Missing link found between pathways involved in cell development

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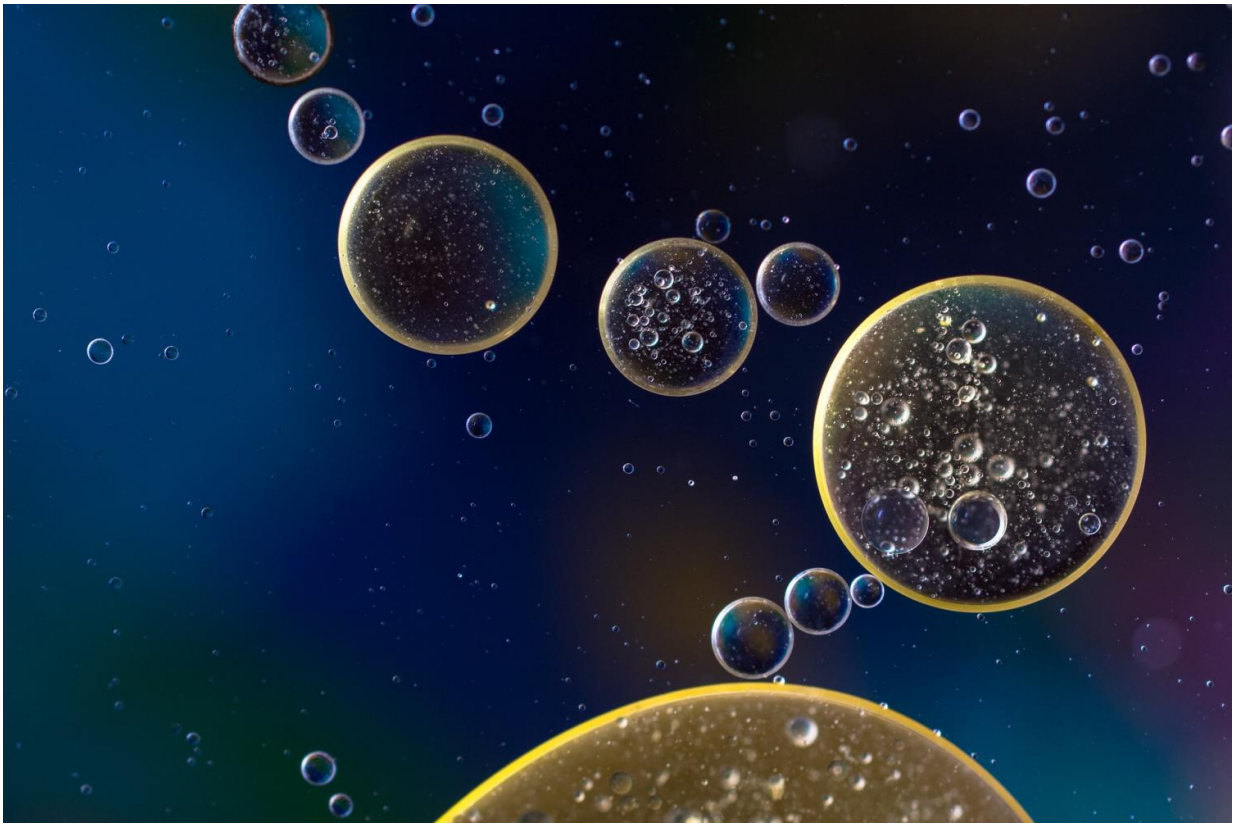

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A new mechanism that coordinates human development in response to signals from outside the cell has been discovered by researchers at the Wellcome Sanger Institute and the Wellcome - MRC Cambridge Stem

Cell Institute. Reported in *Nature*, the study revealed that the SMAD2 and SMAD3 proteins (SMAD2/3) link and coordinate many different pathways in the cell that were previously believed to be separate.

In addition to switching on specific genes on command, researchers saw for the first time that SMAD2/3 precisely regulates the timing of their expression, fine-tuning the processes needed for embryo development and growth.

This new mechanism could be essential for other processes that need a rapid response - such as organ repair, immune response or cancer growth - and this finding could inspire novel methods of studying these processes.

For cells and tissues to function correctly, certain genes need to be switched on and off at the right times in response to signals - called growth factors - from outside the cell. The SMAD2/3 protein is known to be a vital part of this cell signalling process, activated inside the cell and switching on and off genes needed for many varied processes, from embryo development and growth to activating the immune system or cancer.

SMAD2/3 has numerous different functions in different cells, from controlling growth in some cell types to controlling the response to stress in others. It was known to interact with certain DNA-binding proteins called transcription factors, however, until now it was a mystery how it was possible for SMAD2/3 to achieve so many different functions.

The researchers studied developing human pluripotent stem cells - cells that can give rise to all tissues and organs of the human body - investigating the interactions of SMAD2/3 with other proteins. They discovered that that while SMAD2/3 did bind some transcription factors, it also interacted with proteins involved in a whole range of molecular

processes in the cell, coordinating them with the cell signalling.

One such molecular process is the recently discovered mechanism known as RNA editing. When proteins are produced in a cell, the DNA is transcribed into messenger RNA, which is then translated into the proteins that the cell needs. However, RNA editing can make modifications to the RNA to reduce its stability and control how long a protein can be produced for, effectively switching the gene off more rapidly than would be achieved by only halting RNA transcription.

For the first time, researchers saw that SMAD2/3 was able to activate an RNA editing protein, which made specific RNAs unstable and quick to degrade. The SMAD2/3 acted as a link between cell signalling and RNA editing, allowing the cell to switch on, and then rapidly switch off again, genes that are important for development.

Dr Alessandro Bertero, a first author on the paper and former PhD student at the Wellcome - MRC Cambridge Stem Cell Institute, said: "To our knowledge this is the first time that anyone has seen that SMAD2/3 can interact with so many multiple processes, unexpectedly coordinating different cell pathways. Our study shows that SMAD2/3 is like a multi-function Swiss army knife instead of the specialised tool it was previously thought to be, creating a link between various key pathways."

Since the activity of SMAD2/3 is regulated by growth factors, the study sheds light on a novel way that cell function can be controlled by signals from outside the cell.

Dr Ludovic Vallier, lead author on the paper from the Wellcome Sanger Institute and Wellcome - MRC Cambridge Stem Cell Institute, said: "Our study reveals that cell signalling with SMAD2/3 coordinates cellular mechanisms and allows the cells to change state quickly.

Understanding this could be important for studying diseases such as cancer where cellular processes are often investigated in isolation. These findings could also change the way mechanisms such as mRNA processing, DNA repair and transcriptional regulations are studied and open entire new fields of investigation."

More information: The SMAD2/3 interactome reveals that TGFβ controls m6A mRNA methylation in pluripotency, *Nature* (2018). DOI: 10.1038/nature25784

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