How 'pioneer' protein turns stem cells into organs

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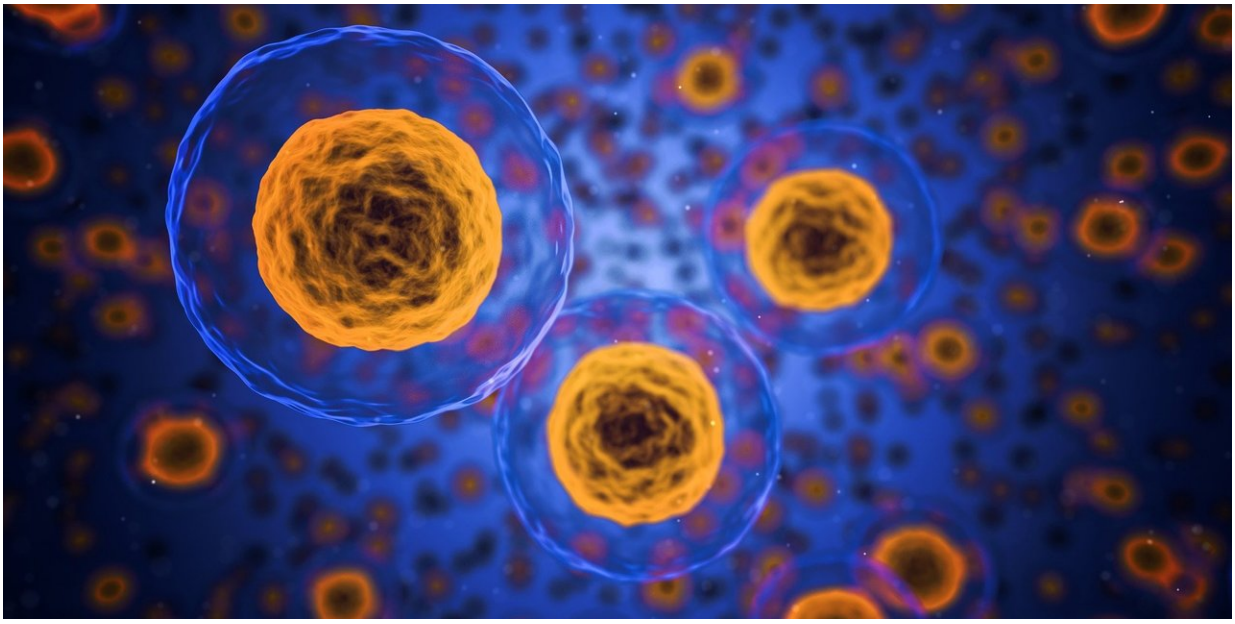

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Early on in each cell, a critical protein known as FoxA2 simultaneously binds to both the chromosomal proteins and the DNA, opening the flood gates for gene activation, according to a new study led by researchers in the Perelman School of Medicine at the University of Pennsylvania. The discovery, published in *Nature Genetics*, helps untangle mysteries of how embryonic stem cells develop into organs.

Molecular signals begin dictating what organs an embryo's stem cells will give rise to in the body—such as the liver or pancreas—within the first two weeks of development. It's an intricate process guided by these so-called "pioneer" transcription factors that gain access to the tightly packed DNA inside each cell so other specialized proteins can get in and activate the necessary genes. However, until now, it's been unclear how these pioneer factors open the DNA.

"We now understand that this pioneer factor, FoxA2, grabs the chromosomal proteins, known as histones, and exposes the DNA region," said the study's corresponding author Kenneth S. Zaret, Ph.D., the Joseph Leidy Professor in the Department of Cell and Developmental Biology and Director of Penn's Institute for Regenerative Medicine (IRM). "That opening allows other specialized, regulatory proteins to access the DNA and activate a network of silent genes that leads to the formation of internal organs."

For decades, researchers in Penn's IRM have been pulling back the curtain on this process as they work toward developing new cells for transplantation and tissue repair as part of treatment for common problems like liver or heart disease. Knowing how regulatory gene proteins work during this early stage can help the field better understand how to control the process of cell development for both clinical research and therapeutic purposes.

Zaret's lab previously discovered pioneer factors in 2002 and has been working to better understand their function and role in early embryonic development. In this latest study, the team of researchers, co-led by Makiko Iwafuchi, Ph.D., who performed the work while at Penn and is now at the University of Cincinnati College of Medicine, first used in vitro genetic techniques to investigate the interaction of FoxA with chromosomal proteins at the same time it interacts with DNA. They found that a small region of the FoxA2 protein—just 10 amino acids of

more than 460—were necessary for the protein to make an opening in the chromatin fiber.

Next, the teams translated those findings into a mouse model, deleting the same sequences in mice to see how those changes would affect embryonic development. Removing those key amino acid signatures significantly impaired embryonic development, caused deformities in organs—including the brain and the heart—and resulted in death in the mice.

"This very small deletion in the protein had a profound effect that mirrored what we had seen in vitro, which surprised us," Zaret said. "We originally thought it would be a broadly acting phenomenon that would be hard to pinpoint, but we nailed it down. To see this biochemistry approach, which others were skeptical of, so clearly illuminate a facet of developmental biology was a real thrill."

Zaret's lab continues to investigate FoxA and other pioneer factors to learn how they may open up the chromatin and interact with chromosomal proteins, similar to FoxA or perhaps in other ways. The current findings serve as a road map.

"Now that we have these results, we are emboldened to investigate diverse other proteins that behave this way," Zaret said. "We know that FoxA2 doesn't act alone in turning on the endoderm program to make organs, and we're currently working to better understand how the different factors play in role in that development."

More information: Makiko Iwafuchi et al. Gene network transitions in embryos depend upon interactions between a pioneer transcription factor and core histones, *Nature Genetics* (2020). DOI: 10.1038/s41588-020-0591-8

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