PA-01

EZH2 Regulates Neuronal Differentiation of Mesenchymal Stem Cells through PIP5K1C-dependent Calcium Signaling

*Ruey-Hwang Chou[1,2], Ling-Tzu Chen[2], Woei-Cherng Shyu[4,5], Su-Ching Hsieh[1], Chen-Shiou Wu[6], Hong-Jie Zeng[3], Su-Peng Yeh[7], **Yung-Luen Yu**[1,2,3,6,*], and Mien-Chie Hung[1,3,8,*]*

Center for Molecular Medicine[1], China Medical Uni. Hospital, Taichung, Taiwan

Dept of Biotechnology[2], Asia Uni., Taichung, Taiwan

Graduate Institute of Cancer Biology[3], China Medical Uni., Taichung, Taiwan

Center for Neuropsychiatry[4], China Medical Uni. Hospital, Taichung , Taiwan

Graduate Institute of Immunology[5], China Medical Uni., Taichung, Taiwan

The Ph.D. Program for Cancer Biology and Drug Discovery[6], China Medical Uni., Taichung, Taiwan

Division of Hematology and Oncology[7], Dept. of Medicine,
China Medical Uni. Hospital, Taichung, Taiwan.

Dept. of Molecular and Cellular Oncology[8], The Uni. of Texas MD
Anderson Cancer Center, Houston, TX, U.S.A.

Background

Enhancer of zeste homolog 2 (EZH2) regulates stem cells renewal, maintenance, and differentiation into different cell lineages including neuron. Changes in intracellular Ca^{2+} concentration play a critical role in the differentiation of neurons. However, whether EZH2 modulates intracellular Ca^{2+} signaling in regulating neuronal differentiation from human mesenchymal stem cells (hMSCs) still remains unclear.

Methods and Results

When hMSCs were treated with a Ca^{2+} chelator or a PLC inhibitor to block IP_3-mediated Ca^{2+} signaling, neuronal differentiation was disrupted. EZH2 bound to the promoter region of PIP5K1C to suppress its transcription in proliferating hMSCs. Interestingly, knockdown of EZH2 enhanced the expression of PIP5K1C, which in turn increased the amount of $PI(4,5)P_2$, a precursor of IP_3, and resulted in increasing the intracellular Ca^{2+} level, suggesting that EZH2 negatively regulates intracellular Ca^{2+} through suppression of PIP5K1C. Knockdown of EZH2 also enhanced hMSCs differentiation into functional neuron both *in vitro* and *in vivo*. In contrast, knockdown of PIP5K1C significantly reduced $PI(4,5)P_2$ contents and intracellular Ca^{2+} release in EZH2-silenced cells and resulted in the disruption of neuronal differentiation from hMSCs.

Conclusions

Here, we provide the first evidence to demonstrate that after induction to neuronal differentiation, decreased EZH2 activates the expression of PIP5K1C to evoke intracellular Ca^{2+} signaling, which leads hMSCs to differentiate into functional neuron lineage. Activation of intracellular Ca^{2+} signaling by repressing or knocking down EZH2 might be a potential strategy to promote neuronal differentiation from hMSCs for application to neurological dysfunction diseases.