Calreticulin mediated control of polycystin-2 expression

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Polycystin-2 or transient receptor potential polycystic 2 (TRPP2) is a membrane glycoprotein that is encoded for by the gene pkd-2, which accounts for ~15% of autosomal dominant polycystic kidney disease. TRPP2 is an independent non selective cation channel localized to either the plasma membrane or the endoplasmic reticulum (ER) that is involved in diverse cellular functions including control of cell cycle, cell wall synthesis, left-right symmetry, cardiac & renal development and mating behavior. In addition, it interacts with polycystin-1 that regulates different cell signaling pathways including JAK/STAT. As a trans-membrane protein, polycystin-2 is expressed, folded and matured in the endoplasmic reticulum. To date no data is available about the nature of endoplasmic reticulum which is responsible for the proper folding of polycystin-2. This led us to the hypothesis that calreticulin, an endoplasmic reticular calcium binding chaperone protein, is involved in stabilizing and transporting polycystin-2 to the plasma membrane.

To test this hypothesis we examined changes in polycystin expression and localization in wild type and calreticulin deficient cells using western blot analysis, and immunocytochemistry. Furthermore, western blot and immunohistochemical analyses were used to examine changes in polycystin expression and localization upon calreticulin over expression in vascular smooth muscle and endothelial cells of transgenic mice.

Our data showed that over expression of calreticulin in either vascular smooth muscle cells or endothelial cells of transgenic mice results in the development of multiple clear cysts in the kidney cortex of these mice. Histopathological analysis of these kidneys resembles those of human polycystic kidney disease. Furthermore, loss of calreticulin function resulted in altered polycystin-2 expression in the mouse embryonic fibroblast cell lines. However, there were no significant changes in the localization of polycystin-2 protein in calreticulin deficient cells when compared to the wild type cells.

Our data supports a possible role for calreticulin in the expression of polycystin-2. Further research is warranted to elucidate the role of calreticulin as a chaperone or regulator of calcium homeostasis in the expression of polycystin-2.