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Sec63 is an Hsp40 co-chaperone that is associated with the Sec61 translocon complex in the endoplasmic reticulum

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Sec63 is an Hsp40 co-chaperone that is associated with the Sec61 translocon complex in the endoplasmic reticulum. Mutations in SEC63 cause polycystic liver disease in humans. Loss of Sec63 in mice induces cyst formation both in liver and kidney which is mitigated by polycystin-1 (PC1) over expression. We now find that inactivation of Sec63 suppressed G protein-coupled receptor proteolysis site (GPS) cleavage-dependent maturation of PC1, showing an unexpected role of Sec63 in this autoproteolytic process that is critical for cystogenesis. Loss of Sec63 selectively activated the IRE1 α -XBP1 branch of the unfolded protein response (UPR), and the inactivation of both Sec63 and XBP1 exacerbated the polycystic kidney phenotype in mice by markedly suppressing GPS cleavage of PC1. Enforced expression of the spliced XBP1s enhanced the GPS cleavage of PC1 in Sec63 deficient cells, suggesting that XBP1 activation normally serves to ameliorate the effects of Sec63 inactivation. XBP1 over expression *in vivo* ameliorated cystic disease caused by a model of reduced PC1 function unrelated to Sec63, indicating a general protective role of XBP1s activity against cystic diseases resulting from defective PC1 maturation. Selective activation of IRE1 α was also achieved by silencing of ERdj4, Sec61 α and BiP, but not by depletion of calnexin, calreticulin or Grp94, implicating the dependence of IRE1 α activation on select ER chaperones. Collectively, we demonstrated that Sec63 function regulates IRE1 α -XBP1 activation that Sec63 and XBP1 control PC1 maturation and that activation of XBP1 can protect against polycystic disease in the setting of impaired maturation of PC1.

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Angiotensin II Type 1 receptor (A1166C) gene polymorphism in Egyptian adult hemodialysis patients

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Genetic variability in the genes of different components of renin-angiotensin system (RAS) is likely to contribute for its heterogeneous association in renal disease patients. Among the candidate genes of RAS, angiotensin II type 1 receptor gene polymorphism (AT1R A1166C) seems to be particularly biologically and clinically relevant to renal diseases. The aim: This study aimed to evaluate the association of AT1R A1166C gene polymorphism in adult Egyptian hemodialysis (HD) patients. Its association with hypertension was also done. Subjects and methods: The study was conducted on 202 adult Egyptian subjects: 100 controls and 102 HD patients. Determination of this polymorphism was done by PCR/RFLP strategy. Results: The study revealed that HD patients had significantly higher frequency in AC and CC AT1R genotypes than controls. But on dividing these patients to normotensive and hypertensive ones, no significant difference in the genotypes was found. The multiple regression analysis revealed no dependent variables on the AT1R A1166C gene polymorphism. Conclusion: This study suggested that CC/AC genotype could serve as a predictor of an early end-stage renal disease (ESRD) and could, in the future, become an important part of the clinical process of renal risk identification.

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