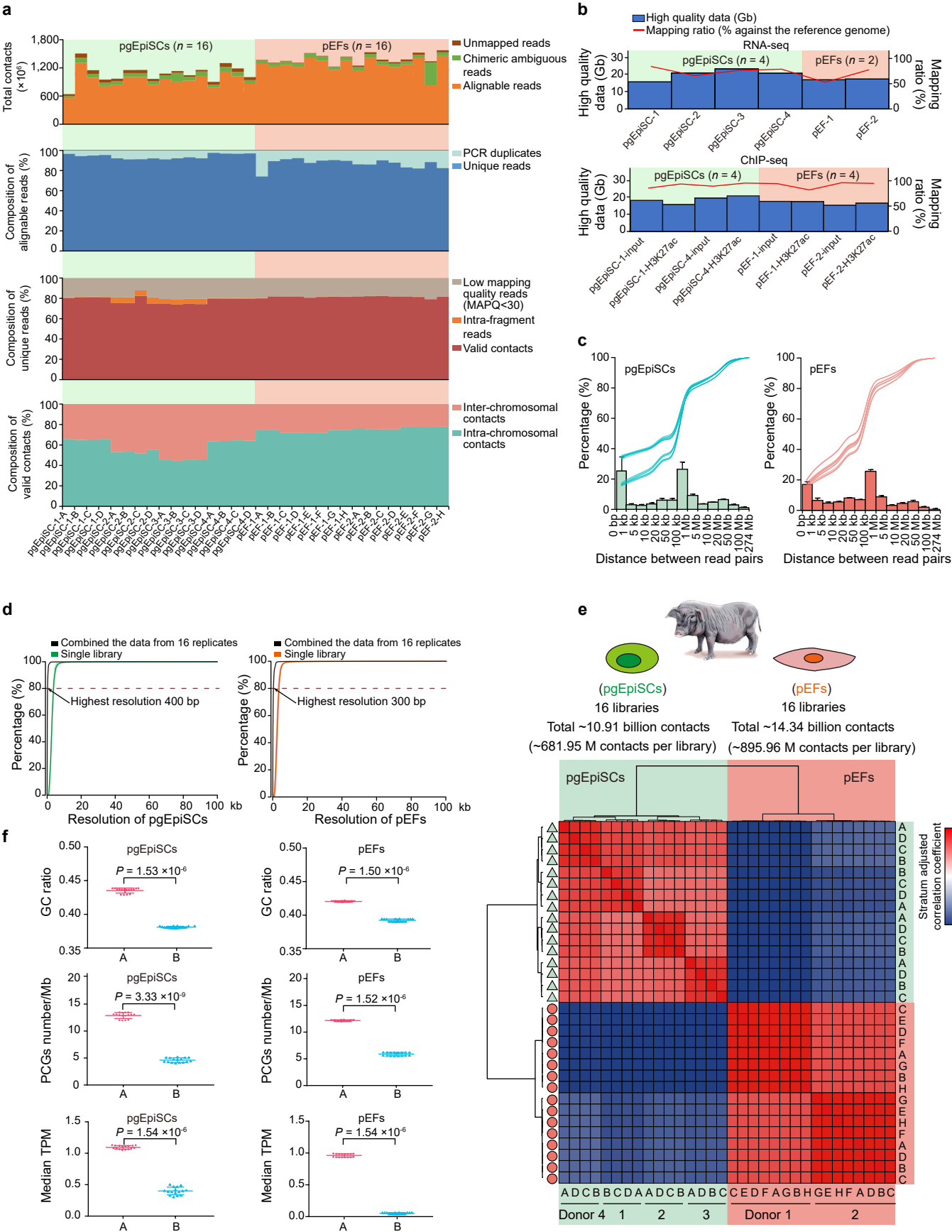


DATA S1-I



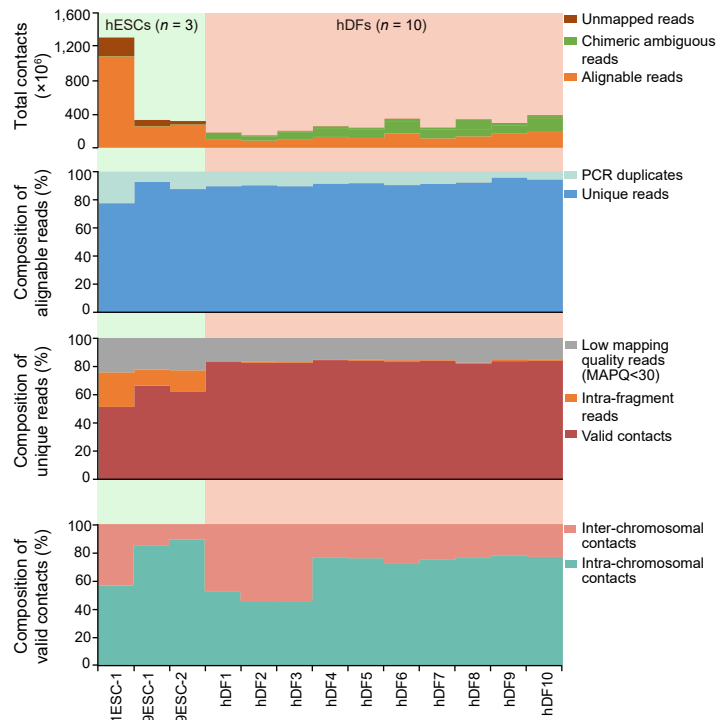
Data S1: Additional Hi-C Maps, rRNA-depleted RNA-seq and ChIP-seq (H3K27ac), Relevant to Main Findings, Related to [Fig. 5](#)

Data S1-I: Hi-C Maps, RNA-seq and ChIP-seq (H3K27ac) of pgEpiSCs and pEFs

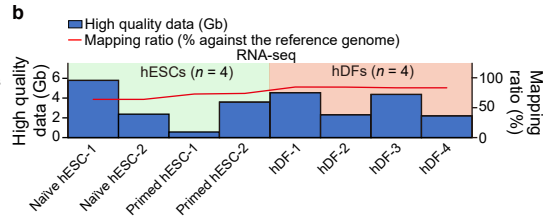
a Data summary of 32 Hi-C data. We separately constructed 16 Hi-C libraries for pgEpiSCs (a total of ~10.9-billion valid contacts with a depth of ~682 M contacts per library) and pEFs (a total of ~14.3-billion valid contacts with a depth of ~896 M contacts per library). The intra-chromosomal read pairs (~531.06 M contacts, or 66.01% of valid contacts per library) are the dominant interactions compared to inter-chromosomal read pairs. **b** Data summary of rRNA-depleted RNA-seq (top panel; ~126 M 150-bp paired-end high-quality reads were generated for each library) and ChIP-seq (H3K27ac) (bottom panel; ~115.78 M high-quality reads for each library). **c** Insert size distribution of intra-chromosomal contacts. The curves represent the cumulative percentages in each library. Note that ~86.00% of intra-chromosomal contacts mainly occurred within 10 Mb. **d** Evaluation of Hi-C resolution. The curve represents the percentage of bins with more than 1 000 intra-chromosomal contacts at different kb resolutions. According to a previously described criterion that the smallest bin size is where 80% of bins have at least 1 000 intra-chromosomal contacts ¹, our Hi-C data of pgEpiSCs and pEFs achieved resolution of at least 5-kb for a single library, and even achieved respective resolutions of 400 bp and 300 bp for pgEpiSCs and pEFs after combining the data from replicates. **e** Estimated interrelationships between 32 intra-chromosomal Hi-C maps at 100-kb resolution of pgEpiSCs (four libraries [A to D] for each of four donors; 16 green triangles) and pEFs (eight libraries [A to G] for each of two donors; 16 red circles) using the pairwise stratum adjusted correlation coefficient (SCC) as implemented in the R package HiCRep ². We generated the normalized intra-chromosomal contact maps at 100-kb resolution for each of 32 libraries (~52 884 contacts in each 100-kb bin), which are highly reproducible between maps derived from the same donor of pgEpiSCs (median SCC = 0.98) and pEFs (SCC = 0.99), followed by between four donors of pgEpiSCs (SCC = 0.95) and two donors of pEFs (SCC = 0.96), but are more dissimilar between pgEpiSCs and pEFs (SCC = 0.71). **f** Compared to the compartment B regions (48.11% of genome in pgEpiSCs and 52.50% of genome in pEFs), the compartment A regions (51.89% of genome in pgEpiSCs and 47.50% of genome in pEFs) are more GC-rich, gene-rich, and have higher transcriptional activities. Statistical significance was calculated by Wilcoxon rank-sum test.

DATA S1-II

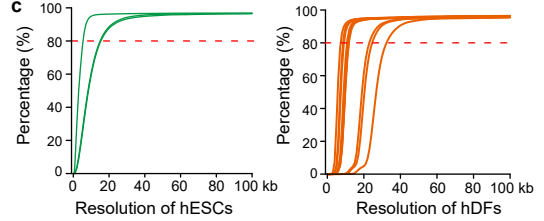
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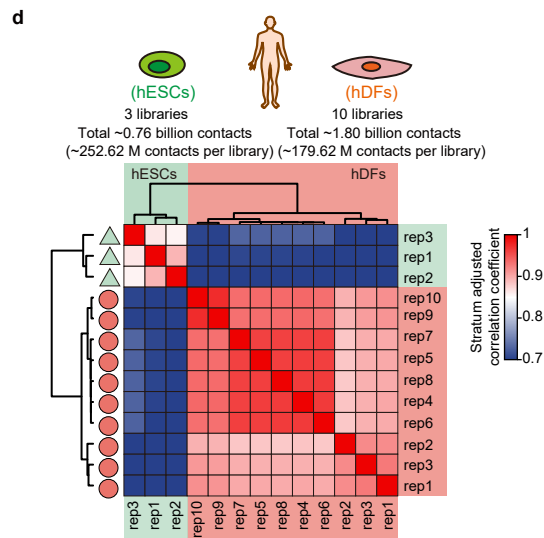
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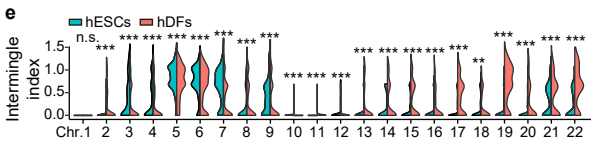
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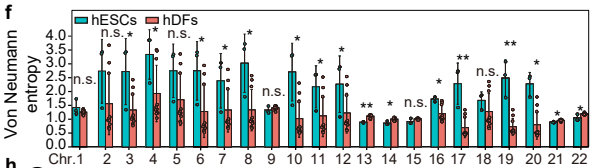
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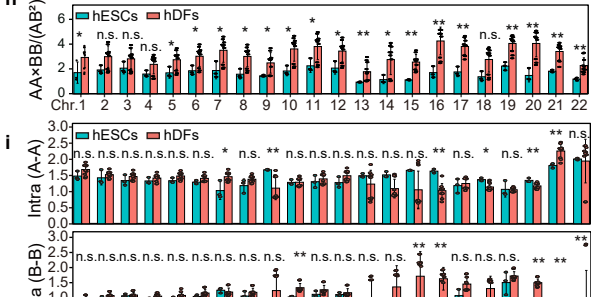
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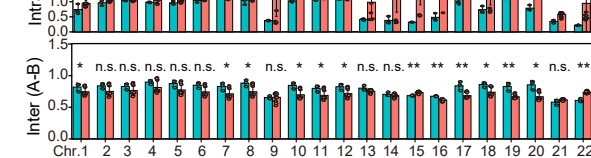
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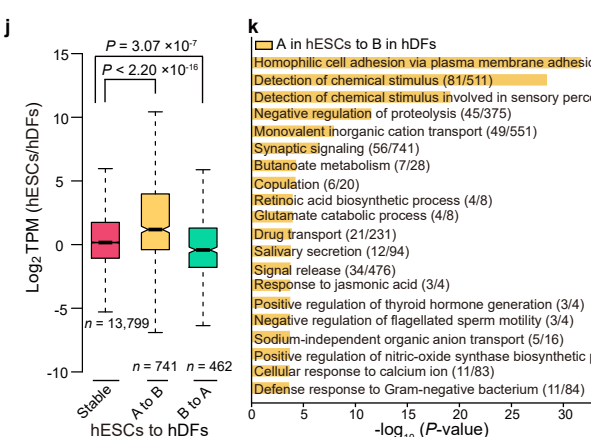
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h



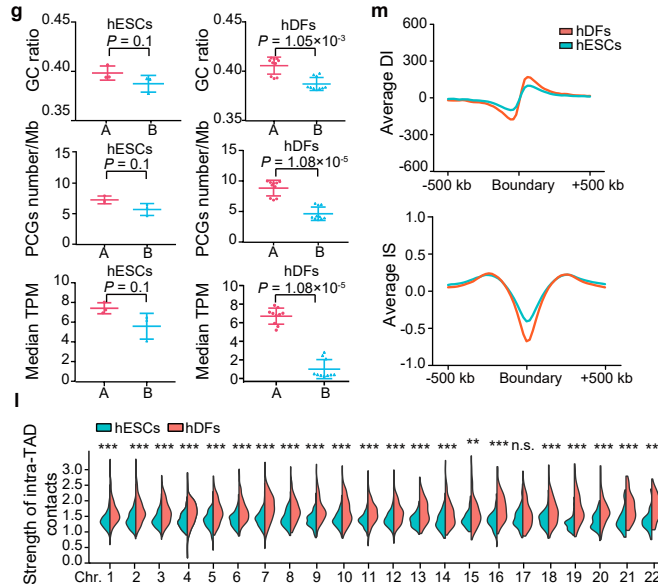
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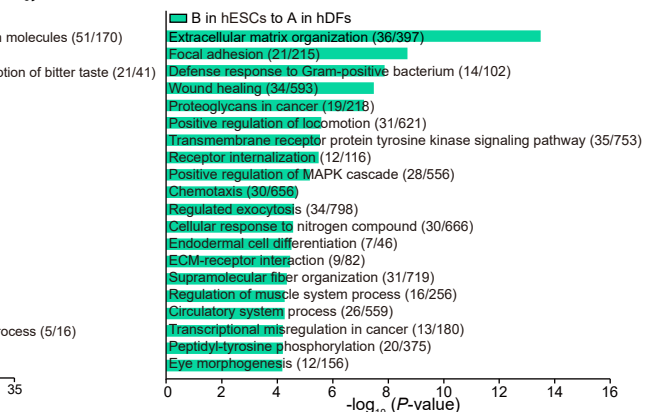
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k

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m



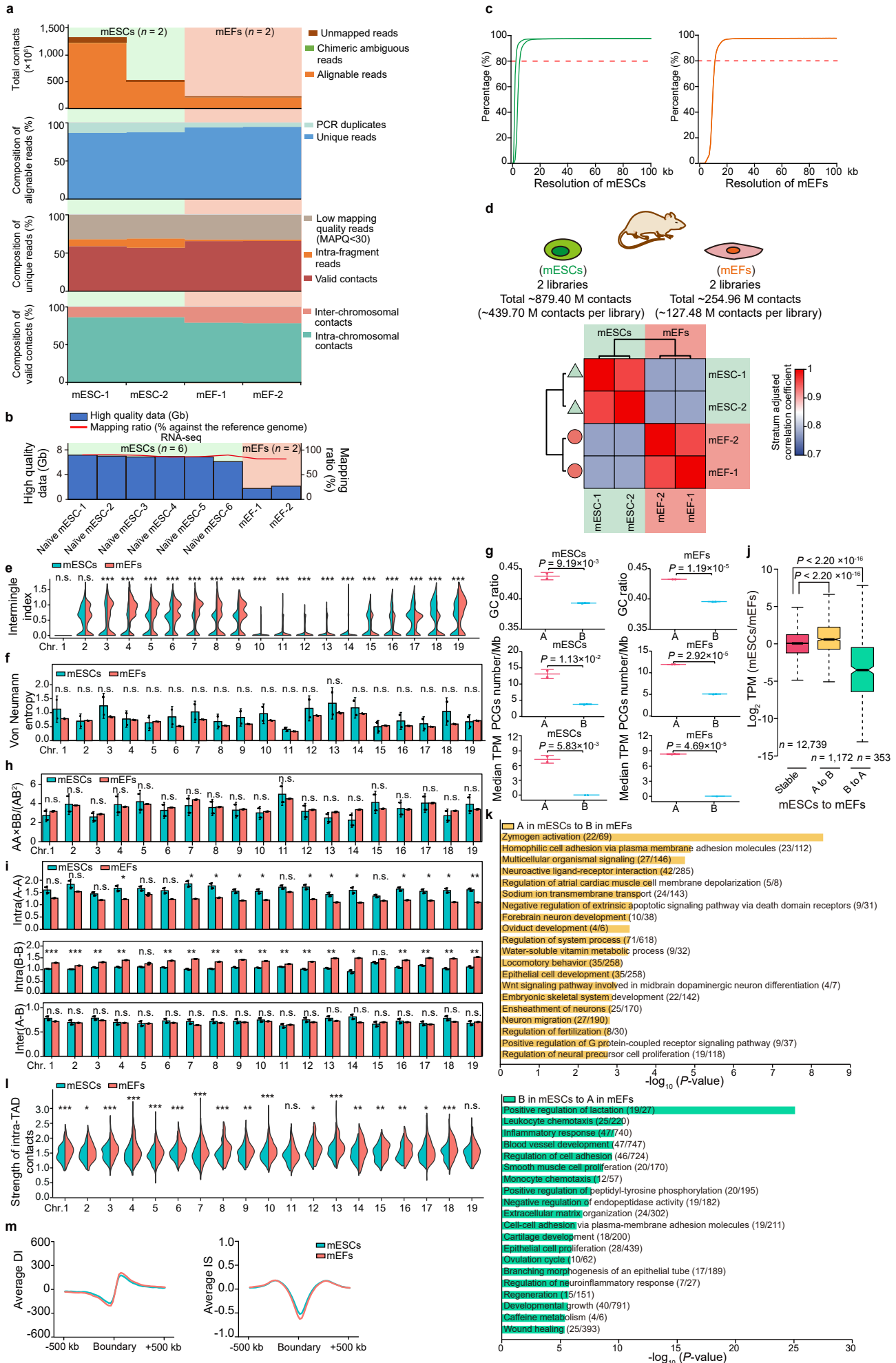
n

Data S1: Additional Hi-C Maps, rRNA-depleted RNA-seq and ChIP-seq (H3K27ac), Relevant to Main Findings, Related to Fig. 5

Data S1-II: Hi-C Maps and RNA-seq of hESCs and hDFs

a Data summary of publicly available Hi-C data for hESCs (three libraries; a total of ~757.87 M valid contacts with a depth of ~252.62 M contacts per library)^{3,4} and hDFs (ten libraries; a total of ~1.80-billion valid contacts with a depth of ~179.62 M contacts per library)⁵. The intra-chromosomal read pairs (~137.54 M contacts, or 69.68% of valid contacts per library) are the dominant interactions compared to inter-chromosomal read pairs. **b** Data summary of human RNA-seq data. **c** Evaluation of Hi-C resolution. Individual replicates achieved resolutions of 6 to 16 kb and 8 to 33 kb for hESCs and hDFs, respectively. **d** Estimated interrelationships between 13 normalized (as implemented in KR algorithm⁶ and quantile algorithm⁷) intra-chromosomal Hi-C maps at 100-kb resolution of hESCs (three green triangles) and hDFs (ten red circles) using the HiCRep tool². The Hi-C maps are highly reproducible between replicates of hESCs (median SCC = 0.87) and hDFs (SCC = 0.92), but are more dissimilar between hESCs and hDFs (SCC = 0.70). **e** Probability of extensive multi-chromosome intermingling (average of Hi-C maps for each cell type) across 22 autosomes based on intra- (at 100-kb resolution) and inter-chromosomal (at 1-Mb resolution) contact maps in hESCs (green) and hDFs (red). **f** The extent of disorder in chromatin structure (quantified by the VNE) at 100-kb resolution in each Hi-C map of hESCs (green) and hDFs (red). Compared to hDFs, the chromatin of hESCs was more permissive and disordered (reflected by the high-entropy statue in hESCs compared to hDFs: 2.03/1.20, $P = 7.35 \times 10^{-4}$, Wilcoxon rank-sum test). **g** Compared to compartment B regions (43.81% of genome in hESCs and 51.86% of genome in hDFs), the compartment A regions (56.19% of genome in hESCs and 48.14% of genome in hDFs) are more GC-rich, gene-rich, and had relatively higher transcriptional activities. **h** Compartmentalization strength ($AA \times BB/AB^2$) across 22 autosomes at 20-kb resolution in each Hi-C map of hESCs (green) and hDFs (red). Note that strength was substantially lost in hESCs compared to hDFs (1.70/3.17, $P = 9.22 \times 10^{-11}$, Wilcoxon rank-sum test). **i** Comparison of compartment contacts across 22 autosomes at 20-kb resolution in each Hi-C map. The dramatic decrease of compartmentalization strength ($AA \times BB/AB^2$) in hESCs compared to hDFs (Supplementary information, Data S1, IIh) is not only attributed to the increased inter-compartment contacts in hESCs (hESCs compared to hDFs: 0.79/0.71, $P = 1.84 \times 10^{-3}$, Wilcoxon rank-sum test), but also resulted in more reduced contacts within the B compartment (hESCs compared to hDFs: 0.82/1.22, $P = 9.94 \times 10^{-5}$, Wilcoxon rank-sum test) and slightly increased contacts within the A compartment (hESCs compared to hDFs: 1.41/1.37, $P = 0.52$, Wilcoxon rank-sum test) in hESCs. **j** Expression changes of genes located in regions exhibiting compartments A/B switching between hESCs and hDFs. Genes detected in at least one cell type are shown. **k** Functional enrichment for 1 072 genes from A status in hESCs to B status in hDFs (yellow bars), and 559 genes from B status in hESCs to A status in hDFs (green bars). The top functional terms of Metascape (<https://metascape.org>)⁸ summary gene set in each enriched cluster are shown, with the constraint of showing no more than 20 terms. The number after each term represents the hit genes out of total genes in this term. **l** The extent of the strength of intra-TAD contacts in hESCs and hDFs. Data represented as violin plots based on the strength of intra-TAD contacts for each TAD. **m** Average directionality index (DI) (left)⁹ and insulation score (IS) (right)¹⁰ in a 1 Mb region centered on shared TAD boundaries between hESCs and hDFs. For (E), (F), (G), (H), (I), (J), and (L), statistical significance was calculated by Wilcoxon rank-sum test (n.s., $P \geq 0.05$; *, $P < 0.05$; **, $P < 0.01$, ***, $P < 0.001$).

DATA S1-III



Data S1: Additional Hi-C Maps, rRNA-depleted RNA-seq and ChIP-seq (H3K27ac), Relevant to Main Findings, Related to Fig. 5

Data S1-III: Hi-C Maps and RNA-seq of mESCs and mEFs

a Data summary of publicly available Hi-C data for mESCs (two libraries; a total of ~ 879.40 M valid contacts with a depth of ~ 439.70 M contacts per library) ¹¹ and mEFs (two libraries; a total of ~254.96 M valid contacts with a depth of ~127.48 M contacts per library) ¹². The intra-chromosomal read pairs (~240.06 M contacts, or 82.59% of valid contacts per library) are the dominant interactions compared to inter-chromosomal read pairs. **b** Data summary of mouse RNA-seq data. **c** Evaluation of Hi-C resolution. Individual replicates achieved resolutions of 3 to 6 kb and 12 kb for mESCs and mEFs, respectively. **d** Estimated interrelationships between four normalized (as implemented in KR algorithm ⁶ and quantile algorithm ⁷) intra-chromosomal Hi-C maps at 100-kb resolution of mESCs (two green triangles) and mEFs (two red circles) using the HiCRep tool ². The Hi-C maps are highly reproducible between replicates of mESCs (SCC = 0.96) and mEFs (SCC = 0.96), but are more dissimilar between mESCs and mEFs (median SCC = 0.78). **e** Probability of extensive multi-chromosome intermingling (average of Hi-C maps for each cell type) across 19 autosomes based on intra- (at 100-kb resolution) and inter-chromosomal (at 1-Mb resolution) contact maps in mESCs (green) and mEFs (red). Note the overall extent of chromosome intermingling is less in the mESCs than in mEFs (0.32/0.40, $P < 2.2 \times 10^{-16}$, Wilcoxon rank sum test). Statistical significance was calculated by Wilcoxon rank-sum test (n.s., $P \geq 0.05$; *, $P < 0.05$; **, $P < 0.01$, ***, $P < 0.001$). **f** The extent of disorder in chromatin structure (quantified by the VNE) at 100-Kb resolution in each Hi-C map of mESCs (green) and mEFs (red), respectively. Compared to mEFs, the chromatin of mESCs was more permissive and disordered (reflected by the high-entropy status in mESCs compared to mEFs: 0.86/0.68, $P = 4.30 \times 10^{-2}$, Wilcoxon rank-sum test). **g** Compared to compartment B regions (49.26% of genome in mESCs and 50.74% of genome in mEFs), the compartment A regions (50.74% of genome in mESCs and 49.26% of genome in mEFs) are more GC-rich, gene-rich and have relatively higher transcriptional activities. **h** Compartmentalization strength [$AA \times BB/AB^2$] across 19 autosomes at 20-kb resolution in each Hi-C map of mESCs (green) and mEFs (red). The compartmentalization was subtly decreased in mESCs compared to mEFs (3.46/3.55, $P = 0.75$, Wilcoxon rank-sum test). **i** Comparison of compartment contacts across 19 autosomes at 20-kb resolution in each Hi-C map. **j** Expression changes of genes located in regions exhibiting compartment switching between mESCs and mEFs. Genes detected in at least one cell type are shown. **k** Functional enrichment for 1 901 genes from A status in mESCs to B status in mEFs (yellow bars), and 572 genes from B status in mESCs to A status in mEFs (green bars). The top functional terms of Metascape (<https://metascape.org>) ⁸ summary gene set in each enriched cluster are shown, with the constraint that no more than 20 terms are portrayed. The number after each term represents the hit genes out of total genes in this term. **l** The extent of TAD intactness in mESCs and mEFs. Data represented as violin plots based on the TAD intactness per TAD. Note the TAD intactness of mESCs was weaker than that in mEFs. **m** Average directionality index (DI) (left) ⁹ and insulation score (IS) ¹⁰ (right) in a 1 Mb region centered on shared TAD boundaries between mESCs and mEFs.

For (e), (g), (j), and (l), statistical significance was calculated by Wilcoxon rank-sum test, (f), (h), and (i) was calculated by Student's *t*-test (n.s., $P \geq 0.05$; *, $P < 0.05$; **, $P < 0.01$, ***, $P < 0.001$).

Reference:

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