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Netrin-1 for Generation of iPS Cells

The 5th Key Reprogramming Factor

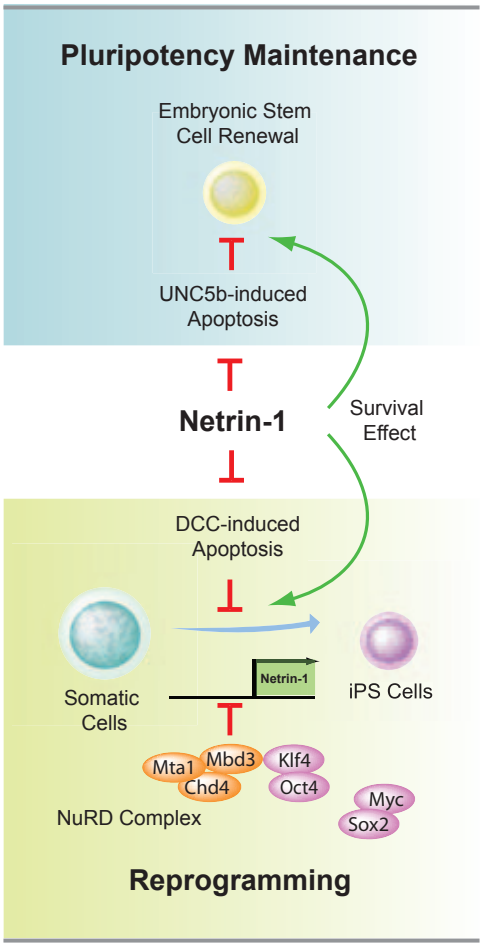

FIGURE: Netrin-1 in reprogramming and pluripotency maintenance.

The generation of induced pluripotent stem (iPS) cells from specialised cells holds great promise in regenerative medicine. iPS cells are derived by introducing a specific set of pluripotency-associated reprogramming factors into a given cell type. The original set of reprogramming factors include the four transcription factors Oct4, Sox2, Klf4 and c-Myc. However, cell reprogramming is not yet fully controlled and limited by constraints, such as programmed cell death, which restricts the number of cells produced.

Recently, Netrin-1 and its receptors DCC (Deleted in Colorectal Carcinoma) or UNC5b, described for their respective survival/death functions in normal and oncogenic contexts, has been identified in a search for soluble regulators/modulators of somatic cell reprogramming to pluripotency [1].

In various somatic cells, Netrin-1 is transcriptionally repressed by the classical reprogramming process. Decrease of Netrin-1 levels, mediated by Oct4/Klf4 through a Mbd3/Mta1/Chd4-containing NuRD complex, leads to apoptosis induction at the early stage of reprogramming and reduces iPS cell generation. This effect through the Netrin-1 receptor DCC can be corrected by external addition of recombinant Netrin-1 that constrains apoptosis and improves reprogramming efficiency. Netrin-1 also protected embryonic stem cells from apoptosis mediated by its receptor UNC5b. Thus treatment with recombinant Netrin-1 improved the generation of mouse and human iPS cells without impacting the genomic stability of the iPS cells or their ability to differentiate into other tissues.

Based on these findings, Netrin-1 seems to be the **5th Element of classical iPS cell factors.** Together with Netrin-1 the original factors Oct4, Sox2, Klf4 and c-Myc can produce 15 times more induced pluripotent stems cells (iPSCs) under specific culture conditions. This treatment did not affect the quality of cell reprogramming. Further research is ongoing for a better understanding of the mode of action of this protein in stem cell physiology to accelerate the development of clinically useful iPS cells.

LIT [1]: Netrin-1 regulates somatic cell reprogramming and pluripotency maintenance: D. Ozmadenci, et al.; Nat. Commun. **6,** ID7398 (2015)

AdipoGen® provides Stable & Active Netrin-1 Proteins,

described in D. Ozmadenci, et al. (2015) [Lit. 1]

Turn the Page

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*** LIT:** Netrin-1 regulates somatic cell reprogramming and pluripotency maintenance: D. Ozmadenci, et al.; Nat. Commun. **6,** ID7398 (2015)

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Maintains pluripotency of mouse and human embryonic stem cells.

REVIEW: Regulation of embryonic stem cell self-renewal and pluripotency by leukaemia inhibitory factor: H. Hirai, et al.; Biochem. J. **438,** 11 (2011)

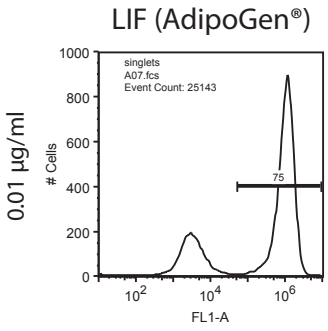

FIGURE: Human Leukemia Inhibitory Factor (LIF) (rec.) (AG-40B-0093) maintains pluripotency of mouse ES cells.

METHOD: Mouse ES oct4 GFP cells were cultured for 3 days in the presence of the indicated concentrations of LIF and followed by flow cytometry analysis of the GFP expression (indicating the expression of Oct4, thus of pluripotency).

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EUROPE/REST OF WORLD
Adipogen AG
TEL +41-61-926-60-40
FAX +41-61-926-60-49
info@adipogen.com

NORTH & SOUTH AMERICA
Adipogen Corp.
TEL +1-858-457-8383
FAX +1-858-457-8484
info-us@adipogen.com

For local distributors please visit our website.

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