Researchers discover a new method to regulate cell plasticity

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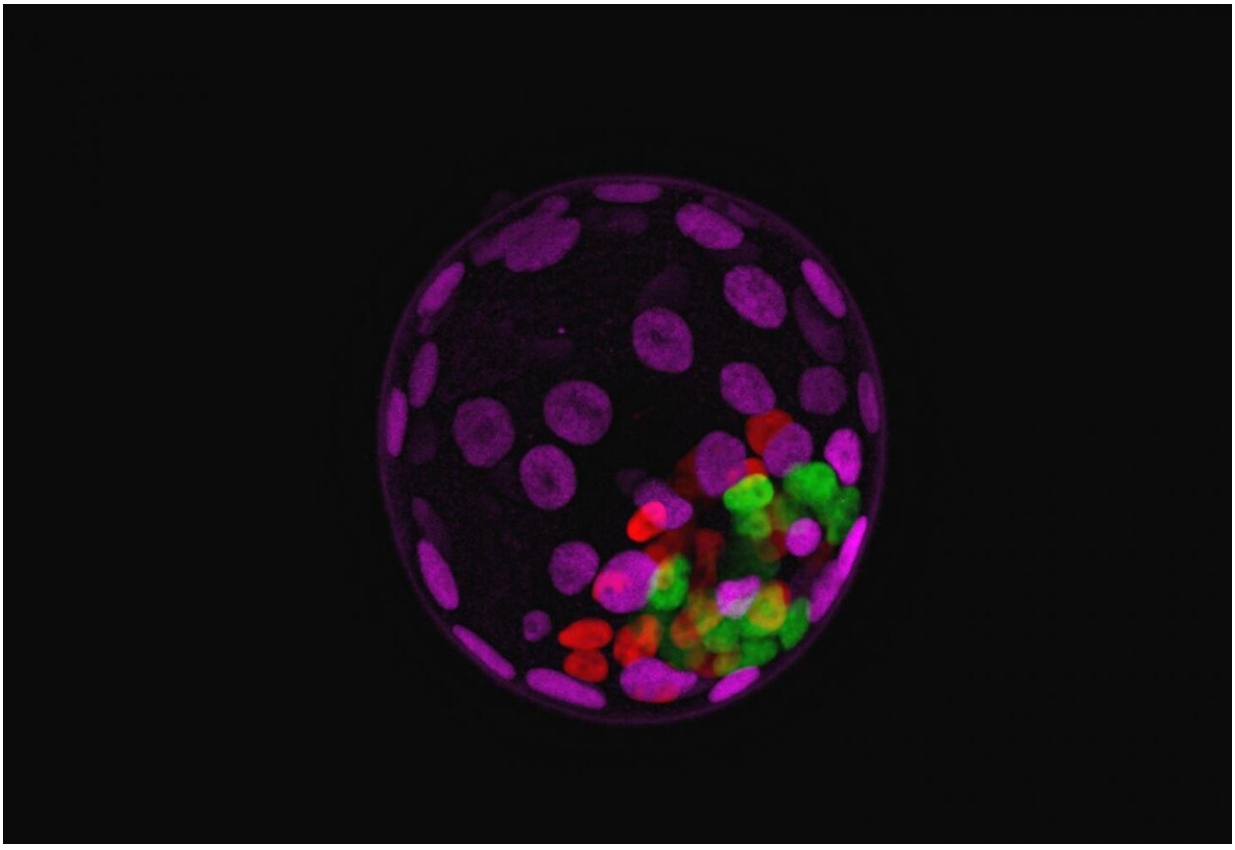

Lynch et al characterize a chemical approach to globally hyper-activate enhancers. This is achieved by inhibiting CDK8 kinase, a negative regulator of the Mediator complex. The reinforcement of enhancers and super-enhancers results in the stabilization of cell identity. This is applied here to stabilize intrinsically unstable human naïve pluripotent cells. This principle may be applicable to other unstable cell types. The picture shows a mouse blastocyst with its three cell types: trophoblasts (CDX2, purple), primitive endoderm cells (GATA6, red), and naïve pluripotent cells (NANOG, green). Credit: Cian J.

Cell plasticity is a property by which a cell can take on different and reversible identities. Cell plasticity is also essential for embryo development and for the correct function of the immune system. This property is also crucial in cancer as many cancer cells use it to gain resistance to chemotherapy and invade and colonize distant parts of the body.

Headed by the ICREA researcher Manuel Serrano, scientists at the Cellular Plasticity and Disease Laboratory at the Institute for Research in Biomedicine (IRB Barcelona) have discovered a way to regulate this plasticity by 'blocking' plastic cells in one of their possible states.

"The identity of each cell type is defined by a particular gene expression program. What makes plastic cells special is that, in addition to their identity genes, they can express at low levels genes belonging to other cell identities. This sort of "background noise" is what allows them to change identity at a given time, and what was once "background noise" becomes the dominant genetic program," explains Serrano.

Regulating gene expression to modulate plasticity

Until now, the methods used to block cell plasticity were based on inhibiting some of the external stimuli that cells receive. But these approaches are usually incompatible with cell multiplication and can end up damaging the cells themselves.

The new method developed by Serrano's lab, which is supported by "la Caixa" Foundation, focuses on the profound mechanism that regulates gene expression, it does not affect cell viability, and it is completely

reversible. The key to this new approach is the inhibition of the protein CDK8.

"We have observed that CDK8 inhibition strengthens the expression of genes that determine cell identity, and this occures at the expense of switching off the "background noise" of alternative identities. So the cells are fixed in a specific identity and they lose their plasticity," says Cian J Lynch, first author of the study and postdoctoral fellow in the same laboratory.

Important implications in biomedicine

Having the capacity to regulate cell plasticity can have many advantages in a biomedical research context as it allows researchers to study all the processes in which plasticity is a key element, such as cancer and embryo development. The present study has focused on embryonic stem cells. The great plasticity of this type of cells makes them highly attractive for cell therapy applications. However, this very same plasticity poses a real challenge when it comes to culturing these cells in the lab.

"Because of the intrinsic plasticity of embryonic stem cells, cultures produced in the lab are highly heterogeneous, and previous methods available to reduce plasticity were very harmful to the cells. This was a practical problem with no apparent solution," says Raquel Bernad, co-author of the study who has just completed her Ph.D. The researchers have demonstrated that it is possible to culture embryonic stem cells in the presence of a CDK8 inhibitor, thus making the culture less plastic, more homogeneous and without damaging the cells. Something that had not been achieved until now. Simply removing the CDK8 inhibitor restores plasticity to the cells.

Furthermore, scientists from other laboratories have observed that this

new method may have implications in autoimmune diseases in which the plasticity of T cells make them adopt an overly active state, leading to an exacerbated immune response.

With respect to implications for oncology, "Cell plasticity is known to be a key factor underlying resistance to chemotherapy. By blocking cell plasticity, we hope to improve reactions to chemotherapy by achieving more homogeneous and lasting responses," adds Serrano.

More information: Cian J. Lynch et al, Global hyperactivation of enhancers stabilizes human and mouse naive pluripotency through inhibition of CDK8/19 Mediator kinases, *Nature Cell Biology* (2020). DOI: 10.1038/s41556-020-0573-1 , www.nature.com/articles/s41556-020-0573-1

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