UAEU جامعة الإمارات العربية المتحدة United Arab Emirates University

The College of Graduate Studies and the College of Medicine and Health Sciences Cordially Invite You to a

Master Thesis Defense

Entitled

ELUCIDATION OF THE CELLULAR MECHANISMS UNDERLYING MISSENSE MUTATIONS IN LOW DENSITY LIPOPROTEIN RECEPTOR RELATED PROTEIN 6 (LRP6) ASSOCIATED WITH CARDIOVASCULAR DISEASES

by

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Date & Venue

1:00 pm

Wednesday, 8th of December 2021

(Virtual)

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Abstract: Low-density lipoprotein receptor related protein 6 (LRP6) is a member of the low-density lipoprotein receptors family (LDLRs) which is involved in the clearance of LDL from the bloodstream and the signaling of the canonical wingless signaling pathway. Several genetic variants in the *LRP6* gene have been conclusively associated with cardiovascular diseases (CVDs) and metabolic syndrome. However, the structural and functional implications of those variations have not been fully elucidated. The CVD-associated LRP6 variants could be retained and possibly subjected to endoplasmic reticulum associated degradation (ERAD), a quality control and adaptive process employed by cells to eliminate misfolded proteins to maintain ER homeostasis. The aim of this project is to investigate the subcellular localization, stability, and transport of ten LRP6 missense variants (p.Lys82Asn, p.Arg360His, p.Tyr418His, p.Asn433Ser, p.Arg473Gln, p.Ser488Tyr, p.Arg611Cys, p.Pro1066Thr, p.Pro1206His, and p.Ile1264Val) associated with CVD. The variants were generated by site-directed mutagenesis, then analyzed by confocal immunofluorescence microscopy and western blotting. The immunofluorescence and confocal imaging showed that while the wild-type LRP6 is transported to the plasma membrane, several CAD-associated LRP6 variants were not transported to the same level and instead retained in the ER. To further confirm these observations, the glycosylation profiles of these variants were analyzed by western blotting and the Endoglycosidase-H sensitivity and resistance assay, which demonstrated significant lower maturation rates for the mutant proteins in comparison with wild-type. ER retention of CVD-associated LRP6 variants could contribute to their pathogenicity by loss or reduction of LRP6 function and signaling efficiency, which could be further explored by carrying out functional analysis in the future. This study will lead to a better understanding of the pathogenesis of LRP6 missense variations with potential applications in clinical diagnosis and the development of new therapies.

Keywords: Cardiovascular diseases, metabolic syndrome, Low-density lipoprotein receptor related protein 6, LDLR protein family, Endoplasmic Reticulum Associated Protein Degradation (ERAD), Endoplasmic Reticulum (ER)