PC1 cleavage is not required for embryonic vasculature development.

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Introduction:

Polycystin 1 (PC1) is a large membrane protein that undergoes an autoproteolytic cleavage at a G protein coupled receptor (GPS) site located at the juxtamembrane region. PC1 cleavage occurs shortly after synthesis in the ER, resulting in two fragments that remain noncovalently attached. PC1 cleavage is essential for PC1/PC2 trafficking to the cilium, which is thought to be the major site of polycystin function. The observation that mice with a knock-in mutation that abolishes cleavage (*Pkd1*$^{V/V}$) survive embryogenesis suggests that uncleavable PC1 (PC1^{V}) is sufficient to support vascular development.

Methods:

We analyzed the vascular phenotypes of *Pkd1*$^{V/V}$, *Pkd1*$^{-/-}$ E14.5 embryos and littermate controls, including the placental vascular network. Localization of the polycystin complex to the cilium was assessed by immunostaining of endothelial cells from control and *Pkd1*$^{V/V}$ E14.5 embryos. The ability of PC1^{V}/PC2 complex to traffics beyond the ER was interrogated by analyzing the N-glycan modification of both proteins in placenta labyrinth with PNGase F and endoglycosidase H (Endo H).

Results:

In contrast to *Pkd1* null mutant, *Pkd1*$^{V/V}$ embryos did not display vascular abnormalities including hemorrhage, edema and polyhydramnios. Analysis of the placental labyrinth showed that *Pkd1*$^{V/V}$ and WT animals display comparable number of vessels. We have confirmed by immunostaining of *Pkd1*$^{V/V}$ ECs that PC2 is not recruited to the cilia. Consistent with this observation, the pool of PC2 protein that co-immunoprcipitated with PC1^{V} from embryonic labyrinth appeared to be fully sensitive to EndoH treatment, indicating that PC1 cleavage is a pre-requisite for the protein complex to traffic beyond the Golgi.

Conclusions:

Our data suggests that embryonic vessel development does not require PC1/PC2 trafficking or activity within the primary cilium and confirms that PC1 cleavage at GPS site is required for the polycystin complex to reach their target cellular structures.

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