteins, and protein degradation within the mitochondrion, as well as interaction with submitochondrial components. On the other hand, extramitochondrial functions are included in the second class, responsible for promoting interactivity with protein 53 (P53), growth factors, centrosomes, endoplasmic reticulum proteins immune system components and metabolic components [4,6,7].

Mortalin, considered the major mitochondrial chaperone in higher eukaryotes, presents a different staining pattern in normal and immortalized cells. Studies show that it is involved in apoptosis and prevention of cell growth in malignant cells from several organs [8]. This specific HSP has recently been described as a sensor of neuronal stress, being a mitochondrial chaperone protein involved in the quality control of proteins imported into the mitochondria. It is thought to have numerous functions such as stress response, intracellular transport, antigen processing, control of cell proliferation, differentiation, and tumorigenesis [9,10].

Mortalin is translated in the cytosol and load into the mitochondria, being expressed in all cell types and tissues studied so far and is thought to perform several essential functions [11,13]. Currently investigations have improved the comprehension of its functionality from an involved protein in mitochondrial import, energy production, and chaperoning of misfolded proteins, to that of a sentinel of stress that has multiple binding partners, or even to a killer protein that contributes to the assistance of many diseases. It has proven to be an attractive target for cancer therapy and, also deserves attention from the perspective of age-related disease treatment and healthy aging [14].

Human mortalin has been successfully purified and described by Luo, et al. [15] which provided its basic biochemical characterization, and the basis for future deepened biophysical and kinetic research of its function and its association to various human pathologies states. Leonard, et al. [16] found signs that mortalin is also responsible in mediating inflammation and endothelial cell permeability associated with acute lung injury. Dores-Silva, et al. [17] demonstrated that this thermal protein tended to interact with membranes resembling the mitochondrial inner membrane, which may be relevant for its function in translocation of proteins into mitochondria. It has several binding partners, being related with various roles, such as stress response and control of cell proliferation to inhibition and/or prevention of apoptosis.

Several structural and functional mechanisms are involved in the activity of this protein, and few changes in its expression levels could take to serious biological effects [18]. According to Wadhwa, et al. [11], some of the functions of mortalin, such as inactivation of P53, could be used as beneficially to immortalize human cells *in vitro* or targeted for tumor therapy, targeting of other functions, such as, chaperonization, mitochondrial biogenesis and intracellular traffic.

## HEAT SHOCK PROTEINS AS BIOMARKERS DISEASES AND THERAPEUTIC TARGETS

### HSP inhibitors

The overexpression of HSPs correlated with favoring the survival of tumor cells make these proteins a potential target for studies on new therapies in various types of malignant neoplasms, thus, HSP inhibitors have been proposed to be beneficial to cancer treatments [2]. These inhibitors, together with chemotherapy, could be used as chemo sensitizing agents, reducing the resistance of tumor cells to chemotherapy, increasing the effectiveness of action with lower doses. Several studies have used techniques that employ the use of siRNA, antisense oligonucleotides and small molecules to inhibit HSPs, both *in vivo and in vitro* [2].

Inhibition studies focusing on HSP27, HSP90 and HSP70 proteins have had surprising results. In a murine orthotopic model, Hadaschik, et al. [19] found that the inhibition of HSP27 was concomitant with the reduction in the growth of human bladder cancer cell lines. It has also been shown that HSP27 inhibition can increase the sensitivity of tumor cell lines, making them more vulnerable to chemotherapy [20].

HSP90 has been selected for many studies of neoplastic biomarkers since the non-toxic levels of inhibitors of this protein have antitumor efficacy [21]. On the other hand, depending on the cell where it is expressed, the level of affinity of HSP90 with the inhibitor changes, suggesting that there is about a 100-fold greater binding strength between HSP90 and its inhibitor when expressed both in tumor cells and in normal cells. This can occur probably due to a change in the conformation of HSP90 expressed in tumor cells that causes a greater affinity to the inhibitor [2,21,22].

Regarding mortalin, inhibition of HSP70 expression was also correlated with reduced growth of human bladder neoplastic cells [23]. He, et al. [24] found that bladder cancer cells became more susceptible to Mitomycin C treatment when HSP70 expression was inhibited. Due to this potential, HSP inhibitors has being increasingly investigated through clinical trials to assess their safety and effectiveness as an anti-tumor therapeutic agent [20].

Given the fact that there are HSPs compartmentalized in mitochondria, these proteins are also possible targets for antitumor therapy based on the use of HSP inhibitors. As inhibitors examples, TRAP-1 is a protein with great potential as a target for anti-HSP therapy, having preferential expression in several tumor cells [25]. Shephardin and Gamitrinibs, a new class of small HSP90 inhibitor molecules projected to accumulate in mitochondria, have proven effective in inhibiting the activity of mitochondrial chaperones. Gaamitrinib, for example, accumulates in the mitochondria in all kinds of cells (normal and tumor) and inhibits ATP-ase action in TRAP-1, resulting in the breakdown of mitochondrial integrity. In an assessment of a preclinical model of prostate cancer, that inhibitor induced apoptosis both of androgen-dependent and nondependent cells, eliminating chemo-resistant prostate cancer cells. Furthermore, that effect occurred without any negative consequence on normal cells, and the inhibitory activity was specific for TRAP-1, without influencing the activity of HSP-90 [26]. In animal models of prostate cancer, Gamitrinib produced localized anticancer activity, that is, without providing systemic toxicity [27].

## Neurological diseases

It is widely accepted that mitochondrial dysfunction and altered mitochondrial dynamics play an important role in the Parkinson's Disease (PD) and Alzheimer's Disease (AD) [28-30]. Thus, mortalin has been the subject of many studies related to these two important diseases [31-34].

The possible involvement of mortalin in the pathogenesis of PD was investigated in rats by Chiasserini, et al. [35] by means of an electrophysiological approach and pharmacological inhibition of mortalin in normal and parkinsonian states. Proteomic assays were utilized to evaluate the changes in striatal protein expression in the 6-hydroxydo-pamine rat Parkinson model. The electrophysiological results of MKT -077 (an analog of rhodamine 123 that function as an inhibitor of HSP70) were evaluated by field potential recordings from corticostriatal brain slices withdrawn from control sham-operated and 6-hydroxydopamine-denervated rats. The slices were also analyzed in the presence of rotenone, an inhibitor of mitochondrial complex I. Comparing rats treated with 6-hydroxydopa mines with sham operated animals, proteomic analysis showed downregulation of mortalin in striata from the animals. The amplitude of the corticostriatal field potential under physiological conditions was reduced by MKT-077, thus induced membrane depolarization and internal currents in the striatal middle spiny neurons. Moreover, was concluded that MKT-077 caused significant alterations in striatal slices from PD animals as well as in slices treated with a submaximal concentration of rotenone, in concentrations that did not elicit electrophysiological effects under physiological conditions, suggesting a crucial link between mortalin function and mitochondrial activity under both normal and pathological situations that mimic the parkinsonism.

Wadhwa, et al. [36] showed that mutation of mortalin has been detected in some PD patients, where mutant mortalin lacked assignments related in combating oncogenesis and caused increased oxidative stress, concluding this mutation contribute to PD, showing for the first time the mechanism and functional significance of mortalin and its point mutations in controlling cell proliferation regarding to oncogenesis and premature aging.

Dysfunction of mortalin related with Parkinson enlarges the susceptibility of cultured cells to proteolytic stress, leading to alterations in the function and morphology of mitochondria. Zhu, et al. [37] produced the first Drosophila model with loss of HSC70-5/mortalin function, and this decreasing in mortalin expression recapitulated some of the defects, such as reduced ATP levels, unnatural posture of wing, decreased lifespan, and decreased spontaneous locomotion and climbing ability. Dopaminergic neurons seem to be more sensitive to these losses than other neuronal subtypes and non-neuronal tissues. Later degenerative incident can be produced by loss of synaptic mitochondria, an early pathological alteration that precedes both behavioral abnormalities and structural alterations at the neuromuscular junction of mortalin-knockdown Drosophila larvae, which exhibit increased mitochondrial fragmentation. Parallel, autophagy is upregulated, indicating that mitochondria are degraded by mitophagy. *Ex vivo* data from human fibroblasts demonstrate that augmented mitophagy represents an early pathological alteration that precedes apoptosis. This model of mortalin loss can be helpful for further unraveling the complex network of signaling pathways underlying the development of mitochondrial parkinsonism.

Mortalin also plays an important role in decreasing the Lewy bodies toxicity, which are abnormal aggregates of proteins that form inside neurons in PD, dementia with Lewy bodies, and some other neurodegenerative diseases [38]. Previous experiments have reported that in PD, its levels are downregulated in neuroglial cells, and other brain tissue samples. Singh, et al. [38] have shown that mortalin in serum is significantly associated with PD and can be a potential biomarker for this illness.

Cook, et al. [28] have reported that levels of this specific HPS have been lower in brain tissue from patients with these kinds of diseases, with expression shown to be lower in neurons from *postmortem* cerebrum samples. The expression of mortalin was detected in primary mouse astrocyte cultures by qPCR and confirmed by Western blot. Experiments in human postmortem tissue using confocal microscopy showed that mortalin was localized in neuroglial cells. Using a quantitative immunofluorescence staining technique, the protein has been moderately reduced in this cell type in Substantia Nigra Pars

Compacta (SNpc), but not in structures of the corpus striatum, in patients with PD compared with age- and sex-matched controls, highlighting the potential contribution of impaired astroglial function to the pathogenesis of PD. In summary, was demonstrated for the first time the presence of mortalin in astrocytes from both healthy subjects and patients with PD. Compared to controls, astroglial mortalin is significantly reduced in the SNpc of Parkinson' patients.

Ferré, et al. [9] observed that downregulation of mortalin led to mitochondrial fragmentation and axonal damage, whereas overexpression of mortalin protected against oxidative stress-mediated axonal degeneration. This demonstrates that the amount of mortalin modulate mitochondrial morphology through a direct effect on DRP1 phosphorylation, emphasizing even more the critical importance of mitochondrial dynamics in neuronal fate in these kinds of neurological diseases.

Many other studies have also investigated the effect of mortalin in others neurological disorders, such as schizophrenia [39-42], cerebral ischemia [43-47], Friedreich's ataxia [48,49], absence seizure [50,51], brain tumors [52], among others [53].

### Endocrine diseases: diabetes

Diabetes is one of the fastest growing pathologies in the world, promoting devastating macrovascular and microvascular complications, such as cardiovascular disease, diabetic kidney disease, diabetic retinopathy, neuropathy, which can lead to blindness, renal failure, lower overall quality of life, and hence death. Mortalin, through its activities in the inflammatory process, mitochondrial function and ergastoplasm stress in many of the pathogenesis of insulin resistance, has promising potency as a therapeutic target in the control of type 2 diabetes mellitus [54].

Have been observed that HSP70-modulating interventions are apt to reduce blood glucose, recover lipid profile, and improve insulin sensitivity [55]. Kavanagh, et al. [56], demonstrated that restore HSP70 deficiencies improves glucose tolerance in diabetic monkeys, concluding that pharmacological inducement of HSP70 using clinically expressive dosages of GGA also readily raised insulin sensitivity and glucose tolerance and provided important proof of concept related to the viability of HSP70-inducing strategies to the therapy of Diabetes Mellitus (DM).

The serum level of HSP70 correlates with disease duration is an important indicator, being significantly higher in patients with diabetes. Thus, higher levels in chronic diabetes versus newly diagnosed diabetes may be a warning of metabolic disturbance in the progress of the pathology [57].

Hyperglycemia-associated HSP70, via the TLR4 pathway, plays an important role in the pathophysiology of diabetic vasculopathies and might be a new target for therapeutic intervention [58]. According to Amawi, et al. [59] expression of HSP70 can be meaningly associated with progression of diabetes and its vascular changes in the liver in induced diabetic animal model.

In DM, mortalin was found to be over-produced in rat pancreas (responsible for insulin sovereignty) kept under continuous stressful conditions. Regular pancreatic insulin-secreting cells are likely to mimic pre-diabetes with prolonged exposure to the stressors. When these cells were exposed to inflammation-facilitating compounds, was observed that there is a raise in secretion of mortalin protein, being associated with lesser survival and expedited ageing, suggesting a potential role of mortalin in the pathogenesis of diabetes. This HSP may also be associated to the atypical expression of other critical diabetic hormones, e.g., glucagon and C-peptide. It is worth emphasizing that while an increase in the overall concentration of mortalin is related to cancer, diabetes and other metabolic diseases, its gene inactivation and down-regulation have been linked to neurodegenerative disorders. Although a few studies have revealed that mortalin has a direct correlation with the onset and progression of DM, more detailed investigations are warranted [60].

### Immune diseases: Human Immunodeficiency Virus (HIV-1)

Human Immunodeficiency Virus (HIV-1) infection, even in the presence of suppressive Antiretroviral Therapy (ART), is identified by a chronic inflammatory state and varying degrees of immune dysfunction. Despite the success of combinatorial ART, this disease remains a major health challenge around the world, with a large number of cases still being reported [61]. In infection with this virus, the activation of neuroglia cells leads to an imbalance in physiological functions, as the impaired astrocytic functions promote toxicity in neurons. This takes to an inflammatory reply that eventually culminates in neurocognitive dysfunction.

In NeuroAIDS, HIV-1 protein, the Transactivator of Transcription (Tat), is found in the liquor of contaminated humans. Wadhwa, et al. [62] investigated the mechanisms of mortalin in modulating HIV-1 Tat-mediated neuroinflammation and concluded that it plays a protective role in combating HIV-1 Tat-mediated damage. They also demonstrated that mortalin can degrade Tat by directly binding to HIV-1 Tat. In the presence of Tat, overexpression of mortalin was able to reduce the cytotoxic sequels of Tat in astrocytes. Indirect neuronal death was also rescued. *In vitro* results were proven as they found attenuated expression of mortalin in autopsy sections from infected patients. In conclusion, was identified a novel role for mortalin in astrocytes transfected with HIV-1 Tat. Mortalin binds to Tat in neuroglial cells, degrading it and making it unavailable for toxicity of cells. This rescued the cell from Tat-mediated deleterious effects on neuroglias cells and, also decreased indirect neuronal death, suggesting a therapeutic function for mortalin against HIV-1 Tat-induced neuronal damage.

Recent studies have also reported a HSP70 expression inversely correlates with viral replication [63], indicating that this may play an important role in the progression and prevention of pathology manifestation.

### Cancer

Neoplasms are a highly complex disorder that frequently consists of diverse cell populations with different proliferative capacities, cell surface antigens and tumorigenic abilities, responding each one differently to each chemotherapeutic agent [6]. Since neoplastic cells live in a persistent state of proteotoxic stress, they rely on the subversion of HSPs to prevent the activation of the apoptosis process. Studies have shown that HSPs are critical for tumor resistance to chemotherapy or radiotherapy and are present in all phases of oncogenesis, such as differentiation, proliferation, apoptosis, angiogenesis, invasion, and metastasis [64].

In function of the participation of these proteins on mitochondrial key activities, they are considered also important targets in cancer research [3,4]. Mortalin is present in a several kinds of cancers, showing to contribute to carcinogenesis in many ways, including

deregulation of apoptosis, deactivation of the tumor suppressor protein p53, and activation of EMT (Epithelial-mesenchymal transition) signaling [6,65-69].

Presupposes that mortalin is associated with resistance of the cells to oxidative stress [70], and has been also associated with proliferation, aggressiveness and chemoresistance of other neoplasms and has also been implicated in the mechanisms of cellular resistance to oxidative stress [8,71-74]. Inhibition of HSP70 transcription has been shown to cause massive death of breast, colon, prostate, and liver tumor cell lines, but not non-tumor cells [75].

Münster, et al. [76] demonstrated that the use of the drug 17-AAG, an HSP90 inhibitor, resulted in a decrease in proliferation of breast cancer cells by interfering with the G1 phase of the cell cycle and causing apoptosis of tumor cells. Thus, the strong association of HSPs with carcinogenesis served as a pretext to study them as biomarkers and targets for antineoplastic therapies [2].

Although HSPs are expressed at all levels in normal urothelium, several studies have associated high expression of some of these proteins with bladder cancer. It has also been observed that the expression of HSP70 family proteins such as HSP70-2 is associated to the phase and grade of bladder tumor [2]. In addition, Garg, et al. [77] showed that HSP70-2 is expressed in 72 to 88% of urothelial tumors but is not normally found in the urothelium.

Yun, et al. [6] reported that upregulation of mortalin collaborates to cancer cell stemness. Some markers of cancer cell stemness were upregulated in mortalin overexpressing cells that demonstrated higher spheroid formation ability. These cells also exhibited higher migration and were less responsive to a range of cancer chemotherapeutic agents. It is worth emphasizing that knockdown of mortalin by specific shRNA sensitized these cells to all compounds managed in this experiment. Researchers reported that low doses of anti-mortalin molecules, such as MKT -077 and CAPE, also promote suchlike sensitization of cancer cells to chemotherapeutic agents, becoming them potential applicants for effective cancer chemotherapy. Was demonstrated that mortalin executes a fundamental role in mitochondrial biogenesis [78]. It has been identified as the sole ATPase unit of the mitochondrial import complex, which is essential for the translocation of most mitochondrial inner membrane and matrix proteins. It binds to Tim44 (inner mitochondrial membrane translocase) and serves as an ATP-driven motor to generate force during protein import [79,81]. According to Starenki, et al. [82] the effects caused by the mortalin depletion was mitochondrial bioenergetics alteration, depolarization of mitochondrial membrane, decreasing of oxygen absorption and extracellular acidification, and raising of oxidative stress in medullary thyroid carcinoma cells. Yun, et al. [6] previously demonstrated expression of retrovirally expressed mortalin in mitochondria, and therefore, the mitochondrial functions of upregulated mortalin may help to increased metabolic demand related with increased proliferative capacity of cancer stem cells G [70].

Cholangiocarcinoma (CC), a malignant cancer that appear from the epithelial cells of the bile ducts, is the second most common primary liver cancer around the world [83]. Li, et al. [84] reported that mortalin is involved in the TGR5-induced increase in CC cell proliferation, being a downstream component regulated by TGR5, which provides CC at least in part by interacting with mortalin and upregulating its expression, showing that both TGR5 and mortalin are positive regulators, serving as potential biomarkers for this type of carcinoma.

Studying the expression of mortalin in colorectal cancer, Xu, et al. [85] showed that high mortalin expression is positively associated with poor overall survival. Overall, mortalin is quite expressed in colorectal cancer and may represent bad prognosis. Mortalin accelerated cancer development by stimulating cell proliferation and the epithelial-mesenchymal transition program. Comparative proteomic assays show overexpression of mortalin in colorectal adenocarcinomas. By immunostaining on a colorectal cancer tissue microarray connected to a patient database, it was reported that overexpression of mortalin correlated with low patient survival. Results demonstrated that mortalin overexpression can predict colorectal cancer outcome, showing that this thermal protein is involved in colorectal cancer [69].

In hepatocellular carcinoma, the main hindrance to the treatment of advanced or recurrent cancer are angiogenesis and sorafenib resistance. Yang, et al. [86] demonstrated that mortalin, which stipulate the phosphorylated alterations of the cancer-associated proteome, induce angiogenesis and sorafenib resistance, being a competing risk coefficient in this type of carcinoma.

In brain tumors, a raise in the number of mortalin-positive cells with malignant progress of brain tumors and their correlation with Ki-67 (a cell proliferation marker)-positive cells showed the involvement of non-pancytosolic mortalin in the malignant mutation of cells *in vivo* [52].

Regarding bladder cancer, there are many studies linking HP70 family overexpression to the expansion and survival of the tumor cells. Targeting the different Hsp70 protein isoforms with siRNA or other drugs resulted in tumor growth inhibition and chemosensitization of bladder tumor cells [2,87]. The expression of Hsp70 has been related not only with cancer cell proliferation and survival, but also with tumor grade and potential therapeutic outcomes [73-74].

Pagliarone, et al. [88] tested whether inhibition of its activity would directly affect the viability of MB49 cells. Therefore, these cells were cultured for 48 h in the presence or absence of the inhibitor MKT -077 at different concentrations and, 48 h after culturing in the absence of the inhibitor, were subjected to a viability assay. According to the data obtained, the authors found that MKT -077 significantly decreased tumor cell viability in a dose-dependent manner mainly under oxidative stress conditions.

In myeloid leukemia and myelodysplasia, the Human chromosome 5q31.1 segment is often deleted, indicating that mortalin may be an applicant gene involved [89]. Many other similar studies have also been conducted with other tumor and cancer, such as ovarian cancer [90], lung cancer [91], KRAS tumor cell [92], with similar results, always considering mortalin as a target in the support for these pathologies.

## CONCLUSION

Mortalin can be an important tool as a disease biomarker, therapeutic target, and therapeutic agent, assisting in the diagnosis and treatment of various diseases. This review presented the potential of mortalin in face of the challenges in the treatment of neurological, endocrine, immunological diseases, and cancers, however, further studies should be conducted to elucidate its complete mechanism within cells. With the recent advances in the biotechnology field, vaccine or antibody treatment based on mortalin will surely be a very important tool.

## AUTHORS CONTRIBUTIONS

All authors participated and contributed to this manuscript publication by reviewing the literature, structuring the text and translating it into English.

## COMPETING INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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