

Can mortalin be a candidate target for cancer therapy?

Review Article

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Summary

Differential staining pattern of mortalin (mot-2/mthsp70/PBP74/GRP75) is a reliable marker for normal and cancerous phenotype of cells. It is an essential protein, sojourns multiple subcellular sites while residing predominantly in mitochondria. It has multiple binding partners and performs multiple functions including mitochondrial import, intracellular trafficking, receptor internalization and inactivation of the tumor suppressor protein p53. The present article updates our understanding on its functions in cellular senescence and immortalization and proposes its use as a target for cancer therapy.

I. Introduction

Mortalin is a member of hsp70 family of proteins. It was first cloned from the cytoplasmic fraction of normal mouse fibroblasts; the immortal cells lack this protein in their cytoplasmic fraction (Wadhwa et al, 1993a). Subsequently, by immunostaining its differential subcellular distribution was recognized in normal and immortal mouse cells (Wadhwa et al, 1993b). A large variety of human normal and immortal cells were demonstrated to have pancytoplasmic and perinuclear cellular distribution of mortalin, respectively. As discussed below, its multiple subcellular sites and binding partners signify its multiple roles, some of which are crucial for continued proliferation of cells.

II. Cancerous mouse and human cells lack the pancytoplasmic distribution of mortalin

Immunostaining of normal and immortal cells with a mortalin specific antibody revealed that it is widely distributed in the cytoplasm of normal cells and is restricted to the perinuclear region in immortal mouse cells. cDNAs encoding the cytoplasmically distributed protein (mot-1) and the perinuclear protein (mot-2) were cloned from normal and immortal mouse fibroblasts, respectively (Wadhwa et al, 1993c). These were shown to be different by two amino acids (Wadhwa et al, 1993c), have contrasting biological activity and coded by two

alleles in mouse (Kaul et al, 2000b). The mot-1 cDNA encoding the pancytoplasmic form of mouse mortalin when introduced into NIH 3T3 cells induced cellular senescence like phenotype in these cells (Wadhwa et al, 1993c). In contrast, the mot-2 cDNA that encoded perinuclear protein resulted in malignant transformation of NIH 3T3 cells (Kaul et al, 1998).

Differential cellular distribution of mortalin in normal and transformed cells was also endorsed by human system. In more than 50 different human immortal cell lines examined, mortalin was observed as nonpancytoplasmically distributed (Wadhwa et al, 1995) (**Figure 1**) in contrast to the normal cells that showed pancytoplasmic staining. Cloning and analyses of mortalin cDNA from normal and transformed human cells, however, revealed no significant difference (Kaul et al, 1998) proposing that there are, at least, two mechanisms operating for differential distribution of mortalin in normal and transformed cells. One is by distinct cDNAs, mot-1 and mot-2, and is found in mouse. The other may involve protein modifications, binding partners or other cellular factors and operates in mouse and human. Such mechanism(s) remains to be elucidated. Human mortalin cDNA clone when expressed in mouse immortal cells led to their malignant transformation similar to the one caused by mouse mot-2 cDNA. Both mouse mot-2 cDNA and human mortalin also led to lifespan extension of normal human fibroblasts (Kaul et al, 2000a). Based on these functional data, human mortalin cDNA was called hmot-2 and its overexpression was suggested to have proliferative function.

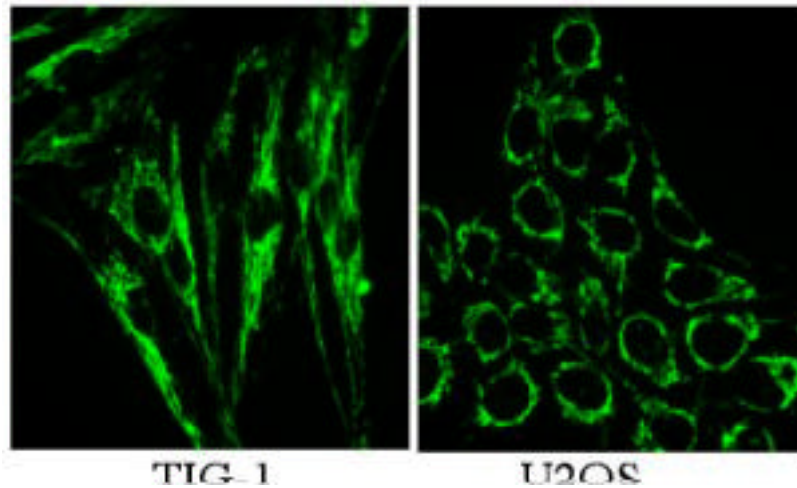


Figure 1. Mortalin immunostaining in normal (skin fibroblasts, TIG-1) and transformed (osteogenic sarcoma, U2OS) human cells.

Subcellular distribution of mortalin shifted from the perinuclear to the pancytoplasmic type when cancerous cells were induced to senescence. For example, introduction of human chromosome 7 to carcinogen-transformed liver fibroblasts (SUSM-1) resulted in their senescence in culture as determined by their proliferation, senescence associated -gal activity. The senescent cells showed pancytoplasmic distribution of mortalin (Nakabayashi et al, 1999). In a similar approach when chromosome-fragments and genes from human chromosome 4 were introduced into cervical carcinoma (HeLa) cells, resulted in an induction of senescence phenotype that was accompanied by a shift in the subcellular distribution of mortalin from a perinuclear to pancytoplasmic type (Bertram et al, 1999). Induction of senescence like growth arrest by bromodeoxyuridine (Michishita et al, 1999) or MKT-077 (a rhodacyanine dye that is selectively toxic to cancer cells) also caused shift of subcellular distribution of mortalin from perinuclear to pancytoplasmic type, characteristic of normal cells (Wadhwa et al, 2000). On the other hand, Simian Virus 40 large T antigen (SV40 LTA) - induced cellular transformation of human lung fibroblast (MRC-5) cells resulted in shift of pancytoplasmic mortalin staining in normal cells to the nonpancytoplasmic staining in its immortal derivatives. Taken together, these studies showing the absence of pancytoplasmic mortalin staining pattern in cancerous cells have assigned mortalin staining as a reliable marker of cellular normal and transformed phenotypes.

III. Multiple subcellular sites and binding partners of mortalin

Mortalin is a highly conserved member of hsp70 family of proteins. It was also cloned as a peptide binding protein (PBP74) (Dahlseid et al, 1994; Domanico et al, 1993), mitochondrial heat shock protein 70 (mthsp70) (Bhattacharyya et al, 1995) glucose regulated protein 75 (GRP75) (Webster et al, 1994) and was found in multiple subcellular sites by a variety of protocols. Confocal laser microscopy of the native protein with protein-specific

antibodies in a variety of cell lines revealed its existence in multiple subcellular sites that includes mitochondria, endoplasmic reticulum, cytoplasmic vesicles and cytosol (Dahlseid et al, 1994; Domanico et al, 1993; Poindexter et al, 2002; Ran et al, 2000; Singh et al, 1997; Soltys and Gupta, 1999, 2000; Wadhwa et al, 1995; Webster et al, 1994). These data suggest its involvement in multiple cellular functions.

In support to its localization at multiple subcellular sites, mortalin was shown to bind to residents of different organelles by a variety of protocols. Far-western screening identified glucose regulated ER chaperone (GRP94) as one of its binding partners. Mortalin-GRP94 interactions were confirmed by mammalian two-hybrid assays, *in vitro* and *in vivo* coimmunoprecipitations (Takano et al, 2001). Mortalin was also isolated as FGF-1 binding protein by FGF-1 affinity chromatography and was shown to aid in its intracellular trafficking (Mizukoshi et al, 1999), mediated by its cell cycle specific phosphorylation (Mizukoshi et al, 2001). ATP-sensitive association of mortalin with IL-1 receptor type was also detected and predicted to have a role in receptor internalization (Sacht et al, 1999). Yeast interactive screen for mortalin binding proteins isolated the mitochondrial proteins hsp60, NADH dehydrogenase, Tim44, Tim23 (unpublished data) and the peroxisomal protein MPD (Wadhwa et al, 2003a) as its binding partners. It appears that mortalin routes through multiple subcellular sites and thus interacts with different proteins therein. Recently, it has been recognized that protein distribution in a cell is more dynamic than was earlier thought. Many other proteins have been detected in subcellular localizations that were considered foreign previously (Soltys and Gupta, 1996, 1997, 1999). The studies warrant further analyses to elucidate the kinetics of mortalin binding to its binding partners, their temporal and special relevance to cellular mortal, immortal and stressed phenotypes including apoptosis.

IV. Mortalin-p53 interactions and p53 function

Mortalin binds to p53 in transformed human cells (Wadhwa et al, 1998). These interactions result in cytoplasmic sequestration of p53 and inhibition of its transcriptional inactivation function (Wadhwa et al, 1998; 2002b). Such inactivation of p53 function could account for lifespan extension of normal human cells. Recently, it has been shown that telomerase in cooperation with mortalin could accelerate the immortalization of normal human cells (Kaul et al, 2003). Binding studies using deletion mutants have demonstrated that an N-terminal region of mortalin binds to the C-terminus of p53, previously shown to be involved in cytoplasmic sequestration of p53 (Kaul et al, 2001; Moll et al, 1992; Wadhwa et al, 2002b). Most recently, it has been shown that p53 also exists in the mitochondria (also a predominant localization of mortalin) and interacts with mortalin/mthsp70, Bcl-2 and hsp60 (Dumont et al, 2003; Mihara et al, 2003) and these interactions are involved in p53-mediated apoptosis by a pathway independent to its nuclear function. In this scenario, if mortalin could interfere with the p53-Bcl-2 interactions it may act as an antiapoptotic factor (**Figure 2**). Such possibilities remain to be tested. On the other hand, abrogation of mortalin-p53 interaction by a cationic rhodacyanine dye analogue (MKT-077) resulted in nuclear translocation and reactivation of p53 function sufficient to cause growth arrest of transformed human cells (Wadhwa et al, 2000; 2002a). In tumors with wild type p53, the abrogation of mortalin-p53 interactions and reactivation of p53 function could be valid for cancer therapy. Most common examples

of these include breast carcinomas, glioblastomas and teratocarcinomas.

V. Mortalin functions other than p53 inactivation

Expression of mortalin could be suppressed in malignant human fibroblasts using specifically designed active hammerhead ribozymes. The cells with decreased expression of mortalin undergo growth arrest and show reactivation of wild type p53 function (Wadhwa et al, 2003b). However, the cells that lack p53 function also experienced growth arrest suggesting that mortalin is involved in functions other than p53 inactivation and are crucial for continued proliferation of cancerous cells. One possibility could be due to its role as mitochondrial importer as demonstrated in yeast with its homologue, SSC1p. The yeast homologue of mortalin, SSC1p, was shown to be vital for mitochondrial import (Geissler et al, 2001; Krimmer et al, 2000) and its knock-out resulted in cell death (Craig et al, 1989). SSC1p was shown to bind to Tim-44, an inner mitochondrial membrane anchor, and forms an essential component of mitochondrial import machinery (Krimmer et al, 2000; Strub et al, 2001). Other proposed functions of SSC1p include unfolding of proteins outside mitochondria, unidirectional translocation across mitochondrial membranes initiated by membrane potential M , completion of import by acting as an ATP-driven motor and degradation of misfolded peptides by m-AAA and PIM1 proteases in mitochondria (Lim et al, 2001; Liu et al, 2001). These functions may be critical for continued proliferation of cancerous cells and thus targeting of mortalin may arrest the growth of these cells.

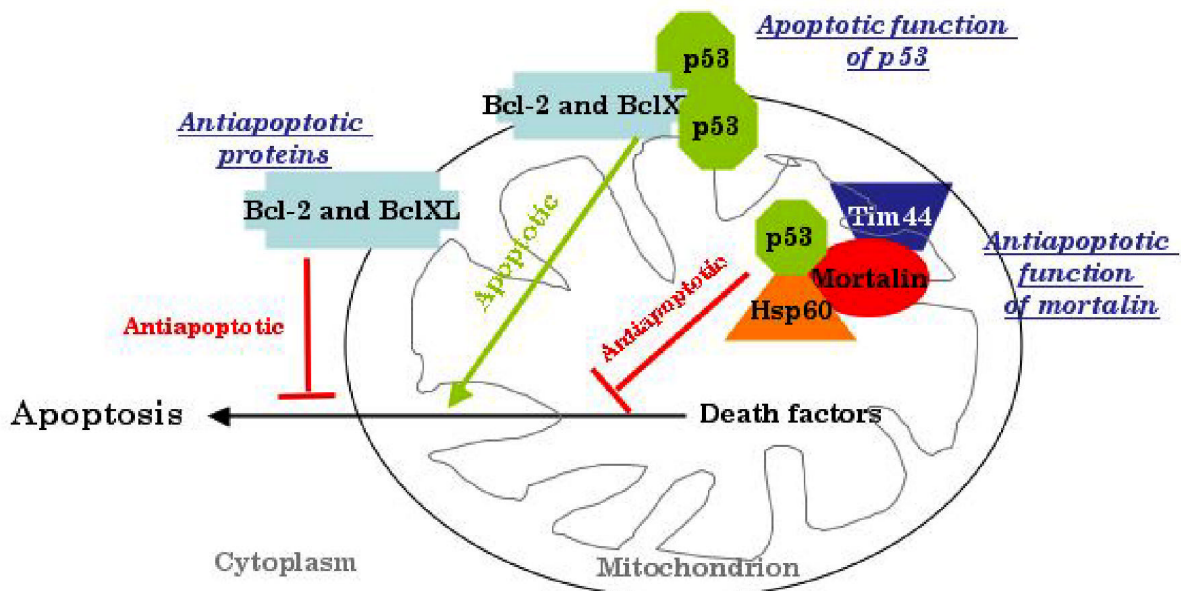


Figure 2. Predictive anti-apoptotic function of mortalin. Its interaction with p53 in mitochondria may lead to abrogation of p53-Bcl-2 association resulting in maintenance of anti-apoptotic functioning of Bcl-2 protein.

Independent studies have assigned multiple functions to mortalin. They range from stress response (Craig et al, 1998; Merrick et al, 1995; Sadekova et al, 1997; Carette et al 2002; Resendez et al, 1986; Schneider and Hood, 2000; Wu et al, 1999), muscle activity (Ibi et al, 1996), mitochondrial biogenesis (Ornatsky et al, 1995; Takahashi et al, 1998), intracellular trafficking (Mizukoshi et al, 1999; 2001; Sacht et al, 1999), antigen processing (Domanico et al, 1993), control of cell proliferation (Kaul et al, 1998; 2000a), differentiation (Xu et al, 1999), fate determination (Rivolta and Holley, 2002), tumorigenesis (Bini et al, 1997; Kaul et al, 1998; Takahashi et al, 1994; Takano et al, 1997) and apoptosis (Marchenko et al, 2000; Taurin et al, 2002; Dumont et al, 2003; Mihara et al, 2003). As expected, an overexpression of mortalin and accentuation of such functions may impart growth or proliferative advantage to cells. Comparative studies on the expression level of mortalin in normal and tumor cells indeed revealed its upregulation in tumors and its decrease during replicative senescence of fibroblasts (unpublished observations). Complete understanding of its various functions and their precise contribution to normal and cancerous phenotypes warrant further studies. Nevertheless there is an evidence showing that the abrogation of one or more functions of mortalin may compromise cell proliferation and thus could serve as a cancer therapeutic tool. The next challenge is to validate this therapeutic approach by analyzing the expression of mortalin in a variety of clinical tumor tissues and to unravel ways to target these functions specifically in cancerous cells without affecting normal cells.

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