layer marker expression was analyzed by qPCR (n=4). (H,I) Human dermal fibroblasts were transduced with lentiviral vector expressing four factors (OSKM) together with dTomato (Day 0). Cells were transfected with POMP siRNA on day 6 post-transduction and were analyzed on days 12-14. Reprogrammed colonies were stained for AP activity and AP^+ colonies were counted. (J) A schematic diagram depicting interconnectivity between Nrf2, proteasome and stemness. Error bars represent standard deviation; *: $p<0.01$ (Student's *t*-test); Scale bar, 100μm; HDF, human dermal fibroblasts.

Supporting Information Fig. S1. Role of Nrf2 in hESCs and cellular reprogramming. (A) H1 and iPS-IMR90 cells were immunostained with anti-Nrf2 antibody. (B) Undifferentiated H9 cells were immunostained with anti-Nrf2 antibody. (C) The expression of Nrf2 target genes, *NQO-1* and *HO-1*, was analyzed in H1 and iPS-IMR90 cells by qPCR (n=3). (D) Nrf2 mRNA level was measured in undifferentiated or differentiated H9 cells by qPCR (n=4). (E,F) *KEAP1* protein (E) and mRNA (F) levels were analyzed in undifferentiated or differentiated H9 cells by immunoblotting and qPCR (n=3), respectively. (G-I) H9 cells were induced to differentiate into neurons by overexpressing NeuroD1. Nrf2 protein (H) and activity levels (I) were analyzed in H9 and H9-derived neurons. (J,K) H9 cells were transfected with Nrf2 siRNAs. Nrf2 protein (J) and mRNA (K) levels were measured by immunoblotting and qPCR (n=4), respectively. (L,M) KEAP1 protein (L) and Nrf2 target gene *NQO-1* mRNA (M) levels were analyzed in human dermal fibroblasts transduced with either control or KEAP1 over-expression lentiviral vector. (N) H9 cells were treated with *tert*-Butylhydroquinone (t-BHQ 20μM) or sulforaphane (SFN 3μM). After 24h, *NQO-1* expression was measured by qPCR (n=3). (O,P) H9 cells were induced to differentiate for 6 days, with or without Nrf2 activators (t-BHQ 20μM or SFN 3μM). The expression of *OCT4* (O) and *NANOG* (P) was analyzed by qPCR (n=4). (Q) Representative flow cytometry plots of Figure 1H. (R) Nrf2 mRNA level was analyzed in HDF and HDF-derived iPSC by qPCR (n=4) (S,T) Human dermal fibroblasts were transduced with lentiviral vector expressing OSKM (OCT4, SOX2, KLF4, c-

MYC) together with dTomato and maintained in a feeder-free system. After 12-14 days, embryonic stem cell-like colonies were immunostained with anti-OCT4 and anti-NANOG antibodies (S). Colonies were stained for alkaline phosphatase (AP) activity (T). (U,V) Control or Nrf2 siRNA was transfected into human dermal fibroblast 6 days post OSKM transduction. On day 12-14, embryonic stem cell-like colonies were immunostained with anti-OCT4 and anti-NANOG antibodies (U). Transduced cells were assessed for dTomato expression (V). (W) HDFs were transfected with Nrf2 siRNA #2 or POMP siRNA #2 6 days post OSKM transduction. AP^+ colonies were counted. Error bars represent standard deviation. *: $p<0.01$, #: $p<0.05$ (Student's *t*-test); Scale bar, 100 μm.

Supporting Information Fig. S2. Regulation of proteasome activity by Nrf2. (A) H9 cells were treated with sulforaphane (3 μM) and trypsin-like and PGPH-like proteasome activities were measured after 24h (n=3). (B) H1 and iPS-IMR90 cells were treated with t-BHQ (20 μM). Chymotrypsin-like proteasome activity was measured after 24h (n=3). (C) H9 cells were transduced with lentiviral vector expressing Nrf2 shRNA. The expression of Nrf2, *NQO-1* and *HO-1* was analyzed by qPCR (n=4). (D) H9 cells were treated with lactacystin for 12h. Nrf2 protein level in cell lysates was analyzed by immunoblotting. (E) *POMP* expression was measured in undifferentiated and differentiated day 8 H1 and iPS-IMR90 cells by qPCR (n=3). (F,G) H9 cells were directly differentiated into neurons by overexpressing NeuroD1. Chymotrypsin-like proteasome activity (F) and *POMP* mRNA(G) level were measured. (H,I) H9 cells were transfected with POMP siRNA. *POMP* protein (H) and mRNA (I) levels were analyzed by immunoblotting and qPCR (n=4), respectively. (J) Chymotrypsin-like proteasome activity was measured in H9 cells transfected with either control siRNA or POMP siRNA #2. Error bars represent standard deviation. *: $p<0.01$, #: $p<0.05$ (Student's *t*-test).

Supporting Information Fig. S3. Role of high proteasome activity in proliferation, differentiation and cellular reprogramming. (A,B) H9 (A) and 293T (B) cells were treated with epoxomicin or lactacystin. After 12h, chymotrypsin-like proteasome activity was measured (n=3). (C,D) H9 (C) or iPS-IMR90 (D) cells were treated with epoxomicin (C) or lactacystin (D), respectively. The RNA level of *OCT4*, *NANOG*, *SOX2* and *TERT* was measured by qPCR. (n=3). (E,F) IPS-IMR90 (E) or H9 (F) cells were treated with lactacystin (E) or epoxomicin (F) for 12h. Cell cycle pattern was measured using propidium iodide assay. (G,H) H9 cells were induced to differentiate by removal of FGF2 and transfected with control or POMP siRNA. After 6 days, cells were immunostained with anti-OCT4 (G) and anti-NANOG (H) antibodies. (I) IPS-IMR90 cells were induced to differentiate with or without lactacystin (0.5 μM). After 8 days, the expression of germ layer markers was analyzed by qPCR (n=3). (J) Differentiating H9 cells were transfected with control or POMP siRNAs. After 8 days, the RNA levels of germ layer markers were measured by qPCR. (n=4). (K,L) Human dermal fibroblasts were transduced with lentiviral vector expressing OSKM together with dTomato (Day 0). Transduced cells were then transfected with POMP siRNA on Day 6. Cells were analyzed on Day 12-14. Transduced cells were assessed for dTomato expression (K). Reprogrammed colonies were subject to alkaline phosphatase activity staining (L). Error bars represent standard deviation. *: $p<0.01$, #: $p<0.05$ (Student's *t*-test); Scale bar, 100μm.