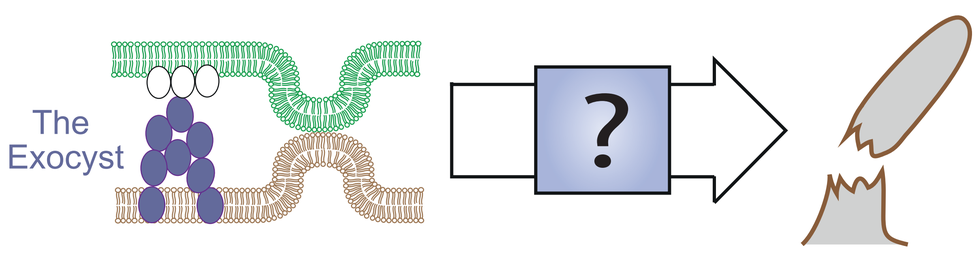
A new protein required for building the cell's antenna

Lauren Adams, Isabelle Jourdain, Helen Dawe

University of Exeter, Geoffrey Pope Building, Stocker Road, Exeter EX4 4QD, UK

1. Introduction



Almost every cell in the human body can build an antenna called a 'cilium'. These are important for coordinating signals during not only embryo development, but throughout life [1-4]. By examining patients who have faulty cilia, we now know of 30+ proteins that are essential for the formation and function of cilia [5,6,7]. However, we do not always understand what role these proteins play, or how their absence leads to disease. My research aims to figure out how a new cilia-related protein - Exoc4 - is involved in building cilia.

2. Symptoms of ciliopathies

Faulty cilia cause a severe class of human diseases, known as 'ciliopathies' [8]. These are estimated to affect 1:1000 people worldwide [9].

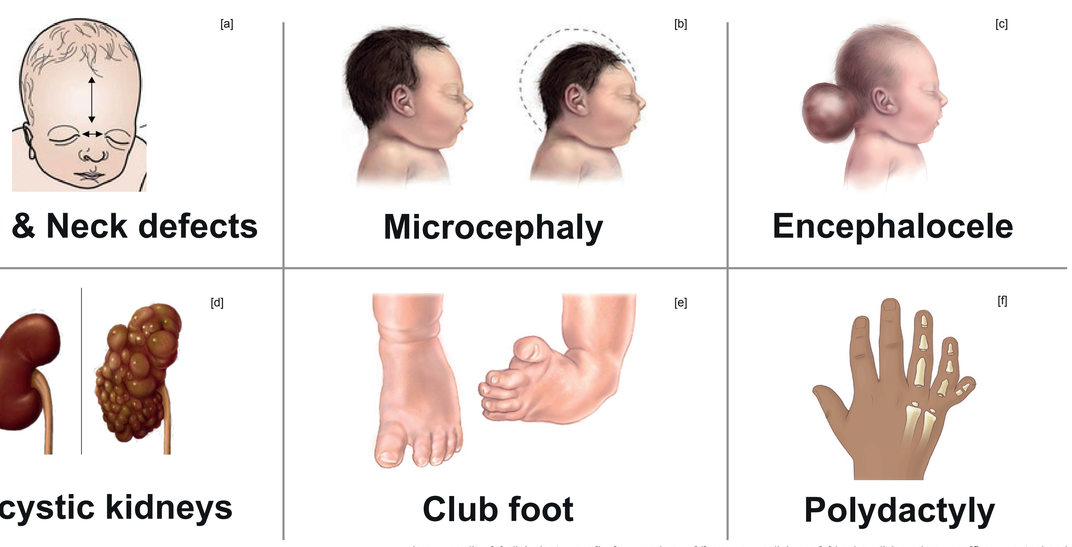
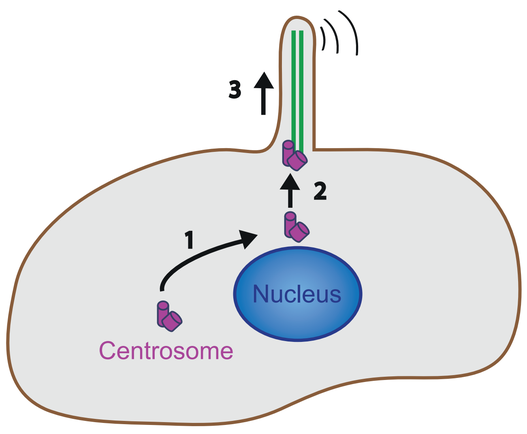


Image credits: [a] clinicalgate.com [b,c] www.cdc.gov [d] www.mayoclinic.org [e] keckmedicine.adam.com [f] www.eatonhand.com

3. How do cilia form?

When a cell decides to build a cilium, it first needs to move the foundations - called the 'centrosome' - to the right place.



Normal cells:

1) Migration Around

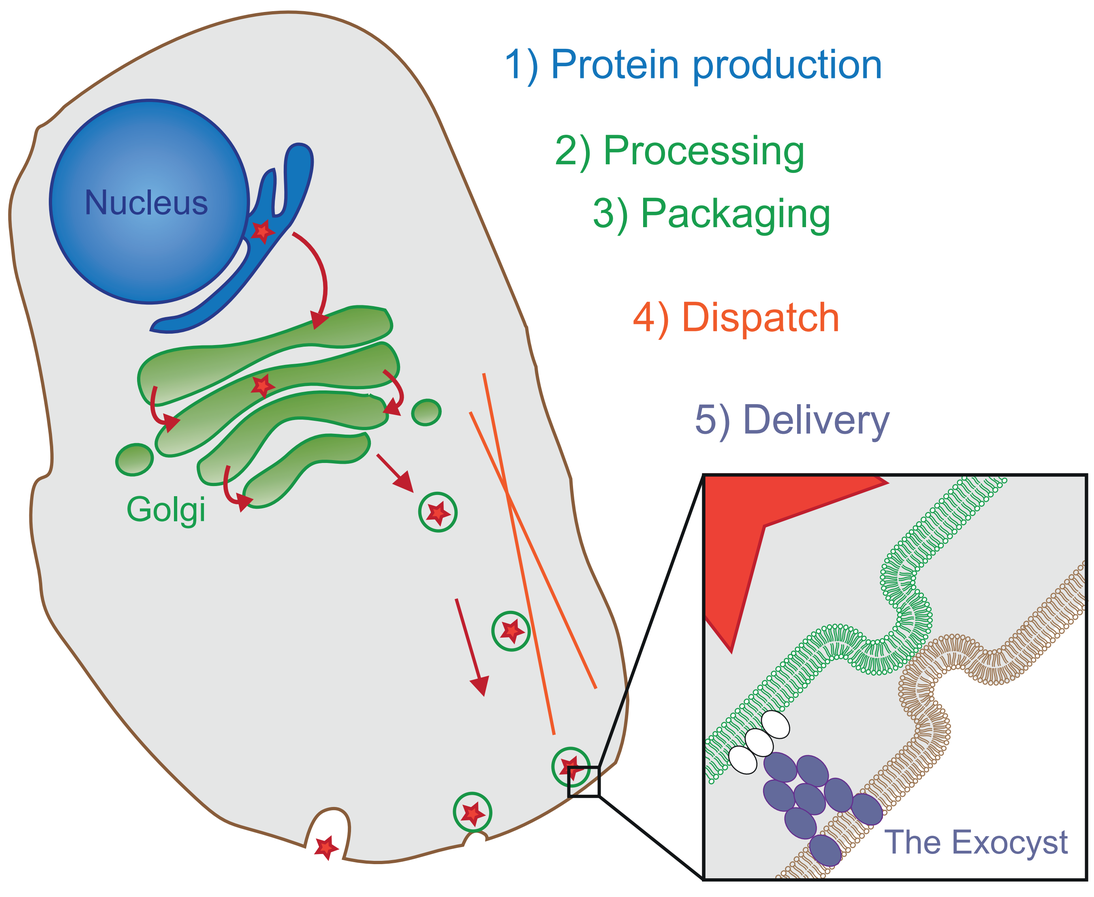
2) Migration Up

3) Build cilia!

4. What we currently know about Exoc4

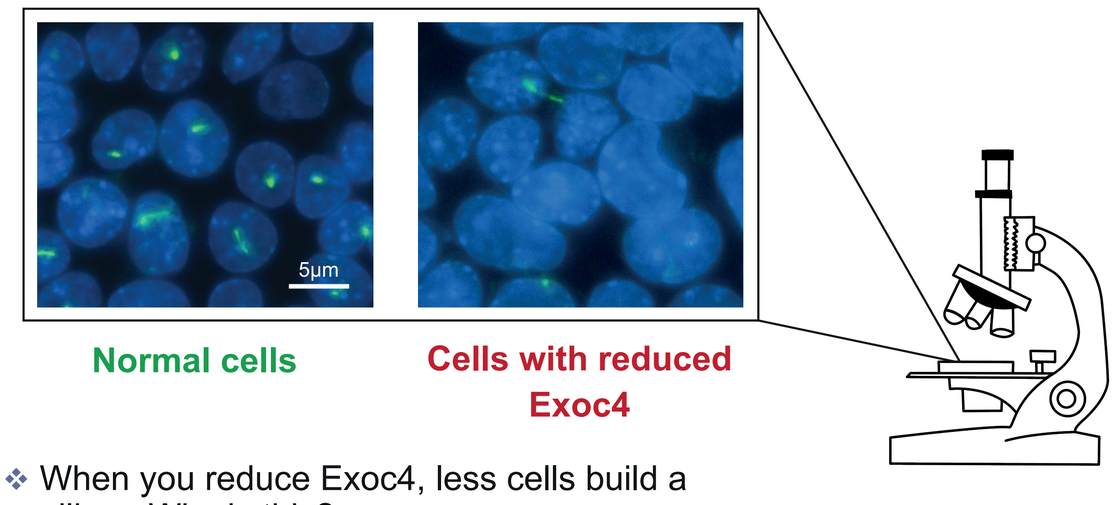
2013: When looking at the DNA of a ciliopathy patient, scientists find a mutation in a protein called **Exoc4** [10].

Exoc4 is part of a group of proteins called "the exocyst", which helps the cell to secrete things. When an envelope (containing proteins) reaches the edge of the cell, the exocyst helps to guide it to the right place, and hold it there while the cargo is released.

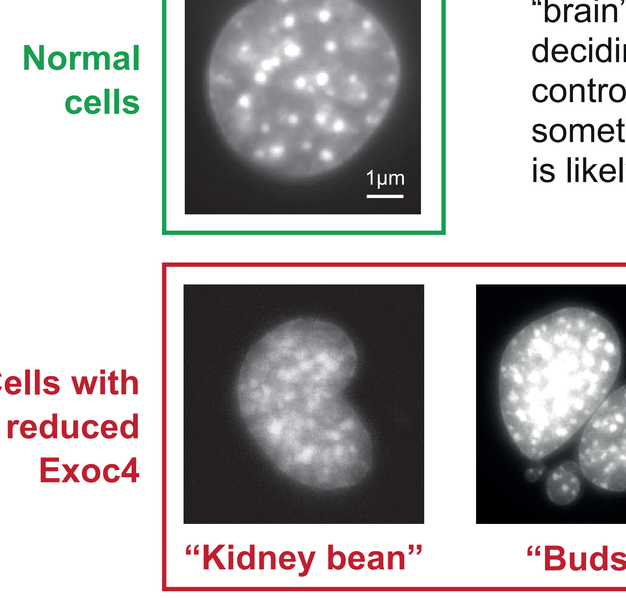


But how does it help to build the cilium?

5. What happens to cilia when you greatly reduce the amount of Exoc4 inside the cell?



- When you reduce Exoc4, less cells build a cilium. Why is this?
- We examined where the centrosome was in these cells, and found that it was not correctly positioned:



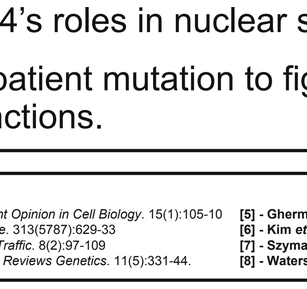
Cells with reduced Exoc4:

- ✓ Migration Around
- × Migration Up
- × Build cilia!

Exoc4 must be needed for the migration of the centrosome. When it does not migrate, there is no foundation on which to build a cilium.

6. Exoc4 also seems to be required for shaping the nucleus

- We noticed that cells with less Exoc4 also had more oddly-shaped nuclei



The nucleus is the control centre, the "brain" of the cell. It is responsible for deciding which proteins are made, and controlling the cell's behaviour. If something is wrong with the nucleus, it is likely to have bad effects for the cell!

7. Future directions

- Investigate how Exoc4 is interacting with the nucleus.
- What effects does an oddly-shaped nucleus have on the rest of the cell?
- Are Exoc4's roles in nuclear shape and building cilia connected?
- Use the patient mutation to figure out which part of Exoc4 is needed for these functions.

References:

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[2] - **Singla *et al.*** (2006), *Science*. 313(5787):629-33
[3] - **Christensen *et al.*** (2007), *Traffic*. 8(2):97-109
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[6] - **Kim *et al.*** (2010), *Nature*. 3464(7291):1048-51
[7] - **Szymanska *et al.*** (2015), *Cilia*. 4(1):O12
[8] - **Waters *et al.*** (2011), *Pediatr Nephrol*. 26(7):1039-56
[9] - **Ciliopathy Alliance;** http://www.ciliopathyalliance.org/
[10] - **Shaheen *et al.*** (2013), *Eur J Hum Gen. 21(7):762-8*