

SUMMARY

[0009] In one aspect, the present disclosure refers to a method of reprogramming a differentiated cell into an undifferentiated cell state, comprising introducing an exosome from an undifferentiated cell into the differentiated cell; wherein the undifferentiated cell is an embryonic stem cell obtained from a cell line selected from the group consisting of H1, H7, H9, and HUES-7 cell lines, or an induced pluripotent stem cell IMR-90-iPSC; wherein the differentiated cell is human lung fibroblast IMR-90, or a differentiated cancer cell selected from the group consisting of MCF7, A431, and DLD-1; and wherein the step of introducing the exosome into the differentiated cell comprises (i) contacting the differentiated cell with the exosome from the undifferentiated cell in a first medium suitable for the uptake of the exosome by the differentiated cell, to thereby reprogram the differentiated cell into the undifferentiated cell state, and (ii) incubating the reprogrammed cell in a second medium, wherein the second medium is ESGRO-2i. While exosome is known to contain pluripotent transcription factors, it is not known if the concentration of such factors as well as presence of other factors within the exosome would lead to reprogramming, when fed to cells. As a matter of fact, in one example, exosome feeding performed by Zhou et al., 2017 (17) led to a decrease in the expression of pluripotent stem cell markers, decreased proliferation and tumorigenicity of the cancer cells, in contrast to the increased expression of pluripotent stem cell markers (Figures 14-15), increased proliferation or clonogenicity (Figure 13), increased tumorigenicity of the reprogrammed cancer cells (Figure 20 which shows a faster increase in tumor size from 4 weeks up to 8 weeks for exosome reprogrammed cells ($n = 4$) when compared to control cells ($n = 3$)) and drug resistance (Figures 16-17) described in the present disclosure. It was observed that MCF7 and A431 cells show a clear increase in expression of the cancer stem cell markers CD24+ and CD44+ when treated with exosomes.

[0010] In another example, there is provided an undifferentiated cell population obtained from the method as described herein.

[0011] In another example, there is provided a method of screening for a candidate agent suitable for cancer treatment, comprising contacting the undifferentiated cell population described herein with a candidate agent and determining the ability of the candidate agent to inhibit the growth of the undifferentiated cell population or kill the undifferentiated cell population. Advantageously, the reprogrammed cancer cells of the present disclosure may have acquired the stem cell-associated characteristic of drug resistance. For example, Figures 16-17 show that EX-iCSCs may be more resistant to sunitinib and doxorubicin compared to non-reprogrammed cells. The screening for a compound that selectively kills the EX-iCSCs could also lead to the identification of a compound that is more effective in killing the cancer stem cell/ tumor-initiating cancer cell population *in vivo*, leading to identification of a more effective cancer drug.

[0012] In another example, there is provided an undifferentiated cell population described herein for use in therapy.

Claims

1. A method of reprogramming a differentiated cell into an undifferentiated cell state, comprising introducing an exosome from an undifferentiated cell into the differentiated cell;
 wherein the undifferentiated cell is an embryonic stem cell obtained from a cell line selected from the group consisting of H1, H7, H9, and HUES-7 cell lines, or an induced pluripotent stem cell IMR-90-iPSC;
 wherein the differentiated cell is human lung fibroblast IMR-90, or a differentiated cancer cell selected from the group consisting of MCF7, A431, and DLD-1; and
 wherein the step of introducing the exosome into the differentiated cell comprises (i) contacting the differentiated cell with the exosome from the undifferentiated cell in a first medium suitable for the uptake of the exosome by the differentiated cell, to thereby reprogram the differentiated cell into the undifferentiated cell state, and (ii) incubating the reprogrammed cell in a second medium, wherein the second medium is ESGRO-2i.
2. The method of claim 1, wherein the exosome contains one or more pluripotent factors selected from a group consisting of NANOG, OCT3/4, SOX2, FGF2, NR5a2, SSEA-4, TR-1-60, TR-1-81, and combinations thereof.
3. The method of claim 1 or 2, wherein the exosome contains one or more miRNAs selected from the group consisting of Let7a, mir-125b, mir-145, mir-182, mir-302b, mir-302d, mir-367, and combinations thereof.
4. The method of any one of the preceding claims, wherein the undifferentiated cell state is a pluripotent cell state or a cancer stem cell-like cell state.
5. The method of claim 4, wherein the cell in a pluripotent cell state has one or more of the following characteristics:
 - (i) has a similar gene and surface marker expression profile as that of an embryonic stem cell and an induced pluripotent stem cell;
 - (ii) is pluripotent; and
 - (iii) is able to form three germ layer tissues.
6. The method of claim 4, wherein the cell in a cancer stem cell-like cell state has one or more of the following characteristics:
 - (i) has a similar gene and surface marker expression profile as a cancer stem cell; and
 - (ii) has similar drug resistance characteristics as a cancer stem cell.

7. The method of claim 1, wherein the first medium comprises Dulbecco's Modified Eagle Medium/Nutrient Mixture F-12 (DMEM/F12), Penicillin-Streptomycin (P/S) and 10% Fetal Bovine Serum (FBS).
8. The method of claim 1 or 7, wherein the contacting in the first medium is for at least 4 hours or more , at least 3 days or more, at least 10 days or more, or at least 14 days or more.
9. The method of claim 1, wherein the incubation in the second medium is 3 hours to 14 days.