Title: Inclusion Body Myopathy with Paget Disease of Bone and/or Frontotemporal Dementia- IBMPFD *GeneReview*: *VCP* Animal Models
Authors: Kimonis V, Donkervoort S, Watts G
Date: July 2011

IBMPFD: *VCP* Animal Models

Mouse Models

Knock-out mouse model. A homozygous knock-out mouse model for *VCP* was embryonically lethal, the heterozygotes apparently being asymptomatic [Muller et al 2007]. Heterozygous p97+/- mice were indistinguishable from their wild-type littermates, whereas homozygous mutants did not survive to birth and died at a peri-implantation stage. These results show that p97 is an essential gene for early mouse development.

Transgenic mice overexpressing the mutant allele. Weihl et al [2007] reported their transgenic mice expressing p97/VCP-WT or the most common IBMPFD mutant, p97/VCP Arg155His, under a muscle-specific promoter. The latter became progressively weaker starting at age six months, a finding that coincided with abnormal muscle pathology including coarse internal architecture, vacuolation, and disorganized membrane morphology with reduced caveolin-3 expression at the sarcolemma. There was an increase in ubiquitin-containing protein inclusions and high molecular-weight ubiquitinated proteins, markers of ubiquitin-proteasome system (UPS) dysfunction Further evidence for the utility of the VCP/p97mouse model came from Custer et al [2010] who showed that mice overexpressing the mutant allele exhibit progressive muscle weakness and pathologic examination of muscle shows classic characteristics of inclusion body myopathy including rimmed vacuoles and TDP-43 pathology. The mice exhibit abnormalities in behavioral testing and pathologic examination of the brain shows widespread TDP-43 pathology. Furthermore, radiologic examination of the skeleton reveals that mutant mice develop severe osteopenia accompanied by focal lytic and sclerotic lesions in vertebrae and femur.

Knock-in *VCP* mouse model. A knock-in mouse model [Bandani et al 2010] with the common R155H mutation showed progressive muscle weakness starting at the age of 6 months. Histology of muscle showed progressive vacuolization of myofibrils and centrally located nuclei, and immunostaining shows progressive cytoplasmic accumulation of TDP-43 and ubiquitin-positive inclusion bodies in quadriceps myofibrils and brain. Increased LC3-II staining of muscle sections representing increased number of autophagosomes suggested impaired autophagy. Increased apoptosis was demonstrated and bone histology and bone marrow derived macrophage cultures in these mice revealed increased osteoclastogenesis suggestive of Paget bone disease

Drosophila Models

Drosophila contains a single VCP homolog TER94, which shares 83% protein sequence identity with human VCP [Pintér et al 1998].

A *Drosophila* VCP (ter94) loss-of-function mutant has been identified as a dominant suppressor of expanded polyglutamine (poly-Q)-induced neuronal degeneration. This suggests that a gene dosage response for VCP expression is crucial to its function in expanded polyglutamine (poly-Q)-induced neuronal degeneration. To further support this, in transgenic *Drosophila*, in which VCP levels were elevated, severe apoptotic cell death was induced, whereas homozygous VCP loss-of-function mutants were embryonically lethal [Hirabayashi et al 2001].

Ritson et al [2010] introduced R152H and A229E mutations into dVCP to create homologs of the R155H and A232E mutations in the *Drosophila* model. Three RNA-binding proteins were identified to dominantly suppress degeneration, one of these was TBPH, the *Drosophila* homolog of TAR (trans-activating response region) DNA-binding protein 43 (TDP-43). Mutation-dependent degenerative phenotypes were observed despite equivalent levels of dVCP expression. Their data indicate that disease-causing mutations in VCP lead to redistribution of TDP-43 to the cytoplasm in vitro and in vivo and TDP-43 redistribution from the nucleus to the cytoplasm was sufficient to induce cytotoxicity. Degeneration associated with VCP mutations was mediated in part by toxic gain of function of TDP-43 in the cytoplasm.
An over expressing TER94 *Drosophila* model showed expression of TER94 mutants in muscle and nervous systems causes tissue degeneration, recapitulating the pathogenic phenotypes in IBMPFD patients. Expression of these TER94-induced neurodegenerative defects are enhanced by elevated expression of wild-type TER94, suggesting that the pathogenic alleles are dominant active mutations. The authors showed that increasing cellular ATP by independent mechanisms could suppress the phenotypes of TER94 mutants. Conversely, decreasing cellular ATP would enhance the TER94 mutant phenotypes linking cellular ATP level and IBMPFD pathogenesis [Chang et al 2011].

References

Badadani M, Nalbandian A, Watts GD, Vesa J, Kitazawa M, Su H, Tanaja J, Dec E, Wallace DC, Mukherjee J, Caiozzo V, Warman M, Kimonis VE. VCP associated inclusion body myopathy and paget disease of bone knock-in mouse model exhibits tissue pathology typical of human disease. PLoS One. 2010;5pii:e13183.

Custer SK, Neumann M, Lu H, Wright AC, Taylor JP. Transgenic mice expressing mutant forms VCP/p97 recapitulate the full spectrum of IBMPFD including degeneration in muscle, brain and bone.Hum Mol Genet. 2010;19:1741-55.

Chang YC, Hung WT, Chang YC, Chang HC, Wu CL, Chiang AS, Jackson GR, Sang TK. Pathogenic VCP/TER94 alleles are dominant actives and contribute to neurodegeneration by altering cellular ATP level in a Drosophila IBMPFD model. PLoS Genet. 2011;7:e1001288

Hirabayashi M, Inoue K, Tanaka K, Nakadate K, Ohsawa Y, Kamei Y, Popiel AH, Sinohara A, Iwamatsu A, Kimura Y, Uchiyama Y, Hori S, Kakizuka A. VCP/p97 in abnormal protein aggregates, cytoplasmic vacuoles, and cell death, phenotypes relevant to neurodegeneration. Cell Death Diffe 2001;8:977-84

Muller JM, Deinhardt K, Rosewell I, Warren G, Shima DT. Targeted deletion of p97 (VCP/CDC48) in mouse results in early embryonic lethality. Biochem Biophys Res Commun 2007;354:459-65

Pintér M, Jékely G, Szepesi RJ, Farkas A, Theopold U, et al. TER94, a Drosophila homolog of the membrane fusion protein CDC48/p97, is accumulated in nonproliferating cells: in the reproductive organs and in the brain of the imago. Insect Biochem Mol Biol 1998;28:91–98.

Ritson GP, Custer SK, Freibaum BD, Guinto JB, Geffel D, Moore J, Tang W, Winton MJ, Neumann M, Trojanowski JQ, Lee VM, Forman MS, Taylor JP.TDP-43 mediates degeneration in a novel Drosophila model of disease caused by mutations in VCP/p97.J Neurosci. 2010;30:7729-39.

Weihl CC, Miller SE, Hanson PI, Pestronk A. Transgenic expression of inclusion body myopathy associated mutant p97/VCP causes weakness and ubiquitinated protein inclusions in mice. Hum Mol Genet 2007;16:919-28