conformational change can take place in the extra cellular domain, the intra cellular domain or both and results in a change in which proteins or molecules are able to bind to the receptor. This outside to inside signaling is a common mechanism that is used to signal cells to divide, initiate programmed cell death and many other processes.

[0010] One commonly used mechanism that regulates the activity of growth factor receptors is ligand-induced dimerization of the receptor's extra cellular domain which in turn brings the intracellular tails close together which makes a good docking site for modifying proteins such as kinases that initiate a signaling cascade that eventuates in a signal to the cell's nucleus that causes the cell to divide.

[0011] Ligand-induced dimerization of the extra cellular domain of growth factor receptors is often accomplished through the binding of ligand dimers; that is two ligands non-covalently bind to each other to form homo- or hetero-dimers which then bind to two receptors that are either the same (homo) or different (hetero).

[0012] An important example of ligand-induced receptor dimerization is NM23 dimers binding to and dimerizing the extra cellular domain of MUC1*, which is the truncated form of the MUC1 transmembrane protein that is tumor and stem cell specific. Whether or not the ligand is a monomer, dimer or a higher order multimer is a function of, among other things, its concentration. For many growth factor receptors, only the dimeric form of the ligand activates the growth factor receptor. Additionally, in primitivebiological systems, there are feedback loops wherein the higher order multimers turn off the function that is promoted by the dimer. For example, the CI protein of Phage lambda turns on transcription of one set of genes when it is bound to DNA as a tetramer but turns off transcription of those genes when, as a function of increased concentration, the CI protein becomes an octamer. Therefore, it would be advantageous to discover if such multimerization-regulated feedback loops that regulate function exist in higher order organisms, such as humans, and to develop methods to manipulate function based on the knowledge of the function of each multimer.

SUMMARY

[0012a] In one aspect, provided herein is an *in vitro* or *ex vivo* method: (a) for generating less mature cells from starting cells comprising inducing the starting cells to revert to a less mature state; or (b) for inhibiting differentiation of embryonic stem cells, induced pluripotent stem cells or progenitor cells; comprising increasing the amount of an NME family member whose multimerization state is the biologically active state and decreasing the amount of an

NME family member whose multimerization state is the biologically inactive state; wherein the NME family member's multimerization state in the biologically inactive state is a hexamer, and wherein the NME family member's multimerization state in the biologically active state is a dimer or a monomer that contains two units able to bind to the same target receptor; wherein the NME family member whose multimerization state is the biologically active state is NME7, NME6 or a mutant or variant of NME1 that favors dimerization or has two binding domains for its cognate ligand; and wherein the NME family member whose multimerization state is the biologically inactive state is NME1 or NME2, wherein the amount of: (i) the NME1 hexamer and/or NME2 hexamer is decreased by increasing the NME7 or NME6, wherein the NME7 or NME6 is increased by introducing a nucleic acid that causes it to be expressed; (ii)the NME1 hexamer and/or NME2 hexamer is decreased by introducing nucleic acids that down-regulate its expression, wherein the nucleic acid that down-regulates is an anti-sense DNA, an inhibitory RNA, siRNA or shRNA; or (iii) the NME7 or NME6 is increased by simultaneously introducing a first nucleic acid that down-regulates NME1 hexamer and/or NME2 hexamer and a second nucleic acid that up-regulates NME7 or NME6, wherein the nucleic acid that down regulates is an anti-sense DNA, an inhibitory RNA, siRNA or shRNA and the nucleic acid that up-regulates is an encoding DNA, RNA, mRNA or plasmid.

[0012b] In another aspect, provided herein is a method as described herein wherein the mutant or variant of NME1 that favors dimerization or has two binding domains for its cognate ligand is NME1 S120G or P96S, or NME6 S139G.

[0013] In one example, the present disclosure is directed to a method for generating less mature cells from starting cells comprising inducing the starting cells to revert to a less mature state comprising increasing the amount of an NME family member whose multimerization state is the biologically active state or decreasing the relative amount of an NME family member whose multimerization state is the biologically inactive state.

[0014] In another example, the disclosure is directed to a method of inhibiting differentiation of embryonic stem cell, induced pluripotent stem cell or progenitor cell comprising increasing the amount of an NME family member whose multimerization state is the biologically active state or decreasing the relative amount of an NME family member whose multimerization state is the biologically inactive state.

[0015] In another example, the disclosure is directed to a method of maintaining or inducing pluripotency in cells comprising decreasing the relative amount of an NME family member whose multimerization state is the biologically inactive state.

[0016] In yet another example, the disclosure is directed to a method of inhibiting differentiation in embryonic stem cell, induced pluripotent stem cell, or progenitor cell, comprising decreasing the relative amount of an NME family member whose multimerization state is the biologically inactive state.

[0017] In any of the methods described above, the NME family member's multimerization state in the biologically inactive state may be a hexamer or higher order multimer. In one example, such NME family member may be NME1 (NM23-H1) or NME2 (NM23-H2).

[0018] In any of the methods described above, the NME family member's multimerization state in the biologically active state may be a dimer or a monomer that contains two units able to bind to the same target receptor. In this regard, such NME family member may be a mutant or variant of NME1 that favors dimerization or has two binding domains for its cognate ligand, or NME6 or NME7.

[0019] In any of the methods described above, the relative amount of the NME family member whose multimerization state is the biologically inactive state may be decreased by adding an NME family member whose multimerization state is the biologically active state. The NME family member whose multimerization state is the biologically active state may be increased by introducing a nucleic acid or small molecule that causes it to be expressed.

[0020] And further, in any of the methods described above, the relative amount of the NME family member whose multimerization state is the biologically inactive state may be decreased by introducing nucleic acids or small molecules that down-regulate its expression.

[0021] In another example, in any of the methods described above, the NME family member whose multimerization state is the biologically inactive state may be decreased and the NME family member whose multimerization state is the biologically active state may be increased by simultaneously introducing a first nucleic acid that down-regulates a first NME

that forms the inactive state and a second nucleic acid that up-regulates the NME that forms the active state.

[0022] In any of the methods described above, the nucleic acid that down-regulates may be an anti-sense DNA, an inhibitory RNA, siRNA or shRNA and the nucleic acid that up-regulates is an encoding DNA, RNA, mRNA, or plasmid. Such nucleic acid may be modified to facilitate entry into the cell. In this regard, the NME family member that may be down regulated may include NME1, NME2 or NME1 and NME2. In this regard, the NME family member that may be up-regulated may be a mutant or variant of NME1, NME2 that prefers dimerization, NME6 or NME7.

[0023] In another example, the present disclosure is directed to a nucleic acid that causes expression of NME1 mutant or variant that prefers dimer formation or has two binding domains of the same ligand; and/or

[0024] a. NME7; and/or

[0025] b. a nucleic acid that causes expression of NME7; and/or

[0026] c. NME6; and/or

[0027] d. a nucleic acid that causes expression of NME6; and/or

[0028] e. a nucleic acid that down-regulates NME1 or NME1 and NME2.

[0029] In still another example, the disclosure is directed to a media for culturing stem or progenitor cells wherein the media contains:

[0030] a. NME1 mutant or variant that prefers dimer formation or has two binding domains of the same ligand; and/or

[0031] b. a nucleic acid that causes expression of NME1 mutant or variant that prefers dimer formation or has two binding domains of the same ligand; and/or

[0032] c. NME7; and/or

[0033] d. a nucleic acid that causes expression of NME7; and/or

[0034] e. NME6; and/or

[0035] f. a nucleic acid that causes expression of NME6; and/or

[0036] g. a nucleic acid that down-regulates NME1 or NME1 and NME2.

[0037] In yet another example, the disclosure is directed to a media for inducing pluripotency or for inducing cells to revert to a less mature state wherein the media contains:

[0038] a. NME1 mutant or variant that prefers dimer formation or has two binding domains of the same ligand; and/or

[0039] b. a nucleic acid that causes expression of NME1 mutant or variant that prefers dimer formation or has two binding domains of the same ligand; and/or

[0040] c. NME7; and/or

[0041] d. a nucleic acid that causes expression of NME7; and/or

[0042] e. NME6; and/or

[0043] f. a nucleic acid that causes expression of NME6; and/or

[0044] g. contains a nucleic acid that down-regulates NME1 or NME1 and NME2.

[0045] The media may also contain nucleic acids that encode some or all of the pluripotency-inducing genes or small molecules including OCT4, SOX2, NANOG, KLF4, and c-Myc.

[0046] In still another example, the disclosure is directed to a host cell that carries a synthetic nucleic acid that causes decreased expression of an NME family member whose multimerization state is the biologically inactive state. The NME family member may be NME1, NME2 or NME1 and NME2.

[0047] In yet another example, the disclosure is directed to a host cell that carries a synthetic nucleic acid that causes increased expression of an NME family member whose multimerization state is the biologically active state. In this regard, the NME family member may include an NME1 mutant or variant that prefers dimer formation or has two binding domains of the same ligand, NME6, or NME7.

[0048] In another example, the disclosure is directed to a host cell that carries a synthetic nucleic acid that causes decreased expression of an NME family member whose multimerization state is the biologically inactive state and a synthetic nucleic acid that causes increased expression of an NME family member whose multimerization state is the biologically active state. In this regard, the NME family member whose expression will be decreased may be NME1 or NME1 and NME2 and the NME family member whose expression will be increased may be an NME1 mutant or variant that prefers dimer formation or has two binding domains of the same ligand, and/or NME6, and/or NME7. The cell may also carry a nucleic acid that causes the expression of a gene that is either not expressed in the host cell or is mutated in the host cell. The host cell may also carry a nucleic acid to down-regulate an unwanted gene and up-regulates a desired or corrected gene. The host cell may be an embryonic stem cell, induced pluripotent stem cell, progenitor cell, or somatic cell.

[0049] In another example, the disclosure is directed to a method of treating a patient wherein the cells described above are administered to the patient. The cells may be

administered by bone marrow transplant, transplant into a specific site, transfusion, injection, or topical treatment. The treatment may be for any disease or condition that would be alleviated by treatment with stem cells, progenitors, or by correction of a genetic abnormality or defect. Or, the cells may be differentiated prior to administration to patient and wherein NME1, NME6 or NME7 are withdrawn during differentiation process.

[0050] In yet another example, the disclosure is directed to a method of treating cancer in a patient comprising administering an agent to the patient such that the agent increases the amount of an NME family member whose multimerization state is the biologically inactive state or decreases the relative amount of an NME family member whose multimerization state is the biologically active state. In this regard, the NME family member whose multimerization state is the biologically active state may be NME7, and the NME family member whose multimerization state is the biologically inactive state may be NME1, NME2 or NME8.

BRIEF DESCRIPTION OF THE DRAWINGS

[0051] The present invention will become more fully understood from the detailed description given herein below, and the accompanying drawings which are given by way of illustration only, and thus are not limitative of the present invention, and wherein;

[0052] Figures 1A-F show photographs of Western blots detecting the presence of NME1 (A,D), NME6 (B,E) or NME7 (C,F) in human stem cells cultured in NM23-S120G dimers, cultured in bFGF over MEFs or human breast cancer cells or the presence of the NME isoforms in a MUC1* pull-down assay.

[0053] Figure 2 is a photograph of a Western blot of human embryonic stem cell lysates probed with an antibody specific for NME7.

[0054] Figure 3 shows photographs of human BGO1v embryonic stem cells that remain pluripotent and undifferentiated after several days in culture in NME1-S120G dimers present at a range of concentrations.

[0055] Figure 4 shows photographs of human BGO1v embryonic stem cells that have differentiated and are no longer pluripotent after several days in culture in NME1-wild type hexamers present at a range of concentrations.

[0056] Figure 5 shows photographs of human BGO1v embryonic stem cells that have differentiated and are no longer pluripotent after several days in culture in a mixture of 20%

What is claimed is:

1. An *in vitro* or *ex vivo* method:

(a) for generating less mature cells from starting cells comprising inducing the starting cells to revert to a less mature state; or

(b) for inhibiting differentiation of embryonic stem cells, induced pluripotent stem cells or progenitor cells;

comprising increasing the amount of an NME family member whose multimerization state is the biologically active state and decreasing the amount of an NME family member whose multimerization state is the biologically inactive state; wherein the NME family member's multimerization state in the biologically inactive state is a hexamer, and wherein the NME family member's multimerization state in the biologically active state is a dimer or a monomer that contains two units able to bind to the same target receptor; wherein the NME family member whose multimerization state is the biologically active state is NME7, NME6 or a mutant or variant of NME1 that favors dimerization or has two binding domains for its cognate ligand; and wherein the NME family member whose multimerization state is the biologically inactive state is NME1 or NME2,

wherein the amount of:

(i) the NME1 hexamer and/or NME2 hexamer is decreased by increasing the NME7 or NME6, wherein the NME7 or NME6 is increased by introducing a nucleic acid that causes it to be expressed;

(ii) the NME1 hexamer and/or NME2 hexamer is decreased by introducing nucleic acids that down-regulate its expression, wherein the nucleic acid that down-regulates is an anti-sense DNA, an inhibitory RNA, siRNA or shRNA; or

(iii) the NME7 or NME6 is increased by simultaneously introducing a first nucleic acid that down-regulates NME1 hexamer and/or NME2 hexamer and a second nucleic acid that up-regulates NME7 or NME6, wherein the nucleic acid that down regulates is an anti-sense DNA, an inhibitory RNA, siRNA or shRNA and the nucleic acid that up-regulates is an encoding DNA, RNA, mRNA or plasmid.

2. The method according to claim 1 (i) or (ii) wherein the nucleic acid is modified to facilitate entry into the cell.

3. The method according to claim 1, wherein the cells are somatic cells, dermablasts, fibroblasts, stem cells, pluripotent stem cells, bone marrow cells, peripheral mobilized blood cells, hematopoietic stem cells or progenitor cells.

4. A method according to any one of claims 1-3 wherein the mutant or variant of NME1

that favors dimerization or has two binding domains for its cognate ligand is NME1 S120G or P96S, or NME6 S139G.