Review of: "A plasma membrane-localized polycystin-1/polycystin-2 complex in endothelial cells elicits vasodilation"

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Potential competing interests: The author(s) declared that no potential competing interests exist.

The authors Charles E Mackay et al., in their manuscript *"A plasma membrane-localized polycystin-1/polycystin-2 complex in endothelial cells elicits vasodilation"* explored the roles of Polycystin-1 (PC-1, PKD1) in endothelial cells (EC) in using EC-specific Pkd1 knockout (Pkd1 ecKO) mice. The authors showed that PC-1 regulated arterial contractility and demonstrated that this event occurred through the formation of an interdependent signaling complex with PC-2 in ECs. Flow stimulated PC-1/PC-2 clustered in the EC plasma membrane, leading to Ca2+ influx, NOS and SK channel activation, vasodilation and a reduction in blood pressure. The following major points need clarifications:

Major Points:

1. Can authors provide a schematics of breeding scheme/strategy? Could author include a table showing genotyping primers and all PCR primers used in this report? Please include gene accession number. Could authors double-check the dose of tamoxifen (50 mg/kg body weight) used to activate Cre recombinase?
2. Reagents and antibodies: Can authors include clone# or catalogue#, city and state, country information?
3. Figure 3: In addition to blood pressure (BP), did authors measure body weight, examine cardiomyocyte enlargement and heart weight?
4. Could authors discuss more clearly which portion (or domain or segments) of PC-1 and PC-2 mediate dimerization? Is this the coiled-coiled region? Can authors address specific amino acid residues that might be involved in the dimerization?
5. If PC-1 and PC-2 formed heterodimeric protein complex, could these two proteins i.e., PC-1 and PC-2 also form oligomers, such as tetramers and larger protein complexes? Could authors do a gradient native gel (SDS-PAGE) to resolve if there are oligomeric protein complexes?
6. Figure 5A: It appears that PC1 and PC2 are abundantly expressed in ECs. Are PC-1 and PC-2 also found in caveolae? No new experiment/data is required.
7. There is sufficient functional data in this manuscript. No additional functional data required.
8. Figure S7A: It is difficult to assess the morphology of endothelial cells and the clusters of PC1 and PC2 proteins. If possible, please include enlarged (blown up images) figure.

Minor comments:

1. Animal experiments could be described more clearly, e.g., depth of anesthesia, use of analgesics. For the benefit of readers, please include proper references.
2. Could discussion be shortened, for example, discussion about cilia could be removed and a graphical summary could be added?
3. Methodologies could benefit from including key references.