Only some cell types have motile cilia

Credit: Brian Mitchell, Salk Institute
Only some cell types have motile cilia

But all animal cell types have a primary cilium

Credit: Brian Mitchell, Salk Institute
Primary cilium
is present in all animal cells: epithelial cells
as well as other types - only one cilium per cell
Primary cilium is composed of microtubules originating from a basal body.
Michael Jennings and Tony Poole, University of Otaga, NZ
First Prize, Nanotechnology Image Competition, 2012
Primary cilia contain sophisticated Intraflagellar Transport (IFT) machinery
Intraflagellar Transport (IFT) in action

This is a primary cilium

Notice this swelling

Cell nucleus

Nucleolus

Adjacent cell

http://www.bowserlab.org/primarycilia/ciliumpage2.htm
Primary cilia were previously thought to be a vestigial organ left from flagellates’ “tails”
Primary cilia

are now recognized as:

- “micro-antennae” receiving information about external environment
- “cellular GPS” informing the cell of its location
- “communication hubs” transducing this information into cell’s decisions regarding proliferation, polarity and differentiation
Living cells sense and respond to their environment by a set of mechanisms known as cell signaling.
Primary cilia transduce some major external signals
into internal signals that govern cellular activity
Sonic hedgehog pathway
Sonic Hedgehog Signaling Pathway
Primary cilia help maintain cell polarity
Ca^{2+} signaling pathway
In kidney, primary cilia respond to changes in flow and maintain cell orientation using intracellular Ca signaling through PC1-PC2 complex.
This is quite important for polarization of cell division: cilial axoneme originates from the mother centriole of the centrosome, which orchestrates mitosis.
Which one is centrosome?
In mitosis, primary cilium will disassemble and release centrosome, which will orient mitotic spindle and coordinate cell division in the appropriate direction.
In which direction should these cells divide?
If cilia are unable to sense cellular orientation, correct mitotic spindle polarity will be lost, resulting in non-directional cell division and distorted architecture of the tubule.
Tubular atrophy

Cyst lined by simple cuboidal or flattened cells
Unified theory of cystogenesis

- Multiple genes responsible for cystic kidney diseases have been identified to date
- All products of these genes have been localized to primary cilia or centrosome
Unified theory of cystogenesis

- The general paradigm implicates loss of cell polarity coupled with increased expression of ion and water transport proteins in cyst interior
- In many renal cystic diseases other organs are affected (retinal degeneration, liver fibrosis, extra digits, mental defects, diabetes etc)
Polycystic Kidney Disease
ADPKD – Polycystin 1 and 2, function as part of the multi-protein Ca channel complex
ARPKD – Fibrocystin, function unknown
Autosomal Dominant Polycystic Kidney Disease
Autosomal Dominant Polycystic Kidney Disease (Adult)

Autosomal dominant disease related to defect on chromosome 16 (PKD1, encoding Polycystin 1 (85% of cases) or chromosome 4 (PKD2, encoding Polycystin 2)
1. Abnormal allele of PKD1 or PKD2 does not work;
2. Normal allele produces enough polycystin until it is silenced by some “second hit” resulting in non-directional cell division.
3. The cyst “pinches off” and exhibits autonomous solute and water transport into the cyst which facilitates growth.
Autosomal Dominant Polycystic Kidney Disease

- Kidneys can get up to 4kg
Autosomal Dominant Polycystic Kidney Disease

- ESRD typically by the 4th or 5th decade
Autosomal Dominant Polycystic Kidney Disease

- 40% also have polycystic liver disease (from biliary epithelium)
Autosomal Dominant Polycystic Kidney Disease

- Also intracranial berry aneurysms at the Circle of Willis;
- Lead to death in 4 – 10% of cases due to subarachnoid hemorrhage
Autosomal Dominant Polycystic Kidney Disease

• Mitral valve prolapse in 20 – 50% (usually asymptomatic)
• 40% die of coronary or hypertensive heart disease
Autosomal Dominant Polycystic Kidney Disease

- Dialysis or transplant – excellent prognosis
- Nephrectomy if painful or infected
Autosomal Recessive Polycystic Kidney Disease
Autosomal Recessive Polycystic Kidney Disease (Childhood)

- Rare and distinct from ADPKD
- Defect on chromosome 6 (PKHD1) which encodes protein fibrocystin
- Kidneys are enlarged with smooth external surface
Autosomal Recessive Polycystic Kidney Disease

• Many small cysts give cut kidney a sponge-like appearance
Autosomal Recessive Polycystic Kidney Disease (Childhood)

- Usually presents at birth with serious complications
- Enlarged kidneys may interfere with pulmonary development – stillbirth
- Rapid renal failure may follow

www.ultrasound-images.com/fetal-urogenital.htm
Autosomal Recessive Polycystic Kidney Disease

- Liver also has cysts
- Progressive hepatic fibrosis and bile duct proliferation in older children (“congenital hepatic fibrosis”, Caroli’s Syndrome)
Nephronophthisis
• Rare disease but the most common genetic cause of ESRD in age <30
• Numerous cysts at cortico-medullary junction
• Research into NPHP led to a Unifying Theme of Cystogenesis and understanding of Ciliopathies
Bardet-Biedl Syndrome
Bardet-Biedl Syndrome

A rare autosomal recessive ciliopathy characterized by retinal dystrophy, obesity, polydactyly, renal dysfunction, learning difficulties and hypogonadism
Bardet-Biedl Syndrome
Meckel-Grueberber Syndrome
Meckel-Grueber Syndrome

• A severe ciliopathy characterized by renal cystic dysplasia, polydactyly, occipital encephalocele, and perinatal death
• MKS is an autosomal recessive, genetically heterogeneous disorder
• The five identified MKS genes encode cilia and/or basal body proteins
Meckel-Grueber Syndrome
Joubert Syndrome, “Molar Tooth” Sign

Senior-Loken Syndrome, Situs Inversus

Bardet-Biedl Syndrome, Hexadactily
Von Hippel-Lindau
Von Hippel-Lindau

- Autosomal dominant syndrome characterised by formation of a variety of cysts, vascular tumors and cancers
- Mutation of \textit{VHL} tumor suppressor gene
- VHL protein regulates HIF
  - mutation stimulates angiogenesis and hypervascularization
  - VHL is required for ciliagenesis
Von Hippel-Lindau

- Clinical presentation:
  - Malignancies arise due to “second hit” mutations
  - Lifetime risk of RCCA 40%
Von Hippel-Lindau
Von Hippel-Lindau

Leung et al., Radiographics, 2008
Bosniak classification of renal cysts

1. ~0% are malignant
2. ~0% are malignant
2F. ~25% are malignant
3. ~50% are malignant
4. ~100% are malignant
Von Hippel-Lindau
Von Hippel-Lindau

Leung et al., Radiographics, 2008
Tuberous Sclerosis
Tuberous Sclerosis

• Autosomal dominant disease with hamartomas in kidneys, brain, skin etc
• Mutations in TSC1 or TSC2 genes
• TSC genes regulate elongation of primary cilia (through mTOR signalling)
• 30% patients have renal cysts
Tuberous Sclerosis
Tuberous Sclerosis
Diagnostic work-up of cystic kidney disease

- Presence of bilateral renal cysts
  - Yes
    - Presence of solid renal tumours
      - Yes
        - Angiomyolipoma
        - Renal cell carcinoma
          - TSC
            - Confirm by genetic testing
          - VHL
            - Confirm by genetic testing
      - No
      - Kidney size
    - Normal/small
      - Localization of cysts
        - Cortico-medullary
          - Autosomal recessive
            - NPHP
          - Autosomal dominant
            - MCKD
          - Extrarenal manifestations
            - Polydactyly
              - Juvenile obesity
              - Intellectual disability
              - Anosmia
              - Retinitis pigmentosa
            - Cerebellar vermis hyperplasia/aplasia
              - Retinitis pigmentosa
              - Liver fibrosis
              - Coloboma
              - BBS
              - JBTS
              - SLSN
      - Ubiquitous
    - Enlarged
      - Presence of liver fibrosis
  - No
  - Yes
    - Autosomal dominant
      - ADPKD
    - Autosomal recessive
      - ARPKD
Diagnostic evaluation of cystic kidney disease