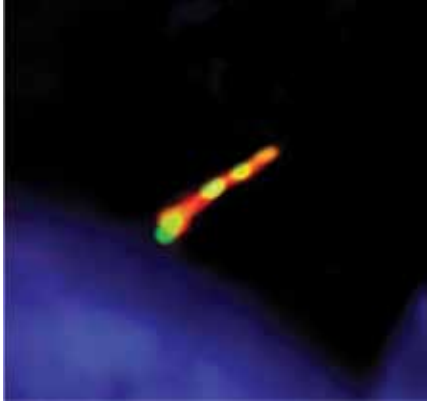
A new look at the **oldest organelle**



Immunofluorescence micrograph of the primary cilium of a human embryonic stem cell, where "blue" is the cell nucleus. "Red" is the cilium and the "Green / Yellow" colors is a receptor in stem cell differentiation

By Chris Tachibana

Cilia, the first cell structures seen by a microscope, are the cell's GPS and the key to disorders from ovarian cancer to congenital heart disease

Cilia probably looked like the cell's eyelashes to Antonie van Leeuwenhoek when he described them in the 1660s—one of the first structures ever seen under a microscope. Cilia are easily visualized because they form long, hair-like extensions from eukaryotic cells. Textbooks say cilia function in cell movement and this is true: single-celled organisms use them to swim around. Epithelial cells use them to sweep mucus and dirt out of the lungs. But primary cilia, which are found on almost all human cells, aren't involved in movement at all. Instead, they act as antennae and central command centers for receiving and processing signals for cell migration, differentiation, and cell cycle entry. Defects in primary cilia are responsible for diseases of the eyes and internal organs, and are involved in multifactorial conditions including developmental disorders, cancer, and diabetes.

- Primary cilia were considered a vestigial organelle ten years ago. Now PubMed has about 30 papers a week on them, says Lotte Bang Pedersen. She and Søren Tvorup Christensen are associate professors in the Department of Cell and Developmental Biology, Section of Cell and Developmental Biology, University of Copenhagen. Together, they head a cilia research group that is a leader in the field.

Pedersen is a founding member of the Nordic Cilia and Centrosome Network, a recently launched group sponsored by Nordforsk of the Nordic Council of Ministers. The network promotes basic and translational cilia research in Medicon Valley and beyond.

-We are bringing together clinical and basic scientists in the field, says Lotte Bang Pedersen. In addition to the Copenhagen Cilia group, members include researchers from the Oslo Hospital Department of Radiology and a group from the Karolinska Institute who are working on cilia defects that may result in dyslexia.

A dynamic antenna for division, wound healing, development and more

Primary cilia have been implicated in conditions ranging from dyslexia to diabetes because of their central function of sensing, receiving, and distributing intercellular communications. Their structure reflects their function as the cell's antenna or receiving tower. Primary cilia are formed during growth arrest and originate from the centrosome, a structure within the cell that is closely involved in cell cycle and cell division control. The microtubule and associated proteins of a primary cilium extend from the centrosome into the extracellular environment, contained within an extension of the cell membrane that teems with receptors and signal tranduction proteins. These shuttle in and out of the primary cilium, depending on the cell's conditions and immediate needs. Having all

these communication systems within the cilium makes for easy coordination and crosstalk between separate signaling pathways.
- Primary cilia act like cellular switches that turn signaling pathways on and off depending on the cell type. For brain cells, it might be satiety signals, because mice with primary cilia defects in hypothalamus cells overeat and become obese, eventually leading to severe strokes. In other cells, a ciliary signal may control the division and differentiation of stem cells during organ development. Cilia defects cause congenital heart defects, which is a major project in the Copenhagen Cilia group, says Søren Tvorup Christensen.
Another important project in the group focuses on the connection between primary cilia and ovarian cancer. This work was recently featured in a news release from the Danish Cancer Society (Kræftens Bekæmpelse), which funds Christensen. His lab found that cancer cells, which often have lost control over cell division, also have defects in formation of primary cilia and this leads to uncontrolled cellular signaling, which promotes tumorigenesis. Pedersen says this is why primary cilia are sometimes called tumor-suppressor organelles and are considered candidate targets for new cancer drugs.
An additional focus of the Copenhagen Cilia group is wound healing, because primary cilia act as the cell's GPS in this process, directing the migration of cells involved in closing a wound. Cultured cells with primary cilia defects cannot migrate properly, and wounds in mice with mutations that affect primary cilia do not heal correctly. There is no lack of additional projects.
- Several hundred genes are related to primary cilia maintenance, function or coordination, in pathways implicated in developmental disorders as well as diseases in adults, including obesity, cancer and heart defects. Some central genes for cilia formation are essential, and mutations cause an arrest in embryonic development. But there are also thousands of peripheral genes to investigate, says Søren Tvorup Christensen.
One upcoming project is generating a total transcriptome related to cilia, to find cilia-related genes that are upregulated and downregulated during assembly, disassembly, differentiation of stem cells and other processes that involve cilia.

Reaching out with local and global partnerships

Using global collaborations, the two professors get the most out of their small group of fewer than 20 students and scientists. Christensen trained at Albert Einstein College of Medicine in New York, and Pedersen at Yale University in Connecticut, before they joined forces to focus on mammalian cells in Copenhagen. Pedersen specializes in organelle assembly and maintenance and Christensen specializes in ciliary signaling in stem cell differentiation, heart development, wound healing and cancer, but they share labs and work as a team. Collaborations with the US labs continue through student exchanges, and other collaborators are at Erasmus Medical Center in Rotterdam, The Netherlands. These connections are important because, as Christensen says; That's the way you have to research today.
- We do basic research on the molecular mechanisms of cilia, because we need to understand the basic mechanism of how these organelles are formed and function to understand the etiology of diseases. But we are always interested in partnering with companies, adds Lotte Bang Pedersen.

Resource websites:

Nordic Cilia and Centrosome Network:
www.nordiccilia.org

University of Copenhagen Cilia Group:
www.bio.ku.dk/english/research/cu/cilia