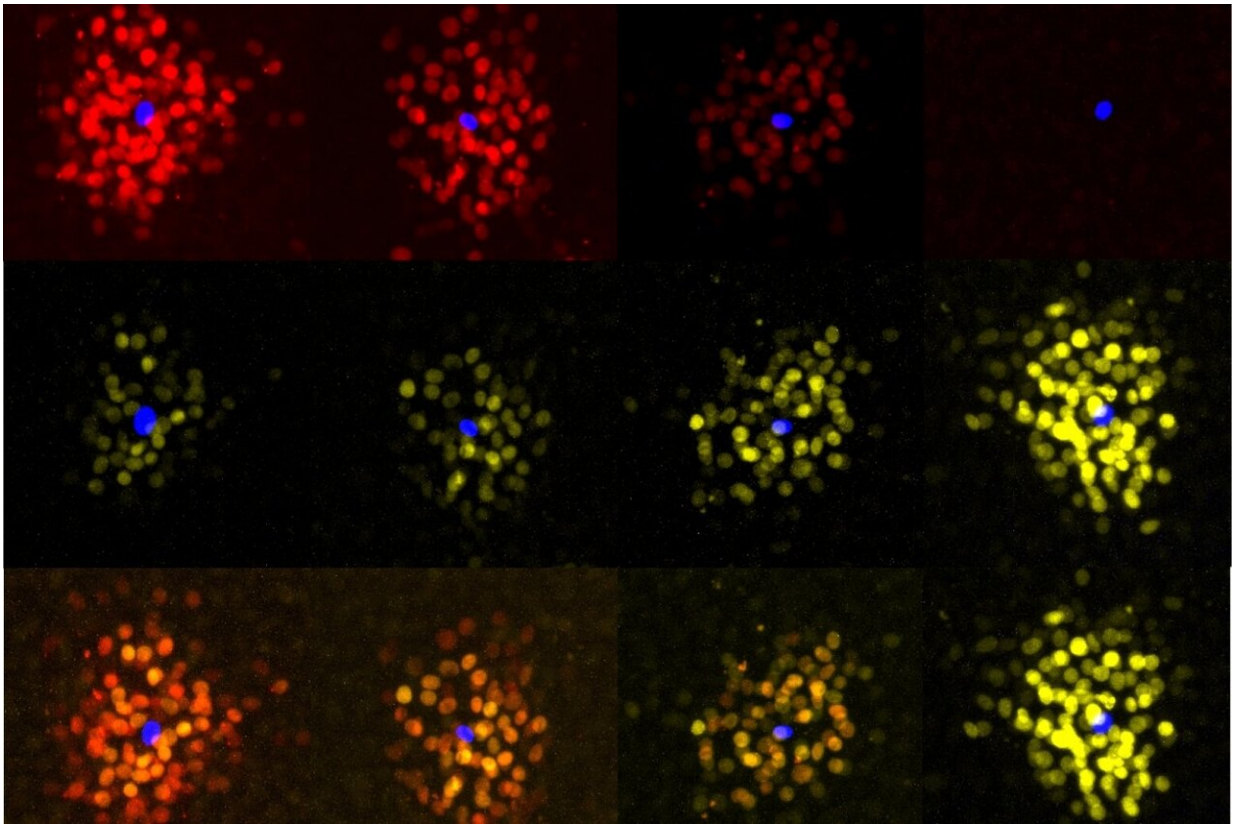
If we imagine the cell as an orchestra, what is conducting the symphony?

March 25 2021, by Conor Gearin



Credit: Pulin Li/Whitehead Institute

Our bodies are made up of trillions of cells, and each of those cells is made up of countless biological molecules with specialized functions that keep the cells alive. When those molecules malfunction, it can lead

to disease. If we imagine the cell as an orchestra, with many musicians who each have a small part to play, then what conducts all of these musicians and keeps them organized and harmonized as they play a symphony?

Whitehead Institute researchers are showing that, like a conductor, certain key molecules tune the cell's behavior to the needs of the occasion. The knowledge of how cells give order to complicated processes could prove crucial to learning how to restore healthy function in diseased cells.

Fine-tuning gene activity

While some features of our cells are hard-coded into the sequence of DNA, altering the chemical structure of DNA can change how the cell reads a gene and whether it gets activated. Such modifications of the genome, many of which are heritable, are called epigenetics. They allow a cell to precisely tune its gene activity. Problems with epigenetics are linked to many disorders, including fragile X syndrome and Rett syndrome. Whitehead Institute Member Mary Gehring uses the Arabidopsis plant as a model system to study how epigenetics shape gene expression.

In a recent study, Gehring and postdoc Xiao-yu Zheng examined epigenetic changes in the endosperm, which provides nutrition to developing seeds. They focused on chromatin—the way that DNA is packaged in the nucleus. Tightly-packed chromatin can inhibit gene expression. However, mapping chromatin has been difficult in the short-lived endosperm of Arabidopsis. Zheng and Gehring showed how a new technique, CUT&RUN, can efficiently map chromatin modifications for the full Arabidopsis endosperm genome, opening avenues for further research into how chromatin influences gene expression in developing seeds. With discoveries like these, Gehring's lab is identifying the key

players that impose order on gene activity.

Gehring is now exploring how to use epigenetics to engineer crops resistant to harsh environments, leading Massachusetts Institute of Technology (MIT) to choose Gehring as a Bose Research Fellow in recognition of highly innovative research. Her lab is beginning to focus on orphan crops—less frequently grown plants that provide a largely untapped source of genetic diversity and often thrive in challenging growing conditions. By linking fundamental mechanisms of gene regulation to real-world problems related to the food supply, Gehring is illustrating the transformative potential of research into how cells control their genome.

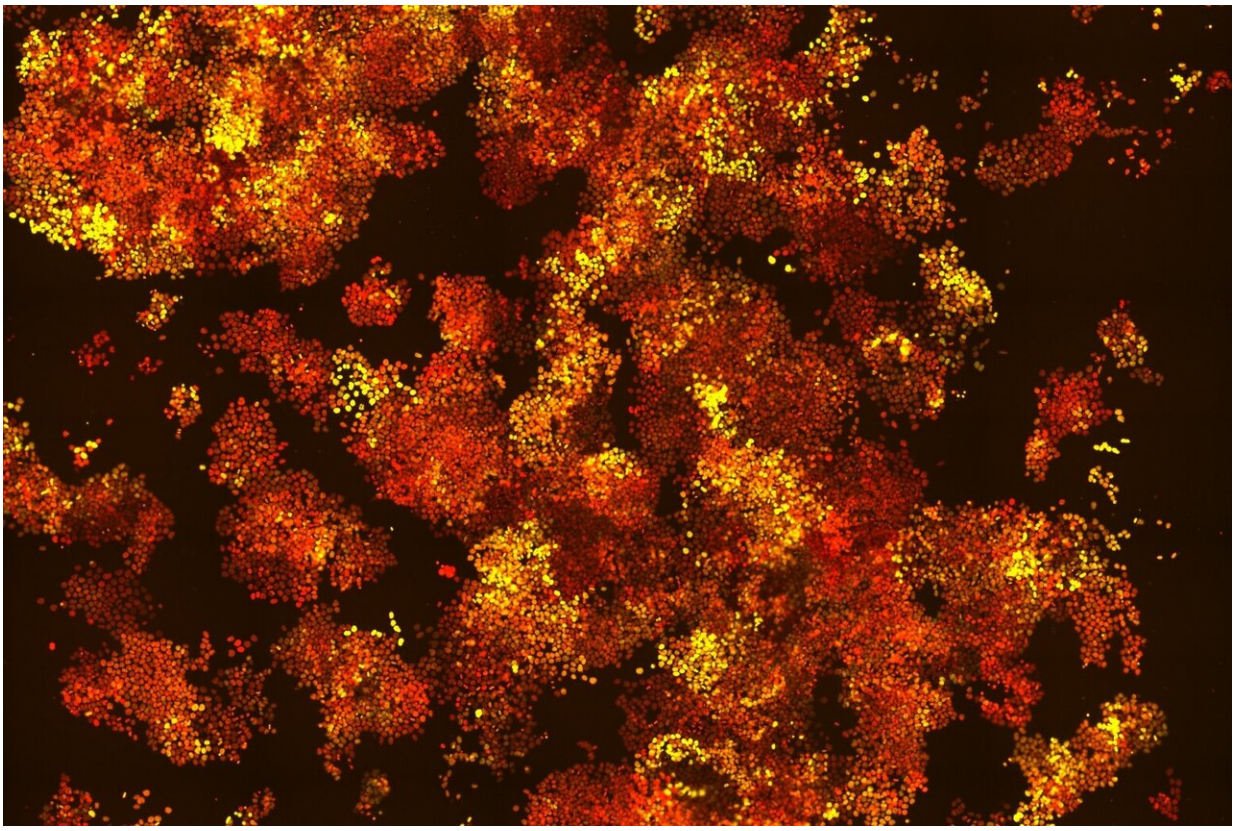
The dance of cell division

For bodies to grow, cells need to divide billions of times to build tissues. A cell dividing into two daughter cells has to split its chromosomes evenly between two new nuclei. Cells have to direct this complex dance routine to make sure the chromosomes end up where they are needed. Whitehead Institute Member Iain Cheeseman investigates the tools our cells use to divide and what goes wrong in cells that cannot divide or cannot stop dividing.

Carrying out the cell divisions that produce egg cells is essential for fertility. Scientists have wanted to know how immature egg cells—oocytes—retain their ability to divide for years before they become viable eggs. In a study led by postdoc Zachary Swartz, the lab investigated the centromere, the part of a chromosome that anchors rope-like fibers that pull apart chromosomes during cell division. A critical part of the anchor is a protein called CENP-A, without which the cell loses its ability to divide. It was thought that CENP-A remains static in cells that go dormant but later divide. Using sea star oocytes as a model, because of their similarities to human oocytes, Swartz and Cheeseman

have shown 25 that CENP-A is slowly but steadily replenished in oocytes, allowing them to remain dormant for years while retaining the ability to divide.

Cheeseman's lab is now pursuing how to rejuvenate centromeres in aging egg cells. Cheeseman was recently named a scholar of the Global Consortium for Reproductive Longevity & Equality for pursuing a better understanding of how centromeres degrade with age. This research could reveal how to one day engineer egg cells to extend the window of female fertility.



Credit: Pulin Li/Whitehead Institute

Engineering how cells harmonize

If you know how the cell conducts its symphony, you can try to compose new tunes for the cell to play. Whitehead Institute Member Pulin Li studies how cells communicate with each other to form multicellular patterns. She focuses on molecules called morphogens—the primary guide for developing tissues, providing the blueprint for the body. Morphogens guide where an embryo's head and limbs should develop as well as the finer details of organs with many cell types, like the brain.

By growing cells in Petri dishes and genetically engineering them to form patterns, Li hopes to uncover the fundamental rules for tissue formation, which could address longstanding questions about development and potentially prove useful for learning how to regenerate body parts or heal damaged tissues. In recognition of her path-breaking work, Li has been named the Eugene Bell Career Development Professor of Tissue Engineering at MIT.

Li's bottom-up approach begins with a simplified system: sender cells broadcasting a message and cells interpreting the message and responding to it. This Petri-dish approach is inspired by what we know of tissue development, in which cells coordinate with each other to determine cell fate and produce a fully functioning tissue. The music of the individual cell has to harmonize with all those around it. Li's lab seeks to apply the knowledge gained from studying development to engineer cells that communicate to form specific patterns. This could help overcome challenges faced by tissue-engineering approaches that rebuild tissue on top of a synthetic scaffold that directs the cell pattern. Li's goal is to engineer cells to form patterns on their own—a bold new approach to tissue engineering and regenerative medicine.

Directing the cell's metabolism

In order to survive, cells need to adjust their metabolism based on the amount of nutrients available. Disruptions to the control of cell growth and metabolism can lead to diseases such as diabetes and cancer. Whitehead Institute Member David Sabatini studies a protein called the mechanistic target of rapamycin (mTOR), a master regulator of cell growth. Sabatini is the co-recipient of the 2020 Sjöberg Prize from the Royal Swedish Academy of Sciences for his role in discovering the mTOR protein and its role in controlling cell metabolism and growth.

Sabatini's lab is studying how new drugs might target mTOR or the proteins that regulate its activity. A study led by postdoc Kacper Rogala described a new structure for mTOR complex 1, a regulatory protein complex that includes the mTOR protein. The study revealed how mTOR complex 1 docks with the lysosome, an organelle that breaks down and recycles materials in the cell. Partner proteins allow the complex to dock only if nutrient levels are high and push it off the lysosome when the cell is starved for nutrients. The docking mechanism is crucial to understanding mTOR complex 1, because the protein complex only activates once on the lysosome. A related study led by former postdoc Kuang Shen and Rogala provided a high-resolution structure for a key mTOR complex 1 activator, FLCN, and a partner protein, FNIP2. Problems with FLCN can lead to tumor formation. These structures are more detailed than any previous work, giving the researchers precise information about how mTOR interacts with its regulatory proteins.

By filling in the gaps of how mTOR senses nutrients and how its partner proteins regulate it, Sabatini's lab moves closer to identifying factors that act on it with high specificity without affecting other important cellular pathways.

Provided by Whitehead Institute for Biomedical Research

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