The tail of polycystin-1 pays the kidney a complement

Michael J. Caplan

Department of Cellular and Molecular Physiology, Yale University School of Medicine, New Haven, Connecticut

FOR THOSE INTERESTED IN THE relationship between cellular signaling pathways and pathophysiology, autosomal dominant polycystic kidney disease (ADPKD) offers almost an embarrassment of riches. ADPKD is the most common potentially lethal genetic disease, affecting \( \geq 1 \) in 1,000 individuals (5). It is the leading genetic cause of end-stage renal disease and accounts for \( \sim 4\% \) of the population of patients requiring renal replacement therapy. Mutations in two genes, PKD1 and PKD2, account for essentially all cases of ADPKD. Although these genes and their protein products, polycystin 1 (PC1) and polycystin 2 (PC2), have been studied extensively for the past two decades, we still do not really understand what they do and why their loss leads to renal cystic disease (1, 15). The more deeply the mechanisms responsible for ADPKD are investigated, the more complex becomes the web of signaling processes that radiate from the two polycystin proteins. A recent review does an excellent job of organizing and summarizing these pathways (4), and the space allotted to the present piece does permit even a cursory discussion of their diversity. It is worth noting, however, that a significant subset of these pathways, including the intriguing process described in the paper by Wu et al. (18a) in a recent issue of the American Journal of Physiology-Renal Physiology, originates with the cleavage and release of the C-terminal tail of PC1 (1, 9, 10, 16, 17).

PC1 is a truly enormous membrane protein, composed of 4,302 amino acids that are predicted to span the bilayer 11 times. The extracellular N terminus is roughly 3,000 residues in length and, during the course of the protein’s posttranslational processing, it is liberated by an autocatalytic cleavage and remains noncovalently attached to a membrane-associated fragment (1, 11). Other cleavages release portions of this membrane-associated fragment, some of which remain embedded in the membrane (18) while others are released into the cytosol as soluble proteins and are able to enter the nucleus (2, 9). While the enzymes responsible for these cleavages and the physiological stimuli that initiate them have yet to be fully elucidated, it is clear that the resultant fragments that enter the nucleus can exert profound effects on transcriptional pathways. A fragment of \( \sim 30 \) kDa contains a nuclear localization sequence (2). This cleavage product, which is referred to as the PC1-CTT, has been shown to act as an inhibitor of cell proliferation and apoptosis through its direct interactions with the TCF and CHOP transcription factors that are integral components of these processes (8, 10). A shorter fragment of \( \sim 17 \) kDa lacks its own nuclear localization sequence but enters the nucleus in association with STAT6 and p100, where it can influence STAT6-mediated transcription activity (9). The larger PC1-CTT also appears to be able to exert complex influences on the activities of STAT1, 3, and 6 as part of the coordinated response to renal injury or other stimuli (16). These pathways are the subject of an excellent recent review (17). Both of these fragments appear to be produced, at least in part, in response to mechanical perturbations and to renal injury, and their release may help to coordinate cellular responses to these stimuli (2, 17).

The paper by Wu et al. (18a) in a recent issue of the journal contributes fascinating new insights into both the physiological roles of PC1 cleavage fragments and the pathways that may be involved in the pathogenesis of ADPKD. Wu et al. report that the \( \sim 30\)-kDa PC1-CTT C-terminal fragment of PC1 stimulates the expression of complement factor B (CFB) via a STAT1-dependent mechanism. This study connects the previous work suggesting that the C-terminal tail of PC1 can activate STAT transcription factors (9, 16) to earlier studies from the present authors and others (7, 13), which indicate that CFB is found at high levels in cyst fluid. In addition, recent results from human studies indicate that the levels of complement proteins, including CFB, are elevated in urinary extracellular vesicles from ADPKD patients and that the levels of at least some of these proteins correlate with total kidney volume (12). Wu et al. (18a) suggest that CFB may act to recruit M2 macrophages, which have been suggested to contribute to cystogenesis (6, 14). The authors find that CFB levels are elevated in human cystic kidneys and in a rodent model. They find that transfection of cells with a cDNA encoding STAT1 results in elevated CFB expression and that STAT1 binds to the CFB promoter. They find that expression of the PC1 C-terminal tail is associated with elevation of CFB levels, and this elevation is reduced by inhibiting STAT1 function as well as by inhibiting the NF-\( \kappa \)B pathway. Additionally, they show that exposing a macrophage cell line to CFB is associated with increased expression of arginase, a M2 marker. Taken together, these intriguing observations suggest that, at least in some contexts, the cleaved C-terminal tail of PC1 can be an active participant in processes that contribute to the pathogenesis of ADPKD. They further suggest that inhibiting the expression of CFB or the pathways that lead to its expression constitutes a potential target for therapeutic development in ADPKD.

It is perhaps somewhat counterintuitive that the PC1-CTT could be involved in ADPKD pathogenesis. After all, the PC1-CTT is a fragment of the PC1 protein encoded by the PKD1 gene, and mutations that eliminate or severely reduce functional PC1 expression are causative of ADPKD. Furthermore, the PC1-CTT has antiproliferative and antiapoptotic activities that might be thought of as “anticystogenic” (8, 10). How can we understand, therefore, that the C terminal portion of the PC1 protein could contribute to a disease that can also be caused by this protein’s absence? This is a difficult question to answer, since we do not have a clear understanding of the physiological role of PC1 or of the nature of the processes that lead to cyst formation in the context of ADPKD. Interestingly, overexpression of the PC1-CTT in zebrafish embryos can induce the formation of pronephric duct cysts, and immunoreactive protein corresponding to the molecular weight of the PC1-CTT has been detected in ADPKD cyst cells (9, 16). It has
been suggested that PC1 may participate in modulating the renal response to injury (3, 19) and that injury may stimulate the production of the PC1-CTT. Since injury repair is a complex and highly choreographed process, it is quite possible that both the absence of the PC1-CTT and excessive or aberrant PC1-CTT activity could lead to abnormal and ultimately pathogenic responses.

Future research will be required to bring together all of the pathways that are impacted by the PC1-CTT and to understand this protein fragment’s normal function and its pathogenic potential.

AUTHOR CONTRIBUTIONS

M.J.C. drafted manuscript; M.J.C. edited and revised manuscript; M.J.C. approved final version of manuscript.

REFERENCES