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Global Nephrology: Sec63 is an Hsp40 co-chaperone that is associated with the Sec61 translocon complex in the endoplasmic reticulum- Sorin Fedeles- Yale School of Medicine

Sorin Fedeles
Yale School of Medicine, USA

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 IRE1α-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 IRE1α was also achieved by silencing of ERdj4, Sec61α and BiP, but not by depletion of calnexin, calreticulin or Grp94, implicating the dependence of IRE1α activation on select ER chaperones. Collectively, we demonstrated that Sec63 function regulates IRE1α-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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