Pushing cells towards a higher pluripotency state

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Stem cells have the unique ability to become any type of cell in the body. Given this, the possibility that they can be cultured and engineered in the laboratory makes them an attractive option for regenerative medicine. However, some conditions that are commonly used for culturing human stem cells have the potential to introduce contaminants, thus rendering the cells unusable for clinical use. These conditions cannot be avoided, however, as they help maintain the pluripotency of the stem cells.

In a study published in *Scientific Reports*, a group from the RIKEN Center for Life Science Technologies in Japan has gained new insight into the role of CCL2, a chemokine known to be involved in the immune response, in the enhancement of stem cell pluripotency. In the study, the researchers replaced basic fibroblast growth factor (bFGF), a critical component of human stem cell culture, with CCL2 and studied its effect. The work showed that CCL2 used as a replacement for bFGF activated the JAK/STAT pathway, which is known to be involved in the immune response and maintenance of mouse pluripotent stem cells. In addition, the cells cultured with CCL2 demonstrated a higher tendency of colony attachment, high efficiency of cellular differentiation, and hints of X chromosome reactivation in female cells, all markers of pluripotency.

To understand the global effects of CCL2, the researchers compared the transcriptome of stem cells cultured with CCL2 and those with bFGF. They found that stem cells cultured with CCL2 had higher expression of genes related to the hypoxic response, such as HIF2A (EPAS1). The study opens up avenues for further exploring the relationship between

cellular stress, such as hypoxia, and the enhancement of pluripotency in cells. Yuki Hasegawa of CLST, who led the study, says, "Among the differentially expressed genes, we found out that the most significantly differentially expressed ones were those related to hypoxic responses, and hypoxia is known to be important in the progression of tumors and the maintenance of pluripotency. These results could potentially contribute to greater consistency of human induced pluripotent stem cells (iPSCs), which are important both for regenerative medicine and for research into diseases processes."

As a way to apply CCL2 towards the culturing of human iPSCs with more consistent quality, the researchers developed dishes coated with CCL2 and LIF protein beads. This allowed stem cells to be cultured in a feeder-free condition, preventing the risk that viruses or other contaminants could be transmitted to the stem cells. While the exact mechanisms of how CCL2 enhances pluripotency has yet to be elucidated, this work highlights the usefulness of CCL2 in stem cell culture.

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