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Loss-of-function mutation in VCP mimics the characteristic pathology as in FTLD-TARDBP

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ABSTRACT

VCP (valosin containing protein), a member of the AAA+ protein family, is critical for many cellular processes and functions. Dominant VCP mutations cause a rare neurodegenerative disease known as multisystem proteinopathy (MSP). The spectrum of mechanisms causing fronto-temporal dementia with TARDBP/TDP-43 inclusions (FTLD-TARDBP) by VCP disease mutations remains unclear. Our recent work identified VCP activity as a mediator of FTLD-TARDBP. Specifically, brain atrophy, behavioral changes, neuronal loss, gliosis, and TARDBP pathology were observed in *vcp* conditional knockout (cKO) mice. We also found that autophago-lysosomal dysfunction, TARDBP inclusions, and ubiquitin-proteasome impairment precede neuronal loss. We further studied conditional expression of the disease-associated mutation VCP^{R155C} in *vcp*-null mice. We observed features similar to those of VCP inactivation, suggesting that VCP mutation is hypomorphic. Furthermore, proteomic, and transcriptomic signatures in *vcp* cKO mice resemble those of GRN/Progranulin carriers. Therefore, VCP is essential for neuronal survival by several mechanisms and could be a therapeutic target aimed at restoring protein homeostasis in patients with FTLD-TARDBP.

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Dominant mutations in C9orf72, GRN, and VCP (valosin containing protein) are associated with fronto-temporal lobar degeneration with TARDBP inclusions (FTLD-TARDBP). The other degenerative phenotypes caused by VCP disease mutations include Paget disease of the bone, amyotrophic lateral sclerosis, and inclusion body myopathy, leading to the inclusive term multisystem proteinopathy (MSP). MSP pathology involves TARDBP inclusions, ubiquitinated aggregates in terminally differentiated tissues such as muscle and neurons. The mechanism of VCP dysfunction in muscles and neurons is unknown. VCP dysfunction leads to aggregation of proteins and defects in the macroautophagy/autophagy lysosomal pathway, causing cell death in some models. VCP belongs to the ATPase associated with diverse cellular activity (AAA) family and is needed to maintain protein homeostasis via the ubiquitin-proteasome system, clear damaged lysosomes through autophagy, and ensure cell survival through the PI3K-AKT pathway. VCP knockdown or VCP mutant expression reduces the proteasomal degradation pathway and enhances apoptosis and endoplasmic reticulum stress. VCP mutant expression also promotes the accumulation of immature autophagic vesicles with high levels of the autophagy marker LC3-II/-I in the brain; similarly, in muscle cells, VCP mutant expression promotes impaired autophagy. These pathological features indicate that *vcp* knockout or VCP disease mutations affect lysosomal function. The specific function of VCP depends upon interaction with a subset of cofactors. For example, if VCP binds to UFD1-NPLOC4/NPL-4, it facilitates proteasome degradation, but its interaction with NSFL1C/p47 promotes membrane remodeling. VCP also interacts with adaptor UBXN6/UBXD1, which activates endocytosis and the autophagy pathway. With VCP disease mutations, interaction with the adaptor proteins is compromised, resulting in loss of adaptor-specific functions. VCP interacts with UBXN6 to sort late endolysosomes (ubiquitinated CAV1), yet VCP disease mutations have impaired interaction that blocks CAV1 transport. We have shown that VCP translocates to lysosomes upon endolysosomal damage, which is marked by LGALS3/Gal3, interacts with the ELDR complex (UBXN6, PLAA, and deubiquitinating enzyme YOD1) for autophagic degradation. The interaction between VCP and the ELDR complex in the context of VCP disease mutations fails, leading to the accumulation of damaged lysosomes through autophagy.

Most VCP mutant mouse models mimic phenotypes other than FTLD. Other VCP disease mutant mice models, including R155H or A232E mutant VCP, recapitulate muscle weakness and myopathology consistent with inclusion body myopathy. CNS pathology, if present, develops after 18 months in the VCP^{RH} mutant mouse model. Therefore, we developed $VCP^{FL/FL}$: *CamkCre* (VCP cKO) and $VCP^{RC/FL}$:*CamkCre* (VCP cRC) mouse models, which recapitulate the full spectrum of FTLD-TARDBP pathology and neurodegeneration [1]. We found loss of cortical width, brain atrophy, and behavior impairment in the cKO model. Inactivating VCP in neurons leads to progressive neuronal loss, gliosis, and TARDBP pathology. We also found that autophago-lysosomal dysfunction and endosomal damage may lead to neurodegeneration. Proteomic analysis revealed increases in lysosomal proteins, lysosomal proteases, and ER stress and decreases in synaptogenesis in the *vcp* cKO mouse.

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Nevertheless, how VCP inactivation leads to neuronal loss is still unclear.

To dissect the relationship of VCP mutations and pathology, we characterized newly generated VCP cRC mouse models. We also characterized $VCP^{RH/WT}$ and $VCP^{RC/WT}$ mice, which have no notable pathology at 12 months old. However, homozygous $VCP^{RC/RC}$ is embryonic lethal, suggesting that mutant VCP loses function during development. Therefore, we developed $VCP^{R155C/fl}$ mice by crossing $VCP^{R155C/WT}$ with $VCP^{fl/fl}$ and further crossed $VCP^{R155C/fl}$ mice with *Camk2a-Cre* mice expressing Cre recombinase under *Camk2a* (calcium/calmodulin-dependent protein kinase II alpha) promoter expressed in the cortex and CA1 region of the brain, referred to as $VCP^{RI55C/fl}$:*CamkCre*. These mice showed consistent loss of neurons, gliosis, and TARDBP pathology between 6 and 12 months of age, behavior impairment, and autophago-lysosomal defects. We also reported the translocation of TARDBP and SQSTM1 from the soluble fraction into the insoluble fraction between 6 and 12 months old. We demonstrated that VCP mutation leads to functional loss, causing VCP-associated MSP1 pathogenesis. The pathological hallmarks that were observed after VCP inactivation in cortical neurons, such as a dysfunctional endo-lysosomal system, neuronal loss, and TARDBP inclusions, mimic the pathological condition observed in FTLD-TARDBP [1].

Proteomic and transcriptomic studies of *vcp* cKO mouse brains signified disrupted ERAD, ubiquitin-proteasome system, and autophagic and endolysosomal systems, similar to changes in the VCP cRC mouse brain. This indicates the possibility of involvement of similar loss of VCP activity with VCP^{R155C} expression. The role of VCP in cellular processes such as proteasome degradation, lysosome function, organelle formation, and endocytosis is well elucidated, including the developmental roles served in spinogenesis and dendritic pruning, but the characteristics of VCP in terminally differentiated neurons are not well known. How VCP regulates neurons, whether mutation in VCP exerts similar effects in neurons as it exhibits in spinal cord and muscle cells, and whether TARDBP connects from muscle to brain through the spinal cord are still unanswered questions, providing a wide scope of study of VCP as a potential target in neurodegeneration.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Reference

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