

DAB2IP modulates primary cilia formation associated with renal tumorigenesis

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ABSTRACT

Background:

Primary cilium is a microtubule-based organelle that projects from the surfaces in most mammalian cell types. Primary cilia protrude into the extracellular milieu (ciliogenesis) as an antenna-like sensor to sense extracellular physical and biochemical signals, then transmit signals into cell to regulate numerous physical and developmental processes. Also, loss of primary cilia is often found in many cancer types, including skin, breast, pancreas, ovarian, prostate and kidney cancers. Our previous studies demonstrate that loss of DAB2/DOC2 Interacting Protein (DAB2IP) is frequently associated with renal cell carcinoma (RCC). Recently, we observed that loss of DAB2IP in normal kidney epithelial cell significantly impairs primary cilia formation. Thus, we hypothesize that the tumor suppressor function of DAB2IP is mediated by regulating primary cilia formation.

Methods:

Serum starvation (1% FBS) was used to induce ciliogenesis throughout this study. Primary cilia were visualized by Immunofluorescence staining, and ciliated cells were calculated into percentage. The interaction of KIF3a with DAB2IP was determined by immunoprecipitation, and the interaction between KIF3a and DAB2IP domains was measured by dot blot assay. Tumorigenesis was determined by using colony formation assay, anchorage independent growth assay, and confirm the tumor take in SCID mice model.

Results:

In this present study, we observed an association of DAB2IP with primary cilia structure in normal kidney cell. Therefore, immunoprecipitation of DAB2IP complex was subjected to mass spectrum analysis and KIF3a was identified as an interactive partner. KIF3a is, the most abundant kinesin-2 family protein expressed in cells, one subunit of the heterotrimeric motor protein necessary for ciliogenesis. Data demonstrate a new mechanism of primary cilia maintenance via the physical interaction between KIF3a and the Pleckstrin homology (PH) domain of DAB2IP in which DAB2IP is able to prevent KIF3a protein turnover. Thus, DAB2IP can stabilize KIF3a proteins localized in the axoneme of primary cilia, which is

critical for the integrity of primary cilia. Furthermore, loss of KIF3a could promote renal tumorigenesis, suggesting that DAB2IP-KIF3a complex associated with primary cilia is one of critical homeostatic machinery in normal kidney epithelia.

Conclusions:

In conclusion, these data highlight a new function of DAB2IP in normal kidney cells by regulating primary cilia formation, which is independent from starvation-induced primary cilia pathway. Mechanistically, KIF3a is identified to be a key target that physically interacts with N-terminal PH domain of DAB2IP to stabilize this protein in maintaining primary cilia complex. As expected, loss of KIF3a can leads to the destruction of primary cilia underlying renal tumorigenesis.