Functional description of the genes higher expressed in ES and iPS cells compared to fibroblasts in mouse

The prevention of differentiation and the promotion of proliferation are necessary to maintain the pluripotency of ES cells during their self-renewal [1]. Genes associated with the specific features of ES cells, included or not in our network of upregulated genes in ES and iPS cells (Figure 3 in the main text, Figures S3 and S4) are described below.

Transcription factors involved in the regulation of pluripotency

Transcription factors associated with the regulation of pluripotency of ES cells by either the suppression of differentiation paths or the promotion of pluripotency are components of our network.

Oct4, Sox2, and Nanog are three major hubs of our network and key regulators of the transcriptional network that controls self-renewal and pluripotency of ES cells [1]. Oct4 and Sox2 are present in most reprogramming cocktails to reprogram the somatic cells into iPS cells. Nanog encodes a homeodomain-containing transcription factor (TF). The deletion of Nanog induces differentiation of ES cells into primitive endoderm, while its overexpression can maintain mouse ES cells in a pluripotent state in the absence of leukemia inhibitory factor (LIF) [2]. Oct4 is a POU-domain TF. The knockdown of Oct4 promotes the expression of endodermal and trophoblast differentiation markers [3] whereas Oct4 overexpression results in a mixed population of differentiated cells expressing markers of endoderm and mesoderm [4]. A tight regulation of the level of Oct4 expression is hence very important for the maintenance of pluripotency. Sox2 is a member of HMG-domain family of transcription factors. Sox2 knockdown in mouse ES cells induces differentiation into multiple lineages, including trophectoderm [1]. Sox2 cooperates with Oct4 to activate Oct4 target genes [1], and it also has been shown to regulate Oct4 expression to maintain its optimal levels required for the pluripotency of ES cells [5]. Oct4, Sox2 and Nanog regulate each other, many other genes in a cooperative fashion and also themselves [1].

Zic3, a member of the Gli family of zinc finger transcription factors, is a downstream target of Oct4, Nanog and Sox2. It has been suggested that Zic3 supports pluripotency by preventing endodermal lineage differentiation, possibly through Nanog-regulated pathways [6].

Nr0b1 and Nr5a2 are orphan nuclear receptors working to maintain the pluripotency of ES cells. Nr5a2 (Lrh1) activates Oct4 expression by binding to the SF-1 response elements in the proximal promoter and proximal enhancer of Oct4. Knockout of Lrh1 results in loss of Oct4 expression at the epiblast stage and early embryonic death [7]. The expression of Nr0b1 (Dax1) is regulated by Oct4 and Stat3 [8]. It has been shown that the knockdown of Dax1 by RNA interference induced differentiation of ES cells towards endoderm [9].

By contrast, Nr6a1 (Gcnf) is a nuclear receptor that represses ES cells phenotype during differentiation [10]. Nr6a1 controls pluripotency by directly repressing the expression of Oct4 and Nanog. In addition Sox2 and Fgf4 are indirectly regulated through Oct4. Although this might appear contradictory, the balance between positive and negative regulators of Oct4 expression is necessary since its level has to be tightly regulated to maintain pluripotency [4].

Sall4, a zinc-finger TF, activates expression of Oct4 [11], and its knockdown influences the expression levels of most commonly used reprogramming genes (Oct4, Sox2, c-Myc and Klf-4) [12]. In addition, Sall4 was reported to bind many genes that are partly regulated by chromatin-based epigenetic events and therefore has been suggested to regulate pluripotency through integration of transcriptional and epigenetic controls [12].
Esrrb belongs to the family of orphan nuclear receptors. Esrrb is known to positively regulate Oct4 and Nanog expression, and its overexpression alone is able to maintain self-renewal and pluripotency of mouse ES cells [13]. Esrrb knockout embryos die around E10.5 due to the impaired placental formation and abnormal chorion development [14].
Zscan10 (Zfp206) – Zinc finger and SCAN domain containing gene – has been reported as a pluripotency-related TF [15], [16]. Zscan10 is directly regulated by Oct4 and Sox2 [15], and the knockdown of this gene increases the proportion of differentiated cells in vitro [16].
Zfp42 encodes a C2H2 zinc-finger protein and is highly expressed in undifferentiated mouse and human ES cells. It has been reported that a RNAi knockdown of Zfp42 in mouse ES cells induced ES cells differentiation to endoderm and mesoderm lineages [17]. However, recent results show that in the absence of Zfp42 mouse ES cells remain pluripotent and contribute whole embryos after blastocyst injection [18].

Genes involved in cell cycle and proliferation

ES cells have an unusual cell cycle structure, characterized by a high proportion of cells in S-phase and a short G1 phase, which can explain the rapid cell division of ES cells comparing to differentiated cells that spend most of their time in G1 [19]. In mouse ES cells the G1 phase control pathways are reduced or absent, a specificity which is also associated with the deregulated proliferation of tumor cells [20].
Mybl2 is a TF involved in the control of cell cycle progression and is essential to all proliferating cells. In the absence of this gene, embryos die just after the implantation due to the inner cell mass defect, generally attributed to a proliferation defect in the cell cycle phase of G1. Mybl2 has been also shown to directly regulate Oct4 expression in mouse ES cells [21].
Lin28a is a cytoplasmic protein with a unique pairing of RNA-binding motifs. Its specific downregulation results in decreased cell proliferation. It has been suggested that Lin28a might regulate transcription of genes important for cell growth (Cdk4, cyclins A and B), whose expression was also reduced upon downregulation of Lin28a [22].
Utf1 is a TF activated by Oct4 and has been shown to contribute to the proliferation of ES cells, possibly by promoting cell cycle progression. Downregulation of Utf1 results in decreased proliferation of ES cells, as well as decreased teratoma formation in vivo [23].

Genes involved in signaling pathways

Nodal, Lefty1 and Lefty2 are members of the TGF-β superfamily, and function to maintain TGF-β/activin/Nodal signaling. Acvr2b encodes a receptor that modulates signals for ligands belonging to TGF-β superfamily. This pathway has been shown to be important for the proliferative capacity of ES cells as the inhibition of TGF-β/activin/Nodal signaling by Smad7 or the specific inhibitor SB-431542 resulted in decreased proliferation of mouse ES cells without decreasing their pluripotency [24].
Gdf3 is also a member of the TGF-β superfamily (as Lefty1, Lefty2 and Nodal) and acts as a BMP signaling inhibitor. It has been reported to have a supportive role in

maintaining pluripotency in mouse ES cells and their ability to differentiate into different cell types. Interestingly, in human ES cells, higher levels of Gdf3 comparing to mouse ES cells are needed to maintain the expression of pluripotency markers. It has been claimed that this is due to the difference of BMP signaling between mouse and human [25].
As reviewed in [1], Eras and Tcl1 are two modulators of phosphoinositol-3-kinase (PIP3K)/Akt signaling pathway that plays an important role in proliferation and maintenance of pluripotency in ES cells. Tcl1 increases the Akt activation by forming a heterodimeric complex with Akt, while Eras activates PIP3K. Eras is not a part of the network but it is included in the list of 346 genes upregulated in ES and iPS cells.
The signaling by the cytokine tyrosine kinase receptor Kit and its ligand – stem cell factor –regulates hematopoietic stem cell (HSC) self-renewal, proliferation and differentiation in mouse and in human [26],[27]. It has been shown that Kit null mouse ES cells are able to self-renew, although Kit signaling is essential for their survival during differentiation upon LIF withdrawal, in contrast to normal differentiation of Kit null inner cell mass or epiblast cells in vivo [28].
Fibroblast growth factor Fgf4 is a major activator of Erk1/2 signaling cascade in mouse ES cells. It has been shown that differentiation of ES cells to neural or mesodermal lineages is arrested in the absence of Fgf-Erk, while the expression of pluripotency markers Oct4, Nanog and Rex1 is not alternated [29].

Self-renewal and pluripotency are very peculiar features of ES cells, but are not enough to define the biology of those cells, and other biological functions are found to be consistently upregulated in ES and iPS cells compared to fibroblasts. Those are described below.

Genes involved in DNA metabolism

The establishment of specific DNA methylation patterns is essential for the development of the early embryo. The importance of DNA methylatransferases Dnmt3a and Dnmt3b for *de novo* methylation and for mouse development has been described [30]. Both Dnmt3a and Dnmt3b are involved in CpG dinucleotide methylation, whereas their function is non-overlapping. Dnmt3b is required for methylation of centromeric minor satellite repeats. Inactivation of both genes blocks *de novo* methylation in mouse ES cells and results in early embryonic lethality. Another DNA methyltransferase, Dnmt3l has been shown to stimulate the activity of Dnmt3a and Dnmt3b [31]. Hells (Lsh), a member of the SNF2 chromatin remodeling family, has been suggested to be involved in the process of gene silencing during embryogenesis mediated by Polycomb repressive complex (PRC) [32]. The authors proposed that Lsh might perform a scaffolding-like function to promote interaction between Dnmt3 and PRC.

Rcor2 (coREST) is a chromatin regulatory protein involved in a transcriptional repression by Gfi proteins [33]. Inhibition of Rcor2, along with the histone demethylase LSD1, perturbs differentiation to hematopoietic lineage. In addition, Rcor2 is a part of the REST repression complex, which mediates suppression of neuronal genes expression [34].

Since mutation in ES cells can potentially affect multiple cell lineages, ES cells have to develop a sensitive mechanism to maintain DNA integrity. This is done either by DNA damage repair, or increased cell cycle regulation (described earlier) and removal of

damaged cells by apoptosis [35]. Although the majority of these genes have not been studied in ES cells, their function in somatic cells has been described. Brca1 belongs to the tumor suppressor gene family and is involved in DNA repair by homologous recombination. Brca1 deficiency in mouse ES cells has been shown to result in decreased homologous recombination frequencies [36]. In addition, as reviewed in [37], Brca1 is involved in a maintenance of genome integrity by regulation of centrosome duplication and G2-M checkpoint control. Homozygous Brca1 mutant embryos die, showing severe abnormalities including growth retardation, mesoderm and neural tube defects [37]. Msh2 and Msh6 are involved in the DNA mismatch repair that is essential for the stability of genome. Mice lacking either of these genes in combination with Msh3 gene had shown an increase in the mutation frequencies compared to the wild-type mice [38]. Ung functions as a major uracil glycosylase during base excision repair to eliminate uracil that was created during somatic hypermutation (SHM) or class switch recombination (CSR). Inactivation of Ung in mice results in defective CSR and in almost complete elimination of transversion mutations from C and G [39]. Cdt1 belongs to a family of replication proteins. It has been claimed to be essential for the efficient loading of minichromosome maintenance (MCM) protein complex onto template DNA [40]. The MCM complex is a DNA replication licensing system that is suggested to act as a replicative helicase in eukaryotes [41]. Mcm5 and Mcm10 are components of this complex. Orc1l is a component of the Origin recognition complex (ORC) that is involved in the initiation of DNA replication in eukaryotes along with MCM complex. Multiple interactions among ORC subunits and MCM proteins have been revealed [42].

Meiosis and germ line development-related genes in the network

Syce1 is a member of the synaptonemal complex, essential for normal progression of meiotic recombination and formation of crossover [43]. Syce1 deficient mice lack mature gametes and therefore are infertile. Syce2, another member of the synaptonemal complex, has been shown to be essential for the complex assembly [44].

Dazl encodes a RNA-binding protein and is expressed in all stages of mouse preimplantation embryo [45]. The functional role of Dazl has been evaluated in light of its contribution to spermatogenesis. In mouse testis Dazl was shown to specifically bind a subset of mRNAs necessary for germ cell development and cell cycle progression, including proteins involved in translation activation and transcription regulation [46]. In human, the presence of Dazl has been detected not only in the stem cells but also in the trophectoderm that cannot give rise to the germ cells, therefore it has been suggested that Dazl might have some role beyond the germ cells development [47]. Authors have proposed that Dazl might be a positive marker for the quality of blastocysts and might even have an influence on the implantation and survival chances of the embryo.

Ddx4 (Vasa) is specifically expressed in germ cell lineage and has a function in germ cell development. It has been found that pre-meiotic translation of Vasa is mediated by Dazl [48].

It is not clear why these meiosis-specific genes are upregulated in ES cells. A possibility is that they have another less well described function relevant to the physiology of pluripotent and self-renewing cells.

Genes involved in other metabolisms

As mentioned earlier, ES cells have a specific cell cycle that allows them to proliferate quickly. Cell cycle is a process that requires high energy associated with high metabolic activity, as metabolic perturbations delay cell cycle entry [49]. Genes that are associated with metabolism in our network are described below. We have noticed that promoters of many of these genes are bound by c-Myc, a TF that, in combination with other TFs, has been widely used to reprogram somatic cells into iPS cells. It has been shown that c-Myc regulates genes involved in metabolism and cell cycle progression, in particular, genes that function in glycolysis, oxidative phosphorylation, and mitochondrial biogenesis [49].

Promoters of the following genes are bound by c-Myc: Gldc, Shmt1, Gsta4, Apoc1, and Gls2.

Gldc (glycine decarboxylase) is a component of a glycine cleavage system (GCS) - a mitochondrial enzyme complex that degrades glycine. An inherited deficiency of Gldc causes an inborn error of metabolism, glycine encephalopathy (GE), characterized by neonatal coma and convulsions. It has been shown that Gldc deficiency leads to reduced levels of GCS, which correlates with increased ischemic injury in mice [50]. Shmt1 encodes cytoplasmic form of serine hydroxymethyltransferase – enzyme which catalyzes the reversible and THF-dependent conversion of serine to glycine and 5,10-methylene-THF. Mice lacking Shmt1 are viable and fertile, although they exhibit abnormalities in hepatic partitioning of methylenetetrahydrofolate [51]. Gsta4 encodes a glutathione S-transferase, an enzyme that is involved in cellular defense against toxic and carcinogenic compounds. Mice lacking this gene have increased sensitivity to oxidative stress, lower litter size, higher fat content in bones, and greater susceptibility to bacterial infection [52]. Gls2 (GA) is a phosphate-activated glutaminase involved in the glutamine metabolism. The activity of Gls2 is thought to be associated with malignancy and tumor. It has been shown that inhibition of Gls2 expression decreases growth and tumorigenicity of tumor cells [53]. It has been suggested recently that cholesterol plays an essential role in mammalian embryonic development [54]. Developmental disorder might be associated with defects in cholesterol biosynthetic pathways essential for fundamental cellular processes, or with cholesterol transport and uptake impairments cause by defects in apolipoproteins, enzymes, or cell-surface receptors that bind lipoproteins. Several genes in our list of upregulated genes are associated with cholesterol transport or metabolism; Apoc1 and Apoe are also part of the network. Apoc1 is a small circulating lipoprotein associated mostly with HDL-mediated cholesterol transport. Apoc1 deficiency leads to decreased plasma lipid concentration, hepatic lipid accumulation, and increased biliary excretion of cholesterol [55]. Apoe is a ligand for the receptor-mediated catabolism of lipoprotein particles. Knockout of Apoe leads to hypercholesterolemia and, consequently, to an increased susceptibility to the development of atherosclerosis [56]. Lsr (included in the list of 355 upregulated genes) encodes the lipolysis-stimulated lipoprotein receptor – a protein that recognizes apoB/E-containing lipoproteins in the presence of fatty acids. Complete inactivation of Lsr gene is embryonic lethal in mice [57]. The assumption is that Lsr is involved in the clearance of lipoproteins by liver, and is essential for liver and embryonic development.

Akp2 (Alpl, TNAP) encodes a membrane bound enzyme. Akp2 is possibly involved in the process of bone matrix mineralization, by controlling the extracellular levels of PPi concentration required for normal bone mineralization [58]. Mutations in the TNAP gene result in the inborn error of metabolism known as hypophosphatasia [59].

Aquaporin-3 (Aqp3) is a water/glycerol transporting protein. As described in [60], Aqp3-deficient mice were resistant to skin tumors and showed impaired cell proliferation in epidermis, suggesting that Aqp3 might play an important role in skin tumorogenesis. In addition, Aqp3 is expressed in mouse oocytes where it might play an important role in controlling oocyte quality by controlling water permeability [61].
Gpx2 is one of the two isoforms of glutathion peroxidase (GPX), a major enzyme that have a hydrogen peroxide-reducing activity in the epithelium of the gastrointestinal tract. It has been shown mice deficient in Gpx2 and Gpx1 is more sensitive to bacteria-associated intestinal inflammation and cancer [62].
Sorl1 (Lr11) is a member of LDL receptor family involved in the medial-to-intimal migration of vascular smooth muscle cells, the process that is essential to atherosclerotic plaque formation and remodeling of injured arteries [63].
Spint1 (Hai-1) is a Kunitz-type transmembrane serine protease inhibitor that forms inhibitor complexes with several trypsin-like serine proteases and is required for mouse placental development and embryo survival [64]. Disruption of Spint1 causes embryonic lethality around E10.5, growth retardation and placental failure [64], [65].
St14 (Mt-sp1) is a tumor-associated type II transmembrane serine protease highly expressed in epithelial tissues. St14 deletion results in an impaired development of epidermis, hair follicles and immune system [66]. St14-deficient mice die after the birth due to dehydration resulting from the abnormal epidermal barrier function.
Cdh1 encodes a member of a cadherin family of proteins. This calcium dependent cell-cell adhesion glycoprotein is responsible for the cell adhesion of epithelial cells and maintainance of epithelial cell polarity [67]. It has been shown that homozygous mutant embryos fail to compact properly above the morula stage and to form normal blastocysts [67].
Ooep (Floped) and 2410004A20rik (included in the list of 346 upregulated genes) are components of a subcortical maternal complex (SCMC) that is located in subcortex of eggs and is required for the preimplantation mouse development [68]. Although mouse embryo development lacking SCMC is arrested at 2-stage, authors suggest that the defects arise earlier and could result from abnormalities in cytokinesis, cell cycle progression, or mitotic spindle formation.

Genes involved in tight junctions

Tight junction (TJ) is one form of epithelial and endothelial cell-to-cell connection that is required for the normal blastocyst formation and implantation of the embryo [69]. TJs are complexes composed of integral membrane proteins (occludin, claudins, tricellulin, and JAM family members) and peripheral membrane proteins. Integral membrane proteins are represented in our network by claudins (Cldn4, Cldn6 and Cldn7). Claudins play important roles in the architecture and barrier functions of TJs. As described in [69], the inhibition of Cldn4 and Cldn6 affects the normal formation of blastocysts and causes changes in morphology of developing embryos. Tjp2 and Tjp3 are scaffolding proteins that directly link transmembrane TJ proteins to the actin cytoskeleton. It has been shown that the disruption of Tjp2 leads to the death of the embryo due to an inability to complete gastrulation, while Tjp3 knockout does not cause such effect [70].

Other genes in the network

The expression of F-box-containing protein Fbxo15 has been shown to be regulated by Oct4 and Sox2, and has a very similar expression profile to Oct4 [71]. Fbxo15 is possibly involved in an ubiquitin-proteasome pathway to regulate expression levels of proteins required for the pluripotency. However, as has been shown recently [71], a deletion of Fbxo15 does not affect the morphology, proliferation or pluripotency of mouse ES cells.

Dppa3 (Stella) encodes a protein with a SAP-like domain and a splicing factor motif-like structure [72]. It functions as an important maternal factor and is required for the cleavage stages during early mouse embryogenesis; Dppa3 deficient oocytes fail to reach the 8-cell stage or fail to compact [73].

Hmgb2 encodes a member of the non-histone chromosomal high mobility group protein family. It has been reported that high mobility group B (HMGB) chromosomal proteins could be a stimulus for cell differentiation and tumor progression, since HMGB expression correlates with progression of squamous cell carcinoma in skin [74].

Otx2 is a paired-type homeodomain transcription factor, and is involved in the regulation of development of retinal bipolar cells [75]. In addition, Otx2 is required in the neuroectoderm for the development of a forebrain region [76]. Conditional knockout embryos were unable to form a forebrain region correctly [76].

Spint1 (Hai-1) is a Kunitz-type transmembrane serine protease inhibitor that forms inhibitor complexes with several trypsin-like serine proteases and is required for mouse placental development and embryo survival [64]. Disruption of Spint1 causes embryonic lethality around E10.5, growth retardation and placental failure [64], [65].

Genes that are not in the Medusa network but might be important

In addition to the genes described above, there are genes that are included in our list of 355 upregulated genes but are not in the network, as they do not have any high confidence interaction partner defined in String. However some of those genes have been shown to play important roles in self-renewal and pluripotency of mouse ES cells, as well as in mouse embryogenesis.

Phc1 is a member of the Polycomb group of genes, and is a core component of Polycomb repression complex 1 (PRC1). In ES cells the Polycomb complex directly represses genes that have key roles in a variety of developmental processes, including Hox genes [77]. It has been found that genes occupied by PRCs are enriched with trimethylated Lys27 on histone H3, which is known to be a marker of repressive chromatin.

Klf2 and Klf5 belong to the Krüppel-like family of transcription factors. It has been shown that a triple knockdown of Klf2 and Klf5 along with another member of Klf family – Klf4, results in differentiation of mouse ES cells, suggesting an important function of these genes for the maintainance of self-renewal [78]. Recently, Klf5 has been claimed to be essential for normal self-renewal of mouse ES cells and blastocyst development [79]. ES cells lacking Klf5 show increased expression of several differentiation markers and frequent, spontaneous differentiation, while overexpression of Klf5 suppresses the expression of differentiation-related genes and supports LIF-independent self-renewal. The authors suggested that Klf5 contribute to ES cells proliferation by controlling cell-cycle progression and the colony-forming ability.

Mycn (N-myc) is a member of the Myc family of genes, encoding basic helix-loop-helix leucine zipper transcription factors that are potent oncogenes. As reviewed in [80],

Myc family members are implicated to have a function in regulation of cell proliferation, differentiation and apoptosis. The loss of Myc proteins results in inhibited proliferation and cell growth and accelerates differentiation. Deregulated expression of Myc might also induce apoptosis through the induction of DNA damage. It has been shown also that N-myc and c-Myc are interchangeable, and N-myc expression from c-Myc locus rescues embryonic lethality associated with c-Myc deficiency [81].
Rif1 encodes a mouse ortholog of the yeast Rif1 family of telomere-associated proteins. Rif1 has been found to associate with telomeric DNA in mouse ES cells and physically interact with other mouse telomere-associated proteins, suggesting its role in maintenance of telomere length, which needs to be protected from shortening in cells with high proliferation rates [82].
Trim71 (Mlin41) is a mammalian ortholog of *C.elegans* lin-41 heterochronic gene that is known to control the timing of organ formation during development [83]. Based on its homology and expression pattern, the authors suggested that Mlin41 may be involved in regulating specific genes involved in developmental events, including limb formation. It has been shown recently that a disruption of Mlin41 by gene trapping results in neural tube closure defect during development, and embryonic lethality [84].
Tdgf1 (Cr1) is a member of EGF-CFC family of proteins that function as coreceptors for the TGFβ-related proteins, including Nodal. Tdgf1 has been identified to be a target gene in a canonical Wnt/ β-catenin signaling pathway, and its transient activation along with Wnts proteins is necessary for the promotion of self-renewal and pluripotency of ES cells [85].

Functional description of the genes lower expressed in ES and iPS cells compared to fibroblasts in mouse

We analyzed the genes, and hence functions and pathways which are downregulated in ES and iPS cells compared to fibroblasts, which possibly are also genes differently expressed upon differentiation of pluripotent cells at least into some lineages. The network of downregulated genes is shown in supplementary figure S12.

Genes associated with mesenchymal differentiation

During differentiation cells undergo changes in their size, shape, metabolic activity, responsiveness to signals, and chromatin properties. A majority of genes present in our network have functions associated with mesenchymal differentiation which could be explained by the embryologic origin of fibroblasts. They are indeed derived from primitive mesenchyme - a part of embryonic mesoderm capable of developing into connective tissue, bone, cartilage, vascular system (heart and blood vessels), lymphatic tissue, urogenital system (including kidney), and bone marrow. Genes associated with mesenchymal differentiation are described below in more detail.

Col11a1, Col3a1, Col2a1, Col4a1, Col4a2, Col5a1, Col5a2, Col6a1, Col6a2, Col6a3, Col1a1, Col1a2, and Col5a3 belong to the collagen superfamily of proteins. Fibril-

forming collagens (type I, II, III, V and XI) provide structural integrity to all tissues and organs. As reviewed in [86], type I collagen is a major structural component of most connective tissues and is found throughout all the body, except for the cartilage where type II collagen is prevalent. Type III collagen is usually found in the tissues rich with type I collagen, but especially in highly extensible connective tissues, like skin, lung and blood vessels. Minor fibrillar collagens, type V and IX, are associated with tissues rich with collagens I and II respectively. Collagens type IV and VI are non-fibril forming. Type IV collagen is a major component of almost all basement membranes, and defines structural stability and tissue-specific properties [87]. Type VI collagen expression is associated with skeletal muscle development [88].

Lama2 and Lama4 encode laminin - a major non-collagenous component of basement membranes that mediate cell adhesion, growth migration and differentiation. Lama2 knockout mice show muscular dystrophic symptoms, as well as growth retardation [89]. Lama4 deletion results in impaired microvessel growth [90].

Thbs1 and Thbs2 belong to thrombospondin family of proteins. They have been shown to regulate cell-matrix interactions, collagen fibrillogenesis, and angiogenesis [91]. Mice lacking Thbs2 show connective tissue impairment resulted from the disordered collagen fibril formation, and increased vascular density in skin and subcutaneous tissues [92]. Thbs1 null mice have impaired lung homeostasis, associated with multiple-lineage epithelial hyperplasia and the deposition of collagen and elastin [93]. Thbs1 and Thbs2 signaling is performed through their receptor, integrin-associated protein CD47 [94].

Itga11 belongs to the integrins family of multifunctional cell adhesion receptors. Itga11 is a major receptor for fibrillar collagens, and its disruption in mice causes impaired cell migration and collagen reorganization in periodontal ligament fibroblasts, resulting in severely defective incisors and dwarfism with increased mortality [95].

Dcn belongs to the family of small leucine-rich proteoglycans that play roles in generating and maintaining multiple cell-cell and cell-matrix interactions. Dcn has been shown to govern a collagen fibril growth and its disruption leads to abnormal collagen fibril morphology and skin fragility in mice [96].

Fbn1 belongs to fibrillin family of proteins that serve as structural components of microfibrils Fbn1 has been shown to have an essential role in development and maturation of blood vessels [97].

Fbln5 is an extracellular matrix protein that has been shown to be essential for elastic fiber development [98], [99].

Plat encodes plasminogen activator (tPA), one of the major components in the matrix proteolytic network. Plat deficiency in mice results in extensive fibrin deposition that has effects on growth, fertility and survival [100].

Pappa encodes protein from the superfamily of metalloproteinases that cleaves insulin-like growth factor binding proteins (IGFBPs). It has been shown to be an essential growth regulator during mouse embryogenesis and to promote skeletal muscle formation [101], [102].

Postn, periostin, has been shown to function as a molecular switch that can promote the differentiation of mesenchymal cells into a fibroblastic lineage while repressing their transformation into other mesodermal cell lineages [103]. It is involved in the development of noncardiomyocyte lineages of the heart [103], [104].

Lox and Loxl1 encode members of lysyl-oxidase family. These proteins are known to catalyse lysine-derived cross-links in fibrillar collagens and elastin, and are involved in developmental regulation, tumor suppression, and cell motility [105]. Lox has a critical role in cardiovascular and diaphragmatic development in mice [106]. In addition, it has

been shown to regulate TGF-β1 activity in bone and therefore possibly be involved in bone maintenance and development [106]. Loxl1 is required for elastic fiber homeostasis [107]. As has been shown, Loxl1 knockout leads to impairment in connective tissues resulting in urogenital tract disorders in mice [108].
Ltbp1 and Ltbp2 are members of the LTBP/fibrillin family of extracellular proteins. Ltbp1 regulates TGFβ activity and is essential for the heart development in mice [109]. Ltbp2 is involved in the elastic fiber assembly [110].
Mmp2, Mmp3 and Mmp14 belong to the family of matrix metallopeptidases (MMP). MMPs are enzymes involved in extracellular matrix remodeling associated with embryonic development, cancer formation and progression, and other physiological and pathological processes [111]. MMPs can be divided into two subfamilies, membrane (Mmp14) and nonmembrane (Mmp2, Mmp3). An essential role of Mmp2 and Mmp14 in vascular and skeletal muscle development during embryogenesis has been reported [111]. Mmp3 has a role in controlling the synaptic structure at the neuromuscular junctions [112].
Tissue inhibitors of metalloproteinases Timp2 and Timp3 are protein inhibitors of MMPs. The balance between active MMPs and TIMPs is believed to be required to maintain tissue architecture [113]. Timp3 deletion results in a lung dysfunction and a shorter life span of Timp3-null mice [113]. In addition, mice lacking Timp3 develop vessel and retinal abnormalities [114].
Ncam1 encodes multifunctional cell-surface protein associated with epithelial-mesenchymal transition (EMT). Ablation of Ncam1 expression during EMT inhibits focal adhesion assembly, cell spreading and EMT [115].
Cdh2 encodes the adhesion protein N-cadherin. Cdh2-null mice die at E10 with most dramatic cell adhesion defects in heart, showing an essential role of Cdh2 in early heart development [116].
Cav1 is a main structural component of caveolae - invaginations of plasma membrane in cells like fibroblasts and endothelia. Caveolae plays a role in a variety of physiological processes including transport, signaling and tumor suppression. Cav1-deficient mice exhibit impaired function of cardiovascular system and thickening of lung alveolar septa [117]. Ptrf is another component of caveolae that has been shown to be essential for the caveolae formation [118].
Mgp is a mineral-binding extracellular matrix (ECM) protein produced by vascular smooth-muscle cells and chondrocytes. Mgp-deficient mice exhibit inappropriate calcification of various cartilages, and arterial calcification resulting in the blood-vessel rupture and leading to the death within two months after the birth due [119].
Pik3cg belongs to the pi3/pi4-kinase family of proteins that regulate cellular proliferation, apoptosis, cell motility, and adhesion. It has been shown that mice homozygous for null Pik3cg exhibit defective thymocyte development, T cell activation, and neutrophil migration [120].
Cxcl1, Cxcl12 and Pf4 (Cxcl4) are cytokines that belong to the family of chemokines. Cxcl12 is responsible for B-cell lymphopoiesis and bone-marrow myelopoiesis, and mice lacking this gene display late embryonic lethality [121]. Cxcl1 has been described as a potent neutrophil chemoattractant, synthesized in high levels in keratinocytes, monocytes, and macrophages in response to a variety of endogenous stimuli [122]. Pf4 has been shown to have a role in immune resonse and T-cell trafficking [123], as well as thrombosis [124].
Fst, follistatin, is a single chain autocrine glycoprotein that is known as an antagonist of activin and possibly some other members of TGF-β family members. Fst knockout

resulted in multiple defects, including retarded growth, decreased mass of the diaphragm and intercostal muscles, and skeletal abnormalities [125].
Fstl1 is a distantly related homolog of follistatin, mostly expressed in the mesenchymal component of tissues in mice [126]. It has been shown to promote endothelial cell function and stimulate repair of ischemic tissue [127].
Flnc encodes a muscle-specific member of actin binding proteins that is essential for the normal muscular development. Flnc-deficient mice exhibit defects in primary myogenesis and die shortly after birth due to respiratory failure [128].
Acta1 is actin alpha expressed in the skeletal muscle. Acta1 plays an important role in normal muscle formation. It has been shown that mice lacking Acta1 exhibit reduced body size/weight, muscle weakness and die shortly after birth [129].
Acta2 encodes smooth-muscle alpha-actin. This gene is not essential for the formation of cardiovascular system, but plays an important role in regulating vascular contractility and blood pressure homeostasis [130].
Grem2 is a secreted protein, which acts as an antagonist of bone morphogenetic proteins (BMPs). Grem2 acts as a negative regulator of bone formation, and its suppression promotes osteogenesis in vitro [131].
Vcam1 is a cytokine-inducible cell surface protein expressed on vascular endothelium. Mice embryos lacking Vcam1 die during gestation with severe defects in heart or placenta development [132], [133]. It has been shown also that Vcam1-deficient mice develop mild leukocytosis due to the impaired migration of lymphocytes to the bone marrow [134].
Adam12 encodes metalloprotease-disintegrin that has been suggested to be involved in regulating adipogenesis and myogenesis [135].
Crlf1 is a haemopoietin receptor that has a potential role in haemopoiesis, and the recognition or processing of pheromonal signals or for the mechanics of suckling [136].
Csf1 is a secreted cytokine that regulates macrophage differentiation, survival and function [137]. Csf1 has been shown also to play a role in osteoblast-mediated osteoclastogenesis within the bone microenvironment [138].
Cnn1 is a calmodulin and actin binding protein expressed in smooth muscle. It has been shown that mice lacking this gene exhibit increased bone formation and ossification, suggesting that Cnn1 may play a negative role in osteogenesis [139].
Thy1 is a cell-surface signaling molecule that belongs to the immunoglobulin superfamily. Thy1 is involved in multiple signaling cascades to mediate T cell activation, neurite outgrowth, apoptosis, tumor suppression, wound healing, and fibrosis [140].
Lsp1 is an F-actine binding protein expressed in lymphocytes, macrophages and neutrophils. It has been shown that Lsp1 is involved in controlling leukocyte populations in rested and inflamed peritoneum [141].

Growth factors and receptors

Growth factors and their receptors are widely represented in our network. Growth factors play roles in different biological processes, including cellular growth, proliferation and differentiation.

Tgfb3 belongs to the transforming growth factors-beta (TGF-β) family of proteins that have important roles in many developmental processes including regulation of cell proliferation, differentiation, cell adhesion, skeletal development, hematopoiesis,

inflammatory responses, and wound healing [142]. Tgfb3-deficient mice exhibit defective palatogenesis and lung development [143].
Inhba is also a member of TGF-β superfamily. It is mostly produced in the tissues like adrenal gland and gonads, and has been shown to act as an inhibitor of activin and bone morphogenetic protein (BMP) in mouse adrenocortical cell line [144]. In addition, Inhba has a function as endocrine regulator of pituitary follicle-stimulating hormone (FSH) [145].
Bmp1 is another member of TGF-β superfamily. In mouse Bmp1 has procollagen C-proteinase activity, and its deletion results in defective collagen formation, abnormal ventral body wall development, and reduced ossification of the skull [146].
Igf1 is a polypeptide protein hormone that is required for the correct embryonic development in mice, as well as normal growth, glucose metabolism, organ homeostasis, immune and neurologic systems [147]. Insulin-like growth factor 2 (Igf2) has an important role in embryonic growth. It has been demonstrated that Igf2-deficient mice had a significantly reduced body size, but otherwise appeared to be normal and fertile [148]. Igfbp5 is a binding protein known to regulate activity of IGFs. Igfbp5 has a potential role in regulation of craniofacial osteogenesis [149], myogenesis [150], mammary gland morphogenesis [151], and anterior pituitary development [152].
Ptn, a heparin-binding growth-associated molecule (HB-GAM), is a growth factor that has high affinity to heparin. It has been shown to be involved in diverse developmental processes, including formation and plasticity of neuronal connections [153], and osteogenesis [154].
Fgf7 encodes a member of the fibroblast growth factor (FGF) family. Fgf7 is synthesized by cells of mesenchymal origin; it mediates mesenchymal-epithelial interactions [155], and has been shown to be required for the hair development [156].
Dlk1 is a member of epidermal growth factor (EGF)-like gene family. Dlk1 has been shown to be essential for the normal B-cell development and its deficiency results in changes in cell-cell interactions in bone marrow microenvironment [157]. In addition, Dlk1 is important for normal development and homeostasis of adipose tissue [158].
Pdgfra and Pdgfrb encode cell surface tyrosine kinase receptors for members of the platelet-derived growth factor family. PDGF signaling has been shown to regulate proliferation, migration, and differentiation of mesenchymal cell types [159]. Pdgfrb disruption has been shown to result in abnormal kidney development and hematological disorders [160]. Pdgfra null mice show skeletal defects, increased apoptosis, incomplete cephalic closure, impaired myotome and testis formation [161].
Tgfbr2 is a serine/threonin kinase-containing receptor through which TGF-beta signaling is mediated. Tgfbr2 deletion results in embryonic lethality due to an impaired yolk sac hematopoiesis and vasculogenesis [162].
Nrp1 is a multifunctional transmembrane receptor that binds ligands like secreted semaphorins (Sema) and vascular endothelial growth factors (VEGF). The studies have shown that Nrp1 mediates the activity of its ligands during development of the heart, vasculature, and nervous system [71].
Ghr encodes a transmembrane receptor for growth hormone. Ghr is a critical regulator of postnatal growth and metabolism [163]. It has been reported to be essential for the induction and progression of osteogenesis, and regulation of proportion of hematopoietic and mesenchymal cell progenitors in bone marrow [164].
Irs1 encodes a major substrate for insulin receptor and IGF-1 receptor tyrosine kinases. Deficiency in Irs1 results in impaired skeletal growth and resistance to the glucose-lowering effects of insulin [165].

Egfr is a prototype tyrosine kinase receptor activated upon binding of members of epidermal growth factor (EGF) family. It has been shown that Egfr deficiency results in impaired epithelial development in skin, kidney, lung, liver and gastrointestinal tract [166],[167].

Genes associated with the cytoskeleton

Dynamic rearrangements of cytoskeleton promote morphological changes and cellular migration. Recently, it has been shown that cytoskeletal changes also serve as intracellular signal that can control cellular differentiation [168]. Small GTP-binding proteins of Rho family (Rho, Rac, Cdc42) are involved in multiple signal transduction pathways [169] and regulate a variety of cellular functions, including actin-dependent cytoskeleton morphogenesis, microtubular dynamics, and cell motility [170]. Cdc42ep3 belongs to the family of Cdc42 downstream effector proteins that have been shown to induce actin filament assembly leading to cell shape changes in fibroblasts and epithelial cells [171]. Rhoj (TC10L) and Rhoq (TC10A) are isoforms of the protein TC10, belonging to the subfamily of Rho GTP-ases. TC10 is involved in the insulin-stimulated glucose transport in adipocytes [172]. A crucial role of TC10L in early adipocyte differentiation has been suggested recently [173]. Arhgdib is a regulator of activation cycle of Rho proteins in lymphoid organs [174]. Arhgap24 belongs to the RhoGAP family of proteins that act as negative regulators of Rho GTPases [175].

Transcription factors

One expects transcription factors responsible for differentiation to be down-regulated in ES and iPS compared to fibroblasts. Indeed, several such TFs are shown in our network, and even more are included in the list of 462 downregulated genes. Using STRING, we have examined if these TFs are possible interaction partners. The resulting network (STRING confidence 0.15) is shown in Figure S12 (B), and its members are described below in more detail.

Homeodomain-containing genes encode conserved transcription factors that regulate downstream effectors to direct the morphogenetic events leading to the early body development. Hoxb2 is involved in the development of skeleton, nervous system, muscles, and respiratory system. Hoxb2 deficient mice usually die at birth and have a phenotype that is characterized by atrophy and paralysis of the facial muscles of expression, defects in the formation of the sternum and transformations of cervical vertebrae [176]. Hoxa5 plays a role in the establishment of skeleton and specification of axial identity, as well as the respiratory tract development [177]. Hoxc6 has been shown to have a role in the development of mammary glands [178]. Hoxa9 has a specific function in lumbosacral axial skeleton patterning and in limb morphogenesis [179]. Hoxd13 regulates the early formation of limb skeletal elements [180]. Shox2 has been shown to be essential for the palatogenesis in mice [181]. Meox2 is involved in somite morphogenesis and it´s absence results in defective differentiation of limb muscules [182]. Lhx9 is essential for the mouse gonade development and it´s knockout results in a failed proliferation of the somatic cells of the genital ridge [183]. Prrx1 has been shown to regulate epithelial-mesenchymal interactions required for skeletal

organogenesis [184]. Mice lacking Prrx1 exhibit skeletal defects affecting limb, vertebrae or mandible, and die shortly after the birth.

Twist1 and Twist2 are helix-loop-helix transcription factors. Twist1 has a conserved role in mesodermal differentiation, the development of the limb and branchial arches, and neural crest cell migration [185]. Twist1 and Twist2 have been shown to be a part of the regulatory network controlling osteoblast differentiation [186]. Mice lacking Twist1 are characterized by late embryonic lethality [185], while Twist2 deficient mice exhibit postnatal death [187].

Runx1 belongs to the Runt-related TF family of genes, and is essential regulator of hematopoietic system development. Runx1-deficient mice lack hematopoiesis and usually die as an embryo [188]. Runx1t1 and Runx1 create a TF complex which plays an important role in a normal hematopoiesis, and is a frequent target of chromosomal translocations in leukemia [189]. Runx2 also is a memberof the runt-domain gene family and plays an important role in the skeletogenesis. In particular, it is necessary for complete osteoblastic maturation and endochondral bone formation [190]. In addition, it has been shown that Runx2 is expressed in the hematopoietic stem cells compartment, where it modulates Cbfb-smooth muscle myosine heavy chain (SMMHC)-mediated leukemia development [191].

Ets1 and Elk3 are members of Ets transcription factors family. Ets1 is a proto-oncogene that has been shown to have an important role for the survival and activation of T-cells [192]. Elk3 is involved in the vasculogenesis during mouse development. Mice lacking this gene exhibit vascular defect associated with embryonic lymphangiectasis ([193]).

Hmga2 belongs to the HMGA sub-family of high mobility group (HMG) proteins. Hmga2 plays an important role in mammalian growth and development. As has been demonstrated in [194], Hmga2-deficient mice exhibit reduction in growth, dwarfism and infertility. In addition, this gene has been shown to be essential for the normal cardiac development [195].

Sim2 is a member of the basic helix-loop-helix PAS TF gene family. Sim2 knockout in mice results in postnatal lethality due to craniofacial malformations, lung atelectasis and breathing failure [196],[197].

Egr2 is a member of a family of zinc-finger TF. It plays an essential role during hindbrain development in mice. Mice lacking this gene die shortly after birth with the absence of rhombomeres 3 and 5 of the hindbrain affecting axonal migration [198].

Tbx15 belongs to the T-box family of transcriptional regulators. It has been shown recently that Tbx15 has an essential role during mesenchymal stages of skeletal development by maintaining the appropriate rate of cell proliferation [199].

Fosl2 encodes Fos-related protein Fra-2, a TF that has an important role in cartilliage development in mice [200].

Zic1 encodes a zinc-finger TF involved in the cerebellar development [201]. Zic1-deficient mice show cerebellar hypoplasia with a missing lobule of the anterior lobe.

Foxc1 and Foxc2 are two closely-related forkhead/winged helix TFs. They are required for cardiovascular development [202] and have been shown to regulate arterial cell specification and lymphatic sprouting during mouse embryonic development [203]. In addition, Foxc1 is involved in the gonad development, germ cell migration and folliculogenesis [204], and Foxc2 plays a role in skeletogenesis in cells derived from the neural crest and the mesoderm [204,205].

Nr2f2 belongs to the family of nuclear orphan receptors. This gene is involved in mesenchymal-epithelial interactions required for the normal development of vascular system ([206]).

Hic1 encodes a zinc-finger TF which is epigenetically inactivated in cancer. Hic1 functionally cooperates with p53 to suppress cancer in mice, and loss Hic1 function leads to increased tumorigenesis [207].
Evi1 is a zinc-finger-containing TF that plays important role in cell proliferation, vascularization, and development. Evi1 homozygous mutants die at 10.5 days post coitum, and exhibit widespread hypocellularity, hemorrhaging, and impaired development of the heart, somites and cranial ganglia [208].
Maf is a member of basic leucine zipper (bZip) superfamily. It is required for the differentiation of vertebrate lens, and mice lacking Maf exhibit increased embryonic mortality, defective differentiation of lens fiber, and impaired lens development [209]. In addition, Maf has been shown to be necessary for normal differentiation of chondrocytes during endochondral bone development [210].
Zfpm2 (Fog-2) is multi-zinc-finger TF that plays an essential role in cardiac development. Homozygous Zfpm2 mutant embryos die at midgestation with multiple cardiac defects, including absence of coronary vasculature [211],[212].
Nfib, Nfix and Nfia belong to the nuclear factor I (NFI) family of TFs that have a role in regulation of developmental processes. It has been shown that mice lacking Nfib die at birth from respiratory failure due to the severe lung defects, and also exhibit impaired neuronal development [213]. Nfix knockout in mice leads to the postnatal lethality, gastrointestinal defects, hydrocephalus, impaired bone formation, and defects in corpus callosum development [214]. The disruption of Nfia gene results in perinatal lethality due to the developmental defects including hydrocephalus, agenesis of the corpus callosum and hippocampal commissure [215].
Lbh encodes a conserved transcriptional regulatory protein that is expressed during early limb and heart development [216]. Lbh has been suggested to have in important role during normal cardiogenesis since cardiac defects have been observed in mice with deregulated Lbh expression [217].
Ankrd1 (Carp) belongs to the muscle ankyrin repeat protein (MARP) family. MARP family members have been suggested to play in important structural and gene regulatory role in skeletal muscule [218]. Ankrd1 also serves as a genetic marker of cardiac hypertrophy [218].
Snai1 and Snai2 encode zinc-finger proteins that act as transcriptional repressors. Both genes act as mediators of epithelial-mesenchymal transition (EMT) - a conserved developmental mechanism occurring during organogenesis, including mesoderm and neural tube formation [219], [220], [221]. Snai1 knockout leads to the formation of morphologically abnormal mesoderm, and Snai1-deficient embryos show defects in gastrulation [219], [220].
Fhl2 is a member of LIM domain gene family. It has been shown to regulate cell proliferation by activating cyclin D1 expression [222]. Fhl2 is an early marker of cardiogenic cells; however it is not essential for the normal cardiac development in mice [223].

Genes associated with chromatin remodeling

The expression of developmental genes is usually silenced in ES cells and is activated upon differentiation. Changes in chromatin structure are associated with the activation or silencing of genes during development. In our list of 462 downregulated genes we have noticed a gene that functions as an ATP-dependent chromatin remodeler. Chd3 (Mi-2α) is associated with the NuRD co-repressor complex and could act as a transcriptional repressor. However, it has been shown recently that Chd3 acts also as a

transcriptional activator by interacting with early hematopoietic transcription factor c-Myb [224].

Other genes

Ptprz1 belongs to the family of Protein tyrosine phosphatases (PTPs) that are important for the development and functioning of central nervous system [225]. It has been shown recently that Ptprz1 deletion does not interfere normal development of neurons in mice and its loss can be substituted by other PTP proteins [226].

Lrp1 is a receptor protein involved in the endocytosis. It binds various ligands and promotes intracellular signaling that mediates cellular proliferation and migration of different types of cells [227]. It has been shown that Lrp1 disruption in mice results in lethality of embryos around implantation stage [228].

App is an integral membrane protein concentrated mostly in the synapses of neurons, and associated with the pathogenesis of Alzheimer's disease. It has been shown that App-deficient mice exhibit reduced body weight, decreased locomotor activity and forelimb grip strength suggesting impaired neuronal and muscular function [229].

Tnfrsf1a encodes a receptor that mediated the activity of proinflammatory cytokine tumor necrosis factor (TNF) alpha. Tnfrsf1a has an important role in nonspecific immunity, and mice lacking this gene exhibit a high susceptibility to infections [230], [231], [232].

Tnc is an extracellular matrix glycoprotein. This gene has been implicated to play important functional roles in neural development. As has been demonstrated, Tnc deletion did not have a major effect on the central nervous system in mice, but certain forms of synaptic activity were affected [233].

Nbl1 is a secreted bone morphogenic protein (BMP) antagonist belonging to the TGFbeta protein superfamily. Nbl1 has been suggested to play a role as a neuromodulator in inflammatory pain [234].

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