D IBMPFD Disease-Causing Mutant VCP/p97 Proteins Are Targets of Autophagic-Lysosomal Degradation

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Abstract (600 words limit)

The ubiquitin-proteasome system (UPS) degrades soluble proteins and small aggregates, whereas macroautophagy (autophagy herein) eliminates larger protein aggregates, tangles and even whole organelles in a lysosome-dependent manner. VCP/p97 was implicated in both pathways. VCP/p97 mutations cause a rare multisystem disease called IBMPFD (Inclusion Body Myopathy with Paget's Disease and Frontotemporal Dementia). Here, we studied the role IBMPFD-related mutants of VCP/p97 in autophagy. In contrast with the wild-type VCP/p97 protein or R155C or R191Q mutants, the P137L mutant was aggregate-prone. We showed that, unlike commonly studied R155C or R191Q mutants, the P137L mutant protein stimulated both autophagosome and autolysosome formation. Moreover, P137L mutant protein itself was a substrate of autophagy. Starvation- and mTOR inhibition-induced autophagy led to the degradation of the P137L mutant protein, while preserving the wild-type and functional VCP/p97. Strikingly, similar to the P137L mutant, other IBMPFD-related VCP/p97 mutants, namely R93C and G157R mutants induced autophagosome and autolysosome formation; and G157R mutant formed aggregates that could be cleared by autophagy. Therefore, cellular phenotypes caused by P137L mutant expression were not isolated observations, and some other IBMPFD disease-related VCP/p97 mutations could lead to similar outcomes. Our results indicate that cellular mechanisms leading to IBMPFD disease may be various, and underline the importance of studying different disease-associated mutations in order to better understand human pathologies and tailor mutation-specific treatment strategies.

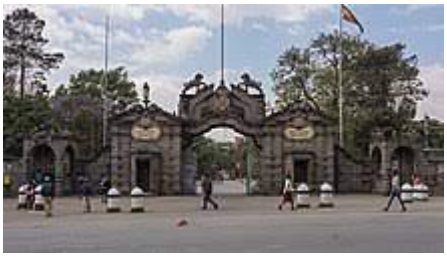
Biography (200 words limit)

Dr. Alin Fikrie He is a Consultant of Palliative Care and Family Medicine at the Postgraduate Education of Family Medicine, Ministry of Health, Saudi Arabia and Consultant of Palliative Care department at King Fahad Medical City since 2010. Dr. AlShammary completed his Bachelor Degree in Medicine (MBBS) at King Saud University, Riyadh in 1997, and received his Arab Board and Jordanian Board of Family Medicine in 2005. He also earned his Saudi Board in Family Medicine in 2004. In 2010, he completed APHN Diploma in Palliative Care at National Cancer Centre, Singapore and Fellowship in Palliative Care at University of British Columbia, Vancouver, in Canada. In 2009, he completed a Palliative Medicine Fellowship at King Faisal Specialist Hospital and Research Centre, Riyadh and Graduate Certificate & Diploma in Palliative Care at Flinders University, Adelaide, Australia. Dr. Sami obtained Master of Medical Education (MME) at King Saud bin Abdulaziz University for Health Sciences, Riyadh onAugust2010

About Research Topic (200 words limit)

In this study, we identified VCP/p97 P137L mutant proteins as autophagy targets. We confirmed that mere expression of the VCP/p97 P137L mutant was sufficient to induce autophagy under basal fed conditions. In contrast with previous reports using commonly studied mutants (R155 or A232), P137L mutant did not cause an autophagosome maturation defect, and it did not prominently influence autophagic vesicle fusion with lysosomes. Strikingly, autophagy activation by starvation led to a lysosomal activity-dependent preferential degradation of the P137L mutant while sparing the wild-type VCP/p97 protein. Autophagy inducer and mTOR inhibitor Torin-1 showed similar effects. P137L mutant was not an isolated case: We demonstrated that another IBMPFD disease-related mutant, the G157R mutant formed aggregates, induced productive autophagy and it was cleared by autophagic degradation. Our results showed that, in contrast with the current litterature, some VCP/p97mutants are targets of autophagic degradation. Additionally they underline the fact that, even though they all lead to the same disease, different IBMPFD-related VCP/p97 mutations may have different functional outcomes at a molecular and cellular level.

About Institution (200 words limit)



The origins of AAU was a two-year college in 1950 by the Jesuit Lucien Matte, at the appeal of His Majesty Emperor Haile Selassie I.[3] It began operations the following year. Over the following two years an affiliation with the University of London, and University of Oxford was developed. Africans from various parts of the continent would receive free scholarships through programs subsidized by the Organisation of African Unity for higher learning. AAU was also known for sending its students abroad for an extended interpersonal educational experience, and having those students return with the exemplary standards of the international community.

The nucleus of AAU was formed with the establishment of the University College of Addis Ababa (UCAA) in 1950.[4] UCAA, which initially consisted of the Faculties of Arts and Science, became a fully fledged college when it was chartered in 1954. In 1955, the Building College was opened. In February 1961, these various colleges and the Theological College were brought together to form the Haile Selassie University. Emperor Haile Selassie I gave his Guenete Leul Palace to serve as the administration building and main campus. He had abandoned the palace, where a number of his ministers and favorites were killed in the wake of the abortive Coup d'état in 1960, in favor of the new Jubilee Palace.[5] Following the 1974 revolution, the university was briefly renamed University of Ethiopia (National University) before it came to assume its present designation, AAU, in 1975.[6] In the wake of the revolution, AAU was closed for two years and students and staff were drafted into what was known as the Development through Cooperation Campaign (zemecha), designed to arise the awareness of the rural population in the spirit of the revolution. The university offered its first Master's programs in 1979 and its first PhD programs in 1987.Nursing and midwifery, medical laboratory Science, Environmental Health Sciences, and BSc pharmacy,.

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