Macrophages Promote Cyst Growth in Polycystic Kidney Disease

Anil Karihaloo*, Farrukh Koraishy*, Sarah C. Huen*, Yashang Lee*, David Merrick†, Michael J. Caplan†, Stefan Somlo† and Lloyd G. Cantley*

Abstract

Polycystic kidney disease (PKD) exhibits an inflammatory component, but the contribution of inflammation to cyst progression is unknown. Macrophages promote the proliferation of tubular cells following ischemic injury, suggesting that they may have a role in cystogenesis. Furthermore, cultured Pkd1-deficient cells express the macrophage chemoattractants Mcp1 and Cxcl16 and stimulate macrophage migration. Here, in orthologous models of both PKD1 and PKD2, abnormally large numbers of alternatively activated macrophages surrounded the cysts. To determine whether pericystic macrophages contribute to the proliferation of cyst-lining cells, we depleted phagocytic cells from Pkd1fl/fl;Pkhd1-Cre mice by treating with liposomal clodronate from postnatal day 10 until day 24. Compared with vehicle-treated controls, macrophage-depleted mice had a significantly lower cystic index, reduced proliferation of cyst-lining cells, better-preserved renal parenchyma, and improved renal function. In conclusion, these data suggest that macrophages home to cystic areas and contribute to cyst growth. Interruption of these homing and proliferative signals could have therapeutic potential for PKD.