Stem Cell and Transcript Research Literatures

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Abstract: The stem cell is the origin of an organism's life that has the potential to develop into many different types of cells in life bodies. In many tissues stem cells serve as a sort of internal repair system, dividing essentially without limit to replenish other cells as long as the person or animal is still alive. When a stem cell divides, each new cell has the potential either to remain a stem cell or become another type of cell with a more specialized function, such as a red blood cell or a brain cell. This article introduces recent research reports as references in the stem cell and transcript related studies.
[Ma H, Young M, Yang Y. **Stem Cell and Transcript Research Literatures**. Stem Cell. 2015;6(2):56-72] (ISSN 1545-4570). http://www.sciencepub.net/stem. 8

Key words: stem cell; transcript; life; research; literature

1. Introduction

The stem cell is the origin of an organism's life that has the potential to develop into many different types of cells in life bodies. In many tissues stem cells serve as a sort of internal repair system, dividing essentially without limit to replenish other cells as long as the person or animal is still alive. When a stem cell divides, each new cell has the potential either to remain a stem cell or become another type of cell with a more specialized function, such as a red blood cell or a brain cell. This article introduces recent research reports as references in the related studies.

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Abrajano, J. J., I. A. Qureshi, et al. "Corepressor for element-1-silencing transcription factor preferentially mediates gene networks underlying neural stem cell fate decisions." Proc Natl Acad Sci U S A. 2010 Sep 21;107(38):16685-90. doi: 10.1073/pnas.0906917107. Epub 2010 Sep 7.

The repressor element-1 (RE1) silencing transcription factor/neuron-restrictive silencer factor (REST/NRSF) silences neuronal genes in neural stem cells (NSCs) and nonneuronal cells through its role as a dynamic modular platform for recruitment of transcriptional and epigenetic regulatory cofactors to RE1-containing promoters. In embryonic stem cells, the REST regulatory network is highly integrated with the transcriptional circuitry governing self-renewal and pluripotency, although its exact functional role is unclear. The C-terminal cofactor for REST, CoREST, also acts as a modular scaffold, but its cell type-specific roles have not been elucidated. We used chromatin immunoprecipitation-on-chip to examine CoREST and REST binding sites in NSCs and their proximate progenitor species. In NSCs, we identified a larger number of CoREST (1,820) compared with REST (322) target genes. The majority of these CoREST targets do not contain known RE1 motifs. Notably, these CoREST target genes do play important roles in pluripotency networks, in modulating NSC identity and fate decisions and in epigenetic processes previously associated with both REST and CoREST. Moreover, we found that NSC-mediated developmental transitions were associated primarily with liberation of CoREST from promoters with transcriptional repression favored in less lineage-restricted radial glia and transcriptional activation favored in more lineage-restricted neuronal-oligodendrocyte precursors. Clonal NSC REST and CoREST gene manipulation paradigms further revealed that CoREST has largely independent and previously uncharacterized roles in promoting NSC multilineage potential and modulating early neural fate decisions.

Akashi, K. "Cartography of hematopoietic stem cell commitment dependent upon a reporter for transcription factor activation." Ann N Y Acad Sci. 2007 Jun;1106:76-81. Epub 2007 Mar 14.

A hierarchical hematopoietic developmental tree has been proposed based on the result of prospective purification of lineage-restricted progenitors. For more detailed mapping for hematopoietic stem cell (HSC) commitment, we tracked the expression of PU.1, a major granulocyte/monocyte (GM)- and lymphoid-related transcription factor, from the HSC to the myelolymphoid progenitor stages by using a mouse line harboring a knockin reporter for PU.1. This approach enabled us to find a new progenitor population committed to GM and lymphoid lineages within the HSC fraction. This result suggests that there should be another developmental pathway independent of the conventional one with myeloid versus lymphoid

bifurcation, represented by common myeloid progenitors and common lymphoid progenitors, respectively. The utilization of the transcription factor expression as a functional marker might be useful to obtain cartography of the hematopoietic development at a higher resolution.

Behre, G., V. A. Reddy, et al. "Proteomic analysis of transcription factor interactions in myeloid stem cell development and leukaemia." Expert Opin Ther Targets. 2002 Aug;6(4):491-5.

Recent results indicate that interactions of transcription factors with other nuclear proteins play an important role in stem cell development, lineage commitment and differentiation in the haematopoietic system, and the pathogenesis of myeloid leukaemias. High-throughput proteomics by mass spectrometric analysis of gel-separated proteins can identify multi-protein complexes and changes in the expression of multiple proteins simultaneously. This review describes an application of proteomic methods (2D gel electrophoresis (GE) and mass spectrometry (MS)), which can be used to identify regulated protein targets of transcription factors important in myeloid differentiation and leukaemia. This global high-throughput functional proteomics approach could lead to new insights into the network of protein-protein interactions and target proteins involved in myeloid stem cell development and leukaemia as well as provide new targets for rational pathogenesis-based therapies of leukaemia and cancer.

Brehm, A., K. Ohbo, et al. "Synergism with germ line transcription factor Oct-4: viral oncoproteins share the ability to mimic a stem cell-specific activity." Mol Cell Biol. 1999 Apr;19(4):2635-43.

Activation of transcription by Oct-4 from remote binding sites requires a cofactor that is restricted to embryonal stem cells. The adenovirus E1A protein can mimic the activity of this stem cell-specific factor and stimulates Oct-4 activity in differentiated cells. Here we characterize the Oct-4-E1A interaction and show that the E1A 289R protein harbors two independent Oct-4 binding sites, both of which specifically interact with the POU domain of Oct-4. Furthermore, we demonstrate that, like E1A, the human papillomavirus E7 oncoprotein also specifically binds to the Oct-4 POU domain. E7 and Oct-4 can form a complex both in vitro and in vivo. Expression of E7 in differentiated cells stimulates Oct-4-mediated transactivation from distal binding sites. Moreover, Oct-4, but not other Oct factors, is active when expressed in cells transformed by human papillomavirus. Our results suggest that different viruses have evolved oncoproteins that share the ability to target Oct-4 and to mimic a stem cell-specific activity.

Bunaciu, R. P. and A. Yen "Activation of the aryl hydrocarbon receptor AhR Promotes retinoic acid-induced differentiation of myeloblastic leukemia cells by restricting expression of the stem cell transcription factor Oct4." Cancer Res. 2011 Mar 15;71(6):2371-80. doi: 10.1158/0008-5472.CAN-10-2299. Epub 2011 Jan 24.

Retinoic acid (RA) is used to treat leukemia and other cancers through its ability to promote cancer cell differentiation. Strategies to enhance the anticancer effects of RA could deepen and broaden its beneficial therapeutic applications. In this study, we describe a receptor cross-talk system that addresses this issue. RA effects are mediated by RAR/RXR receptors that we show are modified by interactions with the aryl hydrocarbon receptor (AhR), a protein functioning both as a transcription factor and a ligand-dependent adaptor in an ubiquitin ligase complex. RAR/RXR and AhR pathways cross-talk at the levels of ligand-receptor and also receptor-promoter interactions. Here, we assessed the role of AhR during RA-induced differentiation and a hypothesized convergence at Oct4, a transcription factor believed to maintain stem cell characteristics. RA upregulated AhR and downregulated Oct4 during differentiation of HL-60 promyelocytic leukemia cells. AhR overexpression in stable transfectants downregulated Oct4 and also decreased ALDH1 activity, another stem cell-associated factor, enhancing RA-induced differentiation as indicated by cell differentiation markers associated with early (CD38 and CD11b) and late (neutrophilic respiratory burst) responses. AhR overexpression also increased levels of activated Raf1, which is known to help propel RA-induced differentiation. RNA interference-mediated knockdown of Oct4 enhanced RA-induced differentiation and G(0) cell-cycle arrest relative to parental cells. Consistent with the hypothesized importance of Oct4 downregulation for differentiation, parental cells rendered resistant to RA by biweekly high RA exposure displayed elevated Oct4 levels that failed to be downregulated. Together, our results suggested that therapeutic effects of RA-induced leukemia differentiation depend on AhR and its ability to downregulate the stem cell factor Oct4.

Chittka, A., J. Nitarska, et al. "Transcription factor positive regulatory domain 4 (PRDM4) recruits protein arginine methyltransferase 5 (PRMT5) to mediate histone arginine methylation and control neural stem cell proliferation and differentiation." J Biol Chem. 2012 Dec 14;287(51):42995-3006. doi: 10.1074/jbc.M112.392746. Epub 2012 Oct 9.

During development of the cerebral cortex, neural stem cells (NSCs) undergo a temporal switch from proliferative (symmetric) to neuron-generating (asymmetric) divisions. We investigated the role of Schwann cell factor 1 (SC1/PRDM4), a member of the PRDM family of transcription factors, in this critical transition. We discovered that SC1 recruits the chromatin modifier PRMT5, an arginine methyltransferase that catalyzes symmetric dimethylation of histone H4 arginine 3 (H4R3me2s) and that this modification is preferentially associated with undifferentiated cortical NSCs. Overexpressing SC1 in embryonic NSCs led to an increase in the number of Nestin-expressing precursors; mutational analysis of SC1 showed that this was dependent on recruitment of PRMT5. We found that SC1 protein levels are down-regulated at the onset of neurogenesis and that experimental knockdown of SC1 in primary NSCs triggers precocious neuronal differentiation. We propose that SC1 and PRMT5 are components of an epigenetic regulatory complex that maintains the "stem-like" cellular state of the NSC by preserving their proliferative capacity and modulating their cell cycle progression. Our findings provide evidence that histone arginine methylation regulates NSC differentiation.

Csaszar, E., G. Gavigan, et al. "An automated system for delivery of an unstable transcription factor to hematopoietic stem cell cultures." Biotechnol Bioeng. 2009 Jun 1;103(2):402-12. doi: 10.1002/bit.22297.

An automated delivery system for cell culture applications would permit studying more complex culture strategies and simplify measures taken to expose cells to unstable molecules. We are interested in understanding how intracellular TAT-HOXB4 protein concentration affects hematopoietic stem cell (HSC) fate; however, current manual dosing strategies of this unstable protein are labor intensive and produce wide concentration ranges which may not promote optimal growth. In this study we describe a programmable automated delivery system that was designed to integrate into a clinically relevant, single-use, closed-system bioprocess and facilitate transcription factor delivery studies. The development of a reporter cell assay allowed for kinetic studies to determine the intracellular (1.4 +/- 0.2 h) and extracellular (3.7 +/- 1.8 h and 78 +/- 27 h at 37 degrees C and 4 degrees C, respectively) half-lives of TAT-HOXB4 activity. These kinetic parameters were incorporated into a mathematical model, which was used to predict the dynamic intracellular concentration of TAT-HOXB4 and optimize the delivery of the protein. The automated system was validated for primary cell culture using human peripheral blood patient samples. Significant expansion of human primitive progenitor cells was obtained upon addition of TAT-HOXB4 without user intervention. The delivery system is thus capable of being used as a clinically relevant tool for the exploration and optimization of temporally sensitive stem cell culture systems.

Djouad, F., C. Bony, et al. "Transcriptomic analysis identifies Foxo3A as a novel transcription factor regulating mesenchymal stem cell chrondrogenic differentiation." Cloning Stem Cells. 2009 Sep;11(3):407-16. doi: 10.1089/clo.2009.0013.

Multipotent mesenchymal stromal cells (MSC) are progenitor cells able to differentiate into several lineages including chondrocytes, and thus represent a suitable source of cells for cartilage engineering. However, the control of MSC differentiation to hypertrophy is a crucial step for the clinical application of MSC in cartilage repair where a stable chondrogenic phenotype without transition to terminal differentiation is the goal to achieve. This study aims at identifying new factors that may regulate this process. Using microarrays, we compared the transcriptional profiles of human MSC and MSC-derived chondrocytes obtained after culture in micropellets. After chondrogenesis induction, 676 genes were upregulated, among which five transcription factors not yet associated with chondrocyte differentiation of adult stem cells. These factors, in particular Foxo3A, are strongly expressed at day 21 and in mature chondrocytes. We investigated the role of Foxo3A using RNA interference. Our results revealed an important role of Foxo3A in the differentiation process of MSC toward chondrogenic fate, both in early and late stages. Indeed, stable Foxo3A knockdown tends to increase cell survival and decrease apoptosis, mainly in early stages of chondrogenesis. Importantly, we show that the loss of Foxo3A in MSC results in an increased expression level of markers specific for mature (aggrecan, collagen II) and hypertrophic (collagen X) chondrocytes. Therefore, our findings suggest that upregulation of Foxo3A over the course of chondrogenic differentiation plays a dual role, mainly inhibiting the differentiation process toward hypertrophy and promoting cell apoptosis.

Dolfini, D., M. Minuzzo, et al. "The short isoform of NF-YA belongs to the embryonic stem cell transcription factor circuitry." Stem Cells. 2012 Nov;30(11):2450-9. doi: 10.1002/stem.1232.

Totipotency of embryonic stem cells (ESCs) is controlled at the transcriptional level by a handful of transcription factors (TFs) that promote stemness and prevent differentiation. One of the most enriched DNA elements in promoters and enhancers of genes

specifically active in ESCs is the CCAAT box, which is recognized by NF-Y, a trimer with histone-like subunits--NF-YB/NF--YC--and the sequence-specific NF-YA. We show that the levels of the short NF-YA isoform--NF-YAs--is high in mouse ESCs (mESCs) and drops after differentiation; a dominant negative mutant affects expression of important stem cells genes, directly and indirectly. Protein transfections of TAT-NF-YAs stimulate growth and compensate for withdrawal of leukemia inhibitory factor (LIF) in cell cultures. Bioinformatic analysis identifies NF-Y sites as highly enriched in genomic loci of stem TFs in ESCs. Specifically, 30%-50% of NANOG peaks have NF-Y sites and indeed NF-Y-binding is required for NANOG association to DNA. These data indicate that NF-Y belongs to the restricted circle of TFs that govern mESCs, and, specifically, that NF-YAs is the active isoform in these cells.

Gangenahalli, G. U., P. Gupta, et al. "Stem cell fate specification: role of master regulatory switch transcription factor PU.1 in differential hematopoiesis." Stem Cells Dev. 2005 Apr;14(2):140-52.

PU.1 is a versatile hematopoietic cell-specific ETS-family transcriptional regulator required for the development of both the inborn and the adaptive immunity, owing to its potential ability to regulate the expression of multiple genes specific for different lineages during normal hematopoiesis. It functions in a cell-autonomous manner to control the proliferation and differentiation, predominantly of lymphomyeloid progenitors, by binding to the promoters of many myeloid genes including the macrophage colony-stimulating factor (M-CSF) receptor, granulocyte-macrophage (GM)-CSF receptor alpha, and CD11b. In B cells, it regulates the immunoglobulin lambda 2-4 and kappa 3' enhancers, and J chain promoters. Besides lineage development, PU.1 also directs homing and long-term engraftment of hematopoietic progenitors to the bone marrow. PU.1 gene disruption causes a cell-intrinsic defect in hematopoietic progenitor cells, recognized by an aberrant myeloid and B lymphoid development. It also immortalizes erythroblasts when overexpressed in many cell lines. Although a number of reviews have been published on its functional significance, in the following review we attempted to consolidate information about the differential participation and role of transcription factor PU.1 at various stages of hematopoietic development beginning from stem cell proliferation, lineage commitment and terminal differentiation into distinct blood cell types, and leukemogenesis.

Hoffmann, A., S. Czichos, et al. "The T-box transcription factor Brachyury mediates cartilage development in mesenchymal stem cell line C3H10T1/2." J Cell Sci. 2002 Feb 15;115(Pt 4):769-81.

The BMP2-dependent onset of osteo/chondrogenic differentiation in the acknowledged pluripotent murine mesenchymal stem cell line (C3H10T1/2) is accompanied by the immediate upregulation of Fibroblast Growth Factor Receptor 3 (FGFR3) and a delayed response by FGFR2. Forced expression of FGFR3 in C3H10T1/2 is sufficient for chondrogenic differentiation, indicating an important role for FGF-signaling during the manifestation of the chondrogenic lineage in this cell line. Screening for transcription factors exhibiting a chondrogenic capacity in C3H10T1/2 identified that the T-box containing transcription factor Brachyury is upregulated by FGFR3-mediated signaling. Forced expression of Brachyury in C3H10T1/2 was sufficient for differentiation into the chondrogenic lineage in vitro and in vivo after transplantation into muscle. A dominant-negative variant of Brachyury, consisting of its DNA-binding domain (T-box), interferes with BMP2-mediated cartilage formation. These studies indicate that BMP-initiated FGF-signaling induces a novel type of transcription factor for the onset of chondrogenesis in a mesenchymal stem cell line. A potential role for this T-box factor in skeletogenesis is further delineated from its expression profile in various skeletal elements such as intervertebral disks and the limb bud at late stages (18.5 d.p.c.) of murine embryonic development.

Hosseinpour, B., M. R. Bakhtiarizadeh, et al. "Predicting distinct organization of transcription factor binding sites on the promoter regions: a new genome-based approach to expand human embryonic stem cell regulatory network." Gene. 2013 Dec 1;531(2):212-9. doi: 10.1016/j.gene.2013.09.011. Epub 2013 Sep 13.

Self-proliferation and differentiation into distinct cell types have been made stem cell as a promising target for regenerative medicine. Several key genes can regulate self-renewal and pluripotency of embryonic stem cells (hESCs). They work together and build a transcriptional hierarchy. Coexpression and coregulation of genes control by common regulatory elements on the promoter regions. Consequently, distinct organization and combination of transcription factor binding sites (TFBSs modules) on promoter regions, in view of order and distance, lead to a common specific expression pattern within a set of genes. To gain insights into transcriptional regulation of hESCs, we selected promoter regions of eleven common expressed hESC genes including SOX2, LIN28, STAT3, NANOG, LEFTB, TDGF1, POU5F1, FOXD3, TERF1, REX1 and GDF3 to predict activating regulatory modules on promoters

and discover key corresponding transcription factors. Then, promoter regions in human genome were explored for modules and 328 genes containing the same modules were detected. Using microarray data, we verified that 102 of 328 genes commonly upregulate in hESCs. Also, using output data of DNA-protein interaction assays, we found that 42 of all predicted genes are targets of SOX2, NANOG and POU5F1. Additionally, a protein interaction network of hESC genes was constructed based on biological processes, and interestingly, 126 downregulated genes along with upregulated ones identified by promoter analysis were predicted in the network. Based on the results, we suggest that the identified genes, coregulating with common hESC genes, represent a novel approach for gene discovery based on whole genome promoter analysis irrespective of gene expression. Altogether, promoter profiling can be used to expand hESC transcriptional regulatory circuitry by analysis of shared functional sequences between genes. This approach provides a clear image on underlying regulatory mechanism of gene expression profile and offers a novel approach in designing gene networks of stem cell.

Ikeda, M., N. Mitsuda, et al. "Arabidopsis WUSCHEL is a bifunctional transcription factor that acts as a repressor in stem cell regulation and as an activator in floral patterning." Plant Cell. 2009 Nov;21(11):3493-505. doi: 10.1105/tpc.109.069997. Epub 2009 Nov 6.

Most transcription factors act either as activators or repressors, and no such factors with dual function have been unequivocally identified and characterized in plants. We demonstrate here that the Arabidopsis thaliana protein WUSCHEL (WUS), which regulates the maintenance of stem cell populations in shoot meristems, is a bifunctional transcription factor that acts mainly as a repressor but becomes an activator when involved in the regulation of the AGAMOUS (AG) gene. We show that the WUS box, which is conserved among WOX genes, is the domain that is essential for all the activities of WUS, namely, for regulation of stem cell identity and size of floral meristem. All the known activities of WUS were eliminated by mutation of the WUS box, including the ability of WUS to induce the expression of AG. The mutation of the WUS box was complemented by fusion of an exogenous repression domain, with resultant induction of somatic embryogenesis in roots and expansion of floral meristems as observed upon ectopic expression of WUS. By contrast, fusion of an exogenous activation domain did not result in expanded floral meristems but induced flowers similar to those induced by the ectopic expression of AG. Our results demonstrate that WUS acts mainly as a repressor and that its function changes from that of a repressor to that of an activator in the case of regulation of the expression of AG.

Jauch, R., C. K. Ng, et al. "Crystal structure and DNA binding of the homeodomain of the stem cell transcription factor Nanog." J Mol Biol. 2008 Feb 22;376(3):758-70. doi: 10.1016/j.jmb.2007.11.091. Epub 2007 Dec 4.

The transcription factor Nanog is an upstream regulator in early mammalian development and a key determinant of pluripotency in embryonic stem cells. Nanog binds to promoter elements of hundreds of target genes and regulates their expression by an as yet unknown mechanism. Here, we report the crystal structure of the murine Nanog homeodomain (HD) and analysis of its interaction with a DNA element derived from the Tcf3 promoter. Two Nanog amino acid pairs, unique among HD sequences, appear to affect the mechanism of nonspecific DNA recognition as well as maintain the integrity of the structural scaffold. To assess selective DNA recognition by Nanog, we performed electrophoretic mobility shift assays using a panel of modified DNA binding sites and found that Nanog HD preferentially binds the TAAT(G/T)(G/T) motif. A series of rational mutagenesis experiments probing the role of six variant residues of Nanog on its DNA binding function establish their role in affecting binding affinity but not binding specificity. Together, the structural and functional evidence establish Nanog as a distant member of a Q50-type HD despite having considerable variation at the sequence level.

La Thangue, N. B., B. Thimmappaya, et al. "The embryonal carcinoma stem cell Ela-like activity involves a differentiation-regulated transcription factor." Nucleic Acids Res. 1990 May 25;18(10):2929-38.

Murine F9 embryonal carcinoma (EC) stem cells have an Ela-like transcription activity that is undetectable in F9 cells differentiated to parietal endoderm-like cells (F9-PE). The Ela-inducible adenovirus E2A promoter has been used to further define this activity and we show that in vitro the transcription of this promoter in F9 EC and F9-PE cell extracts reflects the regulation in vivo. In EC cell extracts several trans-acting protein factors bind to E2A promoter sequences. A distal domain containing a CRE binds proteins present in F9 EC, F9-PE and Hela cell extracts. Sequences between -71 and -50 define a multiplicity of binding activities, termed DRTF1, all of which are down regulated as EC stem cells differentiate. DRTF2, a low abundance, regulated binding activity requires DNA sequences that overlap those required by DRTF1. The CRE and the DRTF1 binding site compete for transcription in vitro, indicating that in EC cell extracts the respective

proteins function as positively acting, binding site dependent transcription factors. Comparison of DRTF1 with the previously defined HeLa cell factor E2F, induced during adenovirus infection, indicates that although both factors recognise the same region of the promoter there are clear differences between them. These data indicate that multiple factors are necessary for efficient transcription of the E2A promoter in F9 EC cell extracts and suggest that DRTF1 is responsible, at least in part, for the developmental regulation of the cellular Ela-like activity.

Lacroix, M., J. Caramel, et al. "Transcription factor E4F1 is essential for epidermal stem cell maintenance and skin homeostasis." Proc Natl Acad Sci U S A. 2010 Dec 7;107(49):21076-81. doi: 10.1073/pnas.1010167107. Epub 2010 Nov 18.

A growing body of evidence suggests that the multifunctional protein E4F1 is involved in signaling pathways that play essential roles during normal development and tumorigenesis. We generated E4F1 conditional knockout mice to address E4F1 functions in vivo in newborn and adult skin. E4F1 inactivation in the entire skin or in the basal compartment of the epidermis induces skin homeostasis defects, as evidenced by transient hyperplasia in the interfollicular epithelium and alteration of keratinocyte differentiation, followed by loss of cellularity in the epidermis and severe skin ulcerations. E4F1 depletion alters clonogenic activity of epidermal stem cells (ESCs) ex vivo and ends in exhaustion of the ESC pool in vivo, indicating that the lesions observed in the E4F1 mutant skin result, at least in part, from cell-autonomous alterations in ESC maintenance. The clonogenic potential of E4F1 KO ESCs is rescued by Bmi1 overexpression or by Ink4a/Arf or p53 depletion. Skin phenotype of E4F1 KO mice is also delayed in animals with Ink4a/Arf and E4F1 compound gene deficiencies. Our data identify a regulatory axis essential for ESC-dependent skin homeostasis implicating E4F1 and the Bmi1-Arf-p53 pathway.

Laga, A. C., C. Y. Lai, et al. "Expression of the embryonic stem cell transcription factor SOX2 in human skin: relevance to melanocyte and merkel cell biology." Am J Pathol. 2010 Feb;176(2):903-13. doi: 10.2353/ajpath.2010.090495. Epub 2009 Dec 30.

SOX2 is a gene located on chromosome 3q26.33 that encodes a transcription factor important to maintenance of embryonic neural crest stem cell pluripotency. We have identified rare SOX2-immunoreactive cells in normal human skin at or near the established stem cell niches. Three subsets of SOX2-positive cells were defined in these regions: those expressing only SOX2 and those that co-expressed SOX2 and either CK20 or microphthalmia-associated transcription factor, which are consistent with dichotomous differentiation of SOX2-expressing precursors along neuroendocrine (Merkel cell) or melanocytic lines, respectively. Examination of Merkel cell carcinomas confirmed nuclear SOX2 expression in this tumor type. In human patient melanoma, strong nuclear expression of SOX2 was noted in a subset of tumors, and the ability to detect SOX2 in lesional cells significantly correlated with primary tumor thickness in a survey cohort. To assess the potential role of SOX2 in melanoma growth, an in vivo tumorigenesis assay was used. Whereas SOX2 knockdown failed to influence proliferation of cultured melanoma cells in vitro, tumor xenografts generated with the SOX2-knockdown cell line showed significant decrease in mean tumor volume as compared with controls. In aggregate, these findings suggest that SOX2 is a novel biomarker for subpopulations of normal skin cells that reside in established stem cell niches and that might relate to Merkel cell and melanocyte ontogeny and tumorigenesis.

Loza-Coll, M. A., T. D. Southall, et al. "Regulation of Drosophila intestinal stem cell maintenance and differentiation by the transcription factor Escargot." EMBO J. 2014 Dec 17;33(24):2983-96. doi: 10.15252/embj.201489050. Epub 2014 Nov 27.

Tissue stem cells divide to self-renew and generate differentiated cells to maintain homeostasis. Although influenced by both intrinsic and extrinsic factors, the genetic mechanisms coordinating the decision between self-renewal and initiation of differentiation remain poorly understood. The escargot (esg) gene encodes a transcription factor that is expressed in stem cells in multiple tissues in Drosophila melanogaster, including intestinal stem cells (ISCs). Here, we demonstrate that Esg plays a pivotal role in intestinal homeostasis, maintaining the stem cell pool while influencing fate decisions through modulation of Notch activity. Loss of esg induced ISC differentiation, a decline in Notch activity in daughter enteroblasts (EB), and an increase in differentiated enteroendocrine (EE) cells. Amun, an inhibitor of Notch in other systems, was identified as a target of Esg in the intestine. Decreased expression of esg resulted in upregulation of Amun, while downregulation of Amun rescued the ectopic EE cell phenotype resulting from loss of esg. Thus, our findings provide a framework for further comparative studies addressing the conserved roles of Snail factors in coordinating self-renewal and differentiation of stem cells across tissues and species.

Maddox, J., A. Shakya, et al. "Transcription factor Oct1 is a somatic and cancer stem cell determinant." PLoS Genet. 2012;8(11):e1003048. doi: 10.1371/journal.pgen.1003048. Epub 2012 Nov 8.

Defining master transcription factors governing somatic and cancer stem cell identity is an important goal. Here we show that the Oct4 paralog Oct1, a transcription factor implicated in stress responses, metabolic control, and poised transcription states, regulates normal and pathologic stem cell function. Oct1(HI) cells in the colon and small intestine co-express known stem cell markers. In primary malignant tissue, high Oct1 protein but not mRNA levels strongly correlate with the frequency of CD24(LO)CD44(HI) cancer-initiating cells. Reducing Oct1 expression via RNAi reduces the proportion of ALDH(HI) and dye efflux(HI) cells, and increasing Oct1 increases the proportion of ALDH(HI) cells. Normal ALDH(HI) cells harbor elevated Oct1 protein but not mRNA levels. Functionally, we show that Oct1 promotes tumor engraftment frequency and promotes hematopoietic stem cell engraftment potential in competitive and serial transplants. In addition to previously described Oct1 transcriptional targets, we identify four Oct1 targets associated with the stem cell phenotype. Cumulatively, the data indicate that Oct1 regulates normal and cancer stem cell function.

Martyre, M. C. and M. C. Le Bousse-Kerdiles "Stem cell dysregulation in myelofibrosis with myeloid metaplasia: current data on growth factor and transcription factor involvement." Semin Oncol. 2005 Aug;32(4):373-9.

Myelofibrosis with myeloid metaplasia (MMM), the rarest Philadelphia chromosome-negative chronic myeloproliferative disorder (MPD), is characterized by extramedullary hematopoiesis and myelofibrosis. The primary molecular defect leading to the clonal amplification of the hematopoietic progenitors is still unknown. In this review, we will focus on current data in favor of a pivotal role for hematopoietic and fibrogenic growth factors and of transcription factors in the dysregulation of the hematopoietic compartment. These data shed novel insight into the genesis of MMM myeloproliferation and led us to propose a model, integrating alterations in the expression and function of nuclear regulatory factors and in the hierarchical and complex network of interactions between hematopoietic cells and stroma in the pathogenetic mechanisms of the disease.

Mendez-Gomez, H. R., E. Vergano-Vera, et al. "The T-box brain 1 (Tbr1) transcription factor inhibits astrocyte formation in the olfactory bulb and regulates neural stem cell fate." Mol Cell Neurosci. 2011 Jan;46(1):108-21. doi: 10.1016/j.mcn.2010.08.011. Epub 2010 Aug 31.

The T-box brain 1 (Tbr1) gene encodes a transcription factor necessary for the maintenance and/or differentiation of glutamatergic cells in the olfactory bulb (OB) and cortex, although its precise function in the development of glutamatergic neurons is not known. Furthermore, Tbr1 has not been reported to regulate the formation of glial cells. We show that Tbr1 is expressed during the initial stages in the generation of glutamatergic mitral neurons from dividing progenitors in the E12.5 mouse OB. Retroviral-mediated overexpression of Tbr1 in cultured embryonic and adult OB stem cells (OBSC) produces a marked increase in the number of TuJ1(+) neurons (including VGLUT1(+) glutamatergic and GABA(+) neurons) and O4(+) oligodendrocytes. Moreover, transduction of Tbr1 inhibits the production of GFAP(+) astrocytes from both cultured OBSC and dividing progenitor cells in vivo. These results show that the expression of Tbr1 in neural stem and progenitor cells prevents them from following an astrocyte fate during OB development. Our findings suggest that the transduction of Tbr1 into neural stem cells could be useful to increase the production of neurons and oligodendrocytes in studies of neuroregeneration.

Merchant, A. A., A. Singh, et al. "The redox-sensitive transcription factor Nrf2 regulates murine hematopoietic stem cell survival independently of ROS levels." Blood. 2011 Dec 15;118(25):6572-9. doi: 10.1182/blood-2011-05-355362. Epub 2011 Oct 28.

Several studies have found that high levels of reactive oxidative species (ROS) are associated with stem cell dysfunction. In the present study, we investigated the role of nuclear factor erythroid-2-related factor 2 (Nrf2), a master regulator of the antioxidant response, and found that it is required for hematopoietic stem progenitor cell (HSPC) survival and myeloid development. Although the loss of Nrf2 leads to increased ROS in most tissues, basal ROS levels in Nrf2-deficient (Nrf2(-/-)) BM were not elevated compared with wild-type. Nrf2(-/-) HSPCs, however, had increased rates of spontaneous apoptosis and showed decreased survival when exposed to oxidative stress. Nrf2(-/-) BM demonstrated defective stem cell function, as evidenced by reduced chimerism after transplantation that was not rescued by treatment with the antioxidant N-acetyl cysteine. Gene-expression profiling revealed that the levels of prosurvival cytokines were reduced in Nrf2(-/-) HSPCs. Treatment with the cytokine G-CSF improved HSPC survival after exposure to oxidative stress and rescued the transplantation defect in Nrf2(-/-) cells

despite increases in ROS induced by cytokine signaling. These findings demonstrate a critical role for Nrf2 in hematopoiesis and stem cell survival that is independent of ROS levels.

Millane, R. C., J. Kanska, et al. "Induced stem cell neoplasia in a cnidarian by ectopic expression of a POU domain transcription factor." Development. 2011 Jun;138(12):2429-39. doi: 10.1242/dev.064931.

The evolutionary origin of stem cell pluripotency is an unresolved question. In mammals, pluripotency is limited to early embryos and is induced and maintained by a small number of key transcription factors, of which the POU domain protein Oct4 is considered central. Clonal invertebrates, by contrast, possess pluripotent stem cells throughout their life, but the molecular mechanisms that control their pluripotency are poorly defined. To address this problem, we analyzed the expression pattern and function of Polynem (Pln), a POU domain gene from the marine cnidarian Hydractinia echinata. We show that Pln is expressed in the embryo and adult stem cells of the animal and that ectopic expression in epithelial cells induces stem cell neoplasms and loss of epithelial tissue. Neoplasm cells downregulated the transgene but expressed the endogenous Pln gene and also Nanos, Vasa, Piwi and Myc, which are all known cnidarian stem cell markers. Retinoic acid treatment caused downregulation of Pln and the differentiation of neoplasm cells to neurosensory and epithelial cells. Pln downregulation by RNAi led to differentiation. Collectively, our results suggest an ancient role of POU proteins as key regulators of animal stem cells.

Oda, M., Y. Kumaki, et al. "DNA methylation restricts lineage-specific functions of transcription factor Gata4 during embryonic stem cell differentiation." PLoS Genet. 2013 Jun;9(6):e1003574. doi: 10.1371/journal.pgen.1003574. Epub 2013 Jun 27.

DNA methylation changes dynamically during development and is essential for embryogenesis in mammals. However, how DNA methylation affects developmental gene expression and cell differentiation remains elusive. During embryogenesis, many key transcription factors are used repeatedly, triggering different outcomes depending on the cell type and developmental stage. Here, we report that DNA methylation modulates transcription-factor output in the context of cell differentiation. Using a drug-inducible Gata4 system and a mouse embryonic stem (ES) cell model of mesoderm differentiation, we examined the cellular response to Gata4 in ES and mesoderm cells. The activation of Gata4 in ES cells is known to drive their differentiation to endoderm. We show that the differentiation of wild-type ES cells into mesoderm blocks their Gata4-induced endoderm differentiation, while mesoderm cells derived from ES cells that are deficient in the DNA methyltransferases Dnmt3a and Dnmt3b can retain their response to Gata4, allowing lineage conversion from mesoderm cells to endoderm. Transcriptome analysis of the cells' response to Gata4 over time revealed groups of endoderm and mesoderm developmental genes whose expression was induced by Gata4 only when DNA methylation was lost, suggesting that DNA methylation restricts the ability of these genes to respond to Gata4, rather than controlling their transcription per se. Gata4-binding-site profiles and DNA methylation analyses suggested that DNA methylation modulates the Gata4 response through diverse mechanisms. Our data indicate that epigenetic regulation by DNA methylation functions as a heritable safeguard to prevent transcription factors from activating inappropriate downstream genes, thereby contributing to the restriction of the differentiation potential of somatic cells.

Orlov, Y., H. Xu, et al. "Computer and statistical analysis of transcription factor binding and chromatin modifications by ChIP-seq data in embryonic stem cell." J Integr Bioinform. 2012 Sep 18;9(2):211. doi: 10.2390/biecoll-jib-2012-211.

Advances in high throughput sequencing technology have enabled the identification of transcription factor (TF) binding sites in genome scale. TF binding studies are important for medical applications and stem cell research. Somatic cells can be reprogrammed to a pluripotent state by the combined introduction of factors such as Oct4, Sox2, c-Myc, Klf4. These reprogrammed cells share many characteristics with embryonic stem cells (ESCs) and are known as induced pluripotent stem cells (iPSCs). The signaling requirements for maintenance of human and murine embryonic stem cells (ESCs) differ considerably. Genome wide ChIP-seq TF binding maps in mouse stem cells include Oct4, Sox2, Nanog, Tbx3, Smad2 as well as group of other factors. ChIP-seq allows study of new candidate transcription factors for reprogramming. It was shown that Nr5a2 could replace Oct4 for reprogramming. Epigenetic modifications play important role in regulation of gene expression adding additional complexity to transcription network functioning. We have studied associations between different histone modification using published data together with RNA Pol II sites. We found strong associations between activation marks and TF binding sites and present it qualitatively. To meet issues of statistical analysis of genome ChIP-sequencing maps we developed computer program to filter out noise signals and find significant association between binding site affinity and number of sequence

reads. The data provide new insights into the function of chromatin organization and regulation in stem cells.

Panman, L., E. Andersson, et al. "Transcription factor-induced lineage selection of stem-cell-derived neural progenitor cells." Cell Stem Cell. 2011 Jun 3;8(6):663-75. doi: 10.1016/j.stem.2011.04.001.

The generation of specific types of neurons from stem cells offers important opportunities in regenerative medicine. However, future applications and proper verification of cell identities will require stringent ways to generate homogeneous neuronal cultures. Here we show that transcription factors like Lmx1a, Phox2b, Nkx2.2, and Olig2 can induce desired neuronal lineages from most expressing neural progenitor cells by a mechanism resembling developmental binary cell-fate switching. Such efficient selection of cell fate resulted in remarkable cellular enrichment that enabled global gene-expression validation of generated neurons and identification of previously unrecognized features in the studied cell lineages. Several sources of stem cells have a limited competence to differentiate into specific neuronal cell types; e.g., dopamine neurons. However, we show that the combination of factors that normally promote either regional or dedicated neuronal specification can overcome limitations in cellular competence and also promote efficient reprogramming in more remote neural contexts, including human neural progenitor cells.

Parisi, S., L. Cozzuto, et al. "Direct targets of Klf5 transcription factor contribute to the maintenance of mouse embryonic stem cell undifferentiated state." BMC Biol. 2010 Sep 27;8:128. doi: 10.1186/1741-7007-8-128.

BACKGROUND: A growing body of evidence has shown that Kruppel-like transcription factors play a crucial role in maintaining embryonic stem cell (ESC) pluripotency and in governing ESC fate decisions. Kruppel-like factor 5 (Klf5) appears to play a critical role in these processes, but detailed knowledge of the molecular mechanisms of this function is still not completely addressed. RESULTS: By combining genome-wide chromatin immunoprecipitation and microarray analysis, we have identified 161 putative primary targets of Klf5 in ESCs. We address three main points: (1) the relevance of the pathways governed by Klf5, demonstrating that suppression or constitutive expression of single Klf5 targets robustly affect the ESC undifferentiated phenotype; (2) the specificity of Klf5 compared to factors belonging to the same family, demonstrating that many Klf5 targets are not regulated by Klf2 and Klf4; and (3) the specificity of Klf5 function in ESCs, demonstrated by the significant differences between Klf5 targets in ESCs compared to adult cells, such as keratinocytes. CONCLUSIONS: Taken together, these results, through the definition of a detailed list of Klf5 transcriptional targets in mouse ESCs, support the important and specific functional role of Klf5 in the maintenance of the undifferentiated ESC phenotype. See: http://www.biomedcental.com/1741-7007/8/125.

Perez-Losada, J., M. Sanchez-Martin, et al. "Zinc-finger transcription factor Slug contributes to the function of the stem cell factor c-kit signaling pathway." Blood. 2002 Aug 15;100(4):1274-86.

The stem cell factor c-kit signaling pathway (SCF/c-kit) has been previously implicated in normal hematopoiesis, melanogenesis, and gametogenesis through the formation and migration of c-kit(+) cells. These biologic functions are also determinants in epithelial-mesenchymal transitions during embryonic development governed by the Snail family of transcription factors. Here we show that the activation of c-kit by SCF specifically induces the expression of Slug, a Snail family member. Slug mutant mice have a cell-intrinsic defect with pigment deficiency, gonadal defect, and impairment of hematopoiesis. Kit(+) cells derived from Slug mutant mice exhibit migratory defects similar to those of c-kit(+) cells derived from SCF and c-kit mutant mice. Endogenous Slug is expressed in migratory c-kit(+) cells purified from control mice but is not present in c-kit(+) cells derived from SCF mutant mice or in bone marrow cells from W/W(v) mice, though Slug is present in spleen c-kit(+) cells of W/W(v) (mutants expressing c-kit with reduced surface expression and activity). SCF-induced migration was affected in primary c-kit(+) cells purified from Slug-/- mice, providing evidence for a role of Slug in the acquisition of c-kit(+) cells with ability to migrate. Slug may thus be considered a molecular target that contributes to the biologic specificity to the SCF/c-kit signaling pathway, opening up new avenues for stem cell mobilization.

Ragu, C., G. Elain, et al. "The transcription factor Srf regulates hematopoietic stem cell adhesion." Blood. 2010 Nov 25;116(22):4464-73. doi: 10.1182/blood-2009-11-251587. Epub 2010 Aug 13.

Adhesion properties of hematopoietic stem cells (HSCs) in the bone marrow (BM) niches control their migration and affect their cell-cycle dynamics. The serum response factor (Srf) regulates growth factor-inducible genes and genes controlling cytoskeleton structures involved in cell spreading, adhesion, and migration. We identified a role for Srf in HSC adhesion and steady-state hematopoiesis. Conditional deletion of Srf in BM cells resulted in a 3-fold expansion of the long- and short-term HSCs and multipotent progenitors (MPPs), which occurs without

long-term modification of cell-cycle dynamics. Early differentiation steps to myeloid and lymphoid lineages were normal, but Srf loss results in alterations in mature-cell production and severe thrombocytopenia. Srf-null BM cells also displayed compromised engraftment properties in transplantation assays. Gene expression analysis identified Srf target genes expressed in HSCs, including a network of genes associated with cell migration and adhesion. Srf-null stem cells and MPPs displayed impair expression of the integrin network and decreased adherence in vitro. In addition, Srf-null mice showed increase numbers of circulating stem and progenitor cells, which likely reflect their reduced retention in the BM. Altogether, our results demonstrate that Srf is an essential regulator of stem cells and MPP adhesion, and suggest that Srf acts mainly through cell-matrix interactions and integrin signaling.

Reinisch, C. M., M. Mildner, et al. "Embryonic stem cell factors undifferentiated transcription factor-1 (UFT-1) and reduced expression protein-1 (REX-1) are widely expressed in human skin and may be involved in cutaneous differentiation but not in stem cell fate determination." Int J Exp Pathol. 2011 Oct;92(5):326-32. doi: 10.1111/j.1365-2613.2011.00769.x. Epub 2011 Mar 29.

Undifferentiated transcription factor-1 (UTF-1) and reduced expression protein-1 (REX-1) are used as markers for the undifferentiated state of pluripotent stem cells. Because no highly specific cytochemical marker for epidermal stem cells has yet been identified, we investigated the expression pattern of these markers in human epidermis and skin tumours by immunohistochemistry and in keratinocyte cell cultures. Both presumed stem cell markers were widely expressed in the epidermis and skin appendages. Distinct expression was found in the matrix cells of the hair shaft. Differentiation of human primary keratinocytes (KC) in vitro strongly downregulated UTF-1 and REX-1 expression. In addition, REX-1 was upregulated in squamous cell carcinomas, indicating a possible role of this transcription factor in malignant tumour formation. Our data point to a role for these proteins not only in maintaining KC stem cell populations, but also in proliferation and differentiation of matrix cells of the shaft and also suprabasal KC.

Rheinbay, E., M. L. Suva, et al. "An aberrant transcription factor network essential for Wnt signaling and stem cell maintenance in glioblastoma." Cell Rep. 2013 May 30;3(5):1567-79. doi: 10.1016/j.celrep.2013.04.021. Epub 2013 May 23.

Glioblastoma (GBM) is thought to be driven by a subpopulation of cancer stem cells (CSCs) that self-renew and recapitulate tumor heterogeneity yet remain poorly understood. Here, we present a comparative analysis of chromatin state in GBM CSCs that reveals widespread activation of genes normally held in check by Polycomb repressors. These activated targets include a large set of developmental transcription factors (TFs) whose coordinated activation is unique to the CSCs. We demonstrate that a critical factor in the set, ASCL1, activates Wnt signaling by repressing the negative regulator DKK1. We show that ASCL1 is essential for the maintenance and in vivo tumorigenicity of GBM CSCs. Genome-wide binding profiles for ASCL1 and the Wnt effector LEF-1 provide mechanistic insight and suggest widespread interactions between the TF module and the signaling pathway. Our findings demonstrate regulatory connections among ASCL1, Wnt signaling, and collaborating TFs that are essential for the maintenance and tumorigenicity of GBM CSCs.

Rice, K. L., D. J. Izon, et al. "Overexpression of stem cell associated ALDH1A1, a target of the leukemogenic transcription factor TLX1/HOX11, inhibits lymphopoiesis and promotes myelopoiesis in murine hematopoietic progenitors." Leuk Res. 2008 Jun;32(6):873-83. Epub 2007 Dec 21.

TLX1/HOX11 is an oncogenic transcription factor in human T-cell leukemia, however, the molecular basis for its transforming activity has remained elusive. The ALDH1A1 gene, whose product participates in retinoic acid synthesis, was previously identified as a TLX1-responsive gene. Here, we confirm regulation of ALDH1A1 transcription by TLX1 and show that ALDH1A1 can profoundly perturb murine hematopoiesis by promoting myeloid differentiation at the expense of lymphopoiesis. Together, these data demonstrate that ALDH1A1 plays a key role in normal hematopoiesis, and confirm ALDH1A1 as a TLX1 transcriptional target that may contribute to the ability of this homeoprotein to alter cell fate and induce tumor growth.

Sansom, S. N., D. S. Griffiths, et al. "The level of the transcription factor Pax6 is essential for controlling the balance between neural stem cell self-renewal and neurogenesis." PLoS Genet. 2009 Jun;5(6):e1000511. doi: 10.1371/journal.pgen.1000511. Epub 2009 Jun 12.

Neural stem cell self-renewal, neurogenesis, and cell fate determination are processes that control the generation of specific classes of neurons at the correct place and time. The transcription factor Pax6 is essential for neural stem cell proliferation, multipotency, and neurogenesis in many regions of the central nervous system, including the cerebral cortex.

We used Pax6 as an entry point to define the cellular networks controlling neural stem cell self-renewal and neurogenesis in stem cells of the developing mouse cerebral cortex. We identified the genomic binding locations of Pax6 in neocortical stem cells during normal development and ascertained the functional significance of genes that we found to be regulated by Pax6, finding that Pax6 positively and directly regulates cohorts of genes that promote neural stem cell self-renewal, basal progenitor cell genesis, and neurogenesis. Notably, we defined a core network regulating neocortical stem cell decision-making in which Pax6 interacts with three other regulators of neurogenesis, Neurog2, Ascl1, and Hes1. Analyses of the biological function of Pax6 in neural stem cells through phenotypic analyses of Pax6 gain- and loss-of-function mutant cortices demonstrated that the Pax6-regulated networks operating in neural stem cells are highly dosage sensitive. Increasing Pax6 levels drives the system towards neurogenesis and basal progenitor cell genesis by increasing expression of a cohort of basal progenitor cell determinants, including the key transcription factor Eomes/Tbr2, and thus towards neurogenesis at the expense of self-renewal. Removing Pax6 reduces cortical stem cell self-renewal by decreasing expression of key cell cycle regulators, resulting in excess early neurogenesis. We find that the relative levels of Pax6, Hes1, and Neurog2 are key determinants of a dynamic network that controls whether neural stem cells self-renew, generate cortical neurons, or generate basal progenitor cells, a mechanism that has marked parallels with the transcriptional control of embryonic stem cell self-renewal.

Santagata, S., K. L. Ligon, et al. "Embryonic stem cell transcription factor signatures in the diagnosis of primary and metastatic germ cell tumors." Am J Surg Pathol. 2007 Jun;31(6):836-45.

The core embryonic stem cell transcription factors (TFs) OCT3/4 (OCT4), NANOG, and SOX2 have shared as well as nonoverlapping roles in stem cell growth and differentiation. These same TFs are also expressed in various types of human germ cell tumors (GCTs), implicating them in regulation of tumor growth and differentiation. Although NANOG and OCT3/4 are sensitive and specific markers for seminoma and embryonal carcinoma, neither factor aids in the clinically important distinction of seminomatous from nonseminomatous tumors. In contrast, expression profiling data suggest that SOX2 may help with this distinction. To determine if a panel of embryonic stem cell TFs (NANOG, OCT3/4, and SOX2) can facilitate the identification and distinction of seminomatous from nonseminomatous GCTs, we evaluated their expression by immunohistochemistry in primary testicular (n=41) and metastatic retroperitoneal (n=43) GCTs. Our results confirm NANOG and OCT3/4 as sensitive and specific markers for primary seminoma and embryonal carcinoma and demonstrate the novel finding that NANOG is a marker for metastatic GCTs. In addition, SOX2 is expressed in embryonal carcinoma but not pure seminoma and is therefore a useful diagnostic marker for distinguishing seminomatous and nonseminomatous GCTs. In summary, we find that the embryonic stem cell TF signature of seminoma is NANOG+, OCT3/4+, and SOX2-, whereas embryonal carcinoma is NANOG+, OCT3/4+, and SOX2+, and expect these immunohistochemical profiles will facilitate the diagnosis of both primary and metastatic GCTs.

Sarlak, G. and B. Vincent "The Roles of the Stem Cell-Controlling Sox2 Transcription Factor: from Neuroectoderm Development to Alzheimer's Disease?" Mol Neurobiol. 2015 Feb 18.

Sox2 is a component of the core transcriptional regulatory network which maintains the totipotency of the cells during embryonic preimplantation period, the pluripotency of embryonic stem cells, and the multipotency of neural stem cells. This maintenance is controlled by internal loops between Sox2 and other transcription factors of the core such as Oct4, Nanog, Dax1, and Klf4, downstream proteins of extracellular ligands, epigenetic modifiers, and miRNAs. As Sox2 plays an important role in the balance between stem cells maintenance and commitment to differentiated lineages throughout the lifetime, it is supposed that Sox2 could regulate stem cells aging processes. In this review, we provide an update concerning the involvement of Sox2 in neurogenesis during normal aging and discuss its possible role in Alzheimer's disease.

Sarrazin, S. and M. Sieweke "Integration of cytokine and transcription factor signals in hematopoietic stem cell commitment." Semin Immunol. 2011 Oct;23(5):326-34. doi: 10.1016/j.smim.2011.08.011. Epub 2011 Sep 19.

In the predominant model of hematopoietic stem cell differentiation lineage commitment is thought to be initiated by stochastic variation in the balance of lineage determining transcription factors, whereas cytokines have been seen in a purely permissive role of stimulating selective survival and proliferation of the down stream progeny. Recent observations, however, indicate that cytokines can also directly instruct cell fate change in uncommitted stem and progenitor cells by activating lineage determining transcription factors. We review the historic and recent

evidence for instructive cytokine signaling and propose a model that integrates cytokine signaling and transcription factor activity in the initial decision making process, where the sensitivity to external instructive signals can be modulated by internal threshold setters. In contrast to a rigid stochastic explanation of lineage commitment this view allows for receptiveness of the hematopoietic stem cell to its environment and exposes lineage commitment as dependent on both instructive signals and cell intrinsically controlled sensitivity to external cues.

Schmitteckert, S., C. Ziegler, et al. "Transcription factor lbx1 expression in mouse embryonic stem cell-derived phenotypes." Stem Cells Int. 2011;2011:130970. doi: 10.4061/2011/130970. Epub 2011 Sep 15.

Transcription factor Lbx1 is known to play a role in the migration of muscle progenitor cells in limb buds and also in neuronal determination processes. In addition, involvement of Lbx1 in cardiac neural crest-related cardiogenesis was postulated. Here, we used mouse embryonic stem (ES) cells which have the capacity to develop into cells of all three primary germ layers. During in vitro differentiation, ES cells recapitulate cellular developmental processes and gene expression patterns of early embryogenesis. Transcript analysis revealed a significant upregulation of Lbx1 at the progenitor cell stage. Immunofluorescence staining confirmed the expression of Lbx1 in skeletal muscle cell progenitors and GABAergic neurons. To verify the presence of Lbx1 in cardiac cells, triple immunocytochemistry of ES cell-derived cardiomyocytes and a quantification assay were performed at different developmental stages. Colabeling of Lbx1 and cardiac specific markers troponin T, alpha-actinin, GATA4, and Nkx2.5 suggested a potential role in early myocardial development.

Siu, M. K., E. S. Wong, et al. "Stem cell transcription factor NANOG controls cell migration and invasion via dysregulation of E-cadherin and FoxJ1 and contributes to adverse clinical outcome in ovarian cancers." Oncogene. 2013 Jul 25;32(30):3500-9. doi: 10.1038/onc.2012.363. Epub 2012 Sep 3.

Ovarian cancer is the most lethal of all gynecological malignancies, and the identification of novel prognostic and therapeutic targets for ovarian cancer is crucial. It is believed that only a small subset of cancer cells are endowed with stem cell properties, which are responsible for tumor growth, metastatic progression and recurrence. NANOG is one of the key transcription factors essential for maintaining self-renewal and pluripotency in stem cells. This study investigated the role of NANOG in ovarian carcinogenesis and showed overexpression of NANOG mRNA and protein in the nucleus of ovarian cancers compared with benign ovarian lesions. Increased nuclear NANOG expression was significantly associated with high-grade cancers, serous histological subtypes, reduced chemosensitivity, and poor overall and disease-free survival. Further analysis showed NANOG is an independent prognostic factor for overall and disease-free survival. Moreover, NANOG was highly expressed in ovarian cancer cell lines with metastasis-associated property and in clinical samples of metastatic foci. Stable knockdown of NANOG impeded ovarian cancer cell proliferation, migration and invasion, which was accompanied by an increase in mRNA expression of E-cadherin, caveolin-1, FOXO1, FOXO3a, FOXJ1 and FOXB1. Conversely, ectopic NANOG overexpression enhanced ovarian cancer cell migration and invasion along with decreased E-cadherin, caveolin-1, FOXO1, FOXO3a, FOXJ1 and FOXB1 mRNA expression. Importantly, we found Nanog-mediated cell migration and invasion involved its regulation of E-cadherin and FOXJ1. This is the first report revealing the association between NANOG expression and clinical outcome of patients with ovarian cancers, suggesting NANOG to be a potential prognostic marker and therapeutic molecular target in ovarian cancer.

Slyper, M., A. Shahar, et al. "Control of breast cancer growth and initiation by the stem cell-associated transcription factor TCF3." Cancer Res. 2012 Nov 1;72(21):5613-24. doi: 10.1158/0008-5472.CAN-12-0119. Epub 2012 Oct 22.

Regulatory factors controlling stem cell identity and self-renewal are often active in aggressive cancers and are thought to promote their growth and progression. TCF3 (also known as TCF7L1) is a member of the TCF/LEF transcription factor family that is central in regulating epidermal and embryonic stem cell identity. We found that TCF3 is highly expressed in poorly differentiated human breast cancers, preferentially of the basal-like subtype. This suggested that TCF3 is involved in the regulation of breast cancer cell differentiation state and tumorigenicity. Silencing of TCF3 dramatically decreased the ability of breast cancer cells to initiate tumor formation, and led to decreased tumor growth rates. In culture, TCF3 promotes the sphere formation capacity of breast cancer cells and their self-renewal. We found that in contrast to ES cells, where it represses Wnt-pathway target genes, TCF3 promotes the expression of a subset of Wnt-responsive genes in breast cancer cells while repressing another distinct target subset. In the normal mouse mammary gland, Tcf3 is highly expressed in terminal end buds,

structures that lead duct development. Primary mammary cells are dependent on Tcf3 for mammosphere formation, and its overexpression in the developing gland disrupts ductal growth. Our results identify TCF3 as a central regulator of tumor growth and initiation, and a novel link between stem cells and cancer.

Sott, C., B. Dorner, et al. "Transforming growth factor-beta relieves stem cell factor-induced proliferation of myelogenous leukemia cells through inhibition of binding of the transcription factor NF-jun." Blood. 1994 Sep 15;84(6):1950-9.

Transforming growth factor-beta (TGF-beta) is a potent inhibitor of growth factor-stimulated hematopoiesis in normal and leukemic conditions. Using the factor-dependent myelogenous leukemia cell lines GF-D8 and Mo7, we show that TGF-beta interferes with stem cell factor (SCF)-induced proliferation by downmodulating c-jun gene expression. The ability of SCF to induce accumulation of c-jun transcripts was abolished when TGF-beta was present in culture. Transcriptional nuclear run-on assays indicated that TGF-beta relieved the capacity of SCF to enhance the transcriptional rate of the c-jun gene. Deletion analysis of the c-jun promoter furthermore showed that SCF was activating the c-jun promoter via the NF-jun transcription factor. Gel mobility shift assays showed that SCF increased the binding activity of NF-jun to its recognition site within 5 to 15 minutes. Binding activity peaked at 1 hour after exposure to SCF and declined to starting levels within 4 hours. The ability of SCF to enhance NF-jun binding activity was also dose-dependent in the range of 5 to 100 ng/mL. Exposure of GF-D8 and Mo7 cells to TGF-beta before the addition of SCF antagonized SCF-induced NF-jun binding. Moreover, whereas SCF was capable of functionally activating a heterologous promoter containing the NF-jun binding site, pretreatment of GF-D8 cells with TGF-beta abolished transcriptional activation of this heterologous promoter. These findings indicate that SCF-mediated activation of c-jun via NF-jun is crucial for the SCF-inducible proliferative response and is inhibited by TGF-beta. In additional experiments, the antisense technique was used. Treatment of GF-D8 and Mo7 cells with an antisense oligodeoxyribonucleotide directed against the translation initiation site of c-jun abolished the capacity of SCF to induce a proliferative response, whereas sense and nonsense oligomers had no effect. Taken together, our data indicate that the counteracting modulation of the binding activity of NF-jun by SCF and TGF-beta regulates the expression of the c-jun gene and thereby the proliferative state of the GF-D8 and Mo7 target.

Stock, K., L. Nolden, et al. "Transcription factor-based modulation of neural stem cell differentiation using direct protein transduction." Cell Mol Life Sci. 2010 Jul;67(14):2439-49. doi: 10.1007/s00018-010-0347-1. Epub 2010 Mar 30.

In contrast to conventional gene transfer strategies, the direct introduction of recombinant proteins into cells bypasses the risk of insertional mutagenesis and offers an alternative to genetic intervention. Here, we explore whether protein transduction of the gliogenic transcription factor Nkx2.2 can be used to promote oligodendroglial differentiation of mouse embryonic stem cell (ESC)-derived neural stem cells (NSC). To that end, a recombinant cell-permeant form of Nkx2.2 protein was generated. Exposure of ESC-derived NSC to the recombinant protein and initiation of differentiation resulted in a two-fold increase in the number of oligodendrocytes. Furthermore, Nkx2.2-transduced cells exhibited a more mature oligodendroglial phenotype. Comparative viral gene transfer studies showed that the biological effect of Nkx2.2 protein transduction is comparable to that obtained by lentiviral transduction. The results of this proof-of-concept study depict direct intracellular delivery of transcription factors as alternative modality to control lineage differentiation in NSC cultures without genetic modification.

Tada, Y., Y. Yamaguchi, et al. "The stem cell transcription factor ZFP57 induces IGF2 expression to promote anchorage-independent growth in cancer cells." Oncogene. 2015 Feb 5;34(6):752-60. doi: 10.1038/onc.2013.599. Epub 2014 Jan 27.

Several common biological properties between cancer cells and embryonic stem (ES) cells suggest the possibility that some genes expressed in ES cells might have important roles in cancer cell growth. The transcription factor ZFP57 is expressed in self-renewing ES cells and its expression level decreases during ES cell differentiation. This study showed that ZFP57 is involved in the anchorage-independent growth of human fibrosarcoma HT1080 cells in soft agar. ZFP57 overexpression enhanced, whereas knockdown suppressed, HT1080 tumor formation in nude mice. Furthermore, ZFP57 regulates the expression of insulin-like growth factor 2 (IGF2), which has a critical role in ZFP57-induced anchorage-independent growth. ZFP57 also promotes anchorage-independent growth in ES cells and immortal fibroblasts. Finally, immunohistochemical analysis revealed that ZFP57 is overexpressed in human cancer clinical specimens. Taken together, these results suggest that the ES-specific transcription factor ZFP57 is a novel oncogene.

van der Flier, L. G., M. E. van Gijn, et al. "Transcription factor achaete scute-like 2 controls intestinal stem cell fate." Cell. 2009 Mar 6;136(5):903-12. doi: 10.1016/j.cell.2009.01.031.

The small intestinal epithelium is the most rapidly self-renewing tissue of mammals. Proliferative cells are confined to crypts, while differentiated cell types predominantly occupy the villi. We recently demonstrated the existence of a long-lived pool of cycling stem cells defined by Lgr5 expression and intermingled with post-mitotic Paneth cells at crypt bottoms. We have now determined a gene signature for these Lgr5 stem cells. One of the genes within this stem cell signature is the Wnt target Achaete scute-like 2 (Ascl2). Transgenic expression of the Ascl2 transcription factor throughout the intestinal epithelium induces crypt hyperplasia and ectopic crypts on villi. Induced deletion of the Ascl2 gene in adult small intestine leads to disappearance of the Lgr5 stem cells within days. The combined results from these gain- and loss-of-function experiments imply that Ascl2 controls intestinal stem cell fate.

Vincent, R., N. Treff, et al. "Generation and characterization of novel tetracycline-inducible pancreatic transcription factor-expressing murine embryonic stem cell lines." Stem Cells Dev. 2006 Dec;15(6):953-62.

Pancreatic development in mammals is controlled in part by the expression and function of numerous genes encoding transcription factors. Yet, how these regulate each other and their target genes is incompletely understood. Embryonic stem (ES) cells have recently been shown to be capable of differentiating into pancreatic progenitor cells and insulin-producing cells, representing a useful in vitro model system for studying pancreatic and islet development. To generate tools to study the relationships of transcription factors in pancreatic development we have established seven unique mouse ES cell lines with tetracycline-inducible expression of either Hnf4alpha, Hnf6, Nkx2.2, Nkx6.1, Pax4, Pdx1, and Ptf1a cDNAs. Each of the cell lines was characterized for induction of transgene expression after exposure to doxycycline (DOX) by quantitative real-time PCR and immunofluorescence microscopy. Transgene expression in the presence of DOX was at least 97-fold that seen in untreated cells. Immunofluorescent staining of DOX-treated cultures showed efficient (>95% of cells) transgene protein expression while showing <5% positive staining in uninduced cells. Each of the ES cell lines maintained their pluripotency as measured by teratoma formation. Furthermore, transgene expression can be efficiently achieved in vivo through DOX administration to mice. The establishment of ES cell lines with temporally controllable induction of critical pancreatic transcription factor genes provides a new set of tools that could be used to interrogate gene regulatory networks in pancreatic development and potentially generate greater numbers of beta cells from ES cells.

Wagh, V., A. Pomorski, et al. "MicroRNA-363 negatively regulates the left ventricular determining transcription factor HAND1 in human embryonic stem cell-derived cardiomyocytes." Stem Cell Res Ther. 2014 Jun 6;5(3):75. doi: 10.1186/scrt464.

INTRODUCTION: Posttranscriptional control of mRNA by microRNA (miRNA) has been implicated in the regulation of diverse biologic processes from directed differentiation of stem cells through organism development. We describe a unique pathway by which miRNA regulates the specialized differentiation of cardiomyocyte (CM) subtypes. METHODS: We differentiated human embryonic stem cells (hESCs) to cardiac progenitor cells and functional CMs, and characterized the regulated expression of specific miRNAs that target transcriptional regulators of left/right ventricular-subtype specification. RESULTS: From >900 known human miRNAs in hESC-derived cardiac progenitor cells and functional CMs, a subset of differentially expressed cardiac miRNAs was identified, and in silico analysis predicted highly conserved binding sites in the 3'-untranslated regions (3'UTRs) of Hand-and-neural-crest-derivative-expressed (HAND) genes 1 and 2 that are involved in left and right ventricular development. We studied the temporal and spatial expression patterns of four miRNAs in differentiating hESCs, and found that expression of miRNA (miR)-363, miR-367, miR-181a, and miR-181c was specific for stage and site. Further analysis showed that miR-363 overexpression resulted in downregulation of HAND1 mRNA and protein levels. A dual luciferase reporter assay demonstrated functional interaction of miR-363 with the full-length 3'UTR of HAND1. Expression of anti-miR-363 in-vitro resulted in enrichment for HAND1-expressing CM subtype populations. We also showed that BMP4 treatment induced the expression of HAND2 with less effect on HAND1, whereas miR-363 overexpression selectively inhibited HAND1. CONCLUSIONS: These data show that miR-363 negatively regulates the expression of HAND1 and suggest that suppression of miR-363 could provide a novel strategy for generating functional left-ventricular CMs.

Webb, C. F., J. Bryant, et al. "The ARID family transcription factor bright is required for both hematopoietic stem cell and B lineage development." Mol Cell Biol. 2011 Mar;31(5):1041-53. doi: 10.1128/MCB.01448-10. Epub 2011 Jan 3.

Bright/Arid3a has been characterized both as an activator of immunoglobulin heavy-chain transcription and as a proto-oncogene. Although Bright expression is highly B lineage stage restricted in adult mice, its expression in the earliest identifiable hematopoietic stem cell (HSC) population suggests that Bright might have additional functions. We showed that >99% of Bright(-/-) embryos die at midgestation from failed hematopoiesis. Bright(-/-) embryonic day 12.5 (E12.5) fetal livers showed an increase in the expression of immature markers. Colony-forming assays indicated that the hematopoietic potential of Bright(-/-) mice is markedly reduced. Rare survivors of lethality, which were not compensated by the closely related paralogue Bright-derived protein (Bdp)/Arid3b, suffered HSC deficits in their bone marrow as well as B lineage-intrinsic developmental and functional deficiencies in their peripheries. These include a reduction in a natural antibody, B-1 responses to phosphocholine, and selective T-dependent impairment of IgG1 class switching. Our results place Bright/Arid3a on a select list of transcriptional regulators required to program both HSC and lineage-specific differentiation.

Webster, J. D., V. Yuzbasiyan-Gurkan, et al. "Expression of the embryonic transcription factor Oct4 in canine neoplasms: a potential marker for stem cell subpopulations in neoplasia." Vet Pathol. 2007 Nov;44(6):893-900.

Neoplastic cells and stem cells share several phenotypic characteristics. Recently, numerous studies have identified adult stem cells that have been hypothesized to be the cellular origin for cancer in several tissues. Oct4 has been consistently associated with pluripotent or stemlike cells, and it is hypothesized that Oct4 is necessary for the maintenance of pluripotency. We hypothesize that Oct4-positive cells are present in all canine neoplasms and that these subpopulations of neoplastic cells might represent "cancer stem" cells. To test this hypothesis, 83 canine neoplasms representing 21 neoplastic diseases were evaluated for Oct4 expression using immunohistochemistry. The results of this study showed that all tumors included in this study contained a subpopulation of Oct4-positive cells, although the proportion of Oct4-positive cells and the intensity of immunoreactivity varied both within and between tumor types. Subpopulations of Oct4-positive cells identified in these tumors are likely to represent "cancer stem" cells and therefore might be responsible for the maintenance and propagation of the tumors. If these cells represent cancer stem cells, and are therefore responsible for the maintenance and growth of the neoplastic cellular population, then these cells should serve as relevant therapeutic targets and offer the greatest potential for curative treatment.

Yuasa, H., Y. Oike, et al. "Oncogenic transcription factor Evi1 regulates hematopoietic stem cell proliferation through GATA-2 expression." EMBO J. 2005 Jun 1;24(11):1976-87. Epub 2005 May 12.

The ecotropic viral integration site-1 (Evi1) is an oncogenic transcription factor in murine and human myeloid leukemia. We herein show that Evi1 is predominantly expressed in hematopoietic stem cells (HSCs) in embryos and adult bone marrows, suggesting a physiological role of Evi1 in HSCs. We therefore investigate the role and authentic target genes of Evi1 in hematopoiesis using Evi1-/- mice, which die at embryonic day 10.5. HSCs in Evi1-/- embryos are markedly decreased in numbers in vivo with defective self-renewing proliferation and repopulating capacity. Notably, expression rate of GATA-2 mRNA, which is essential for proliferation of definitive HSCs, is profoundly reduced in HSCs of Evi1-/- embryos. Restoration of the Evi1 or GATA-2 expression in Evi1-/- HSCs could prevent the failure of in vitro maintenance and proliferation of HSC through upregulation of GATA-2 expression. An analysis of the GATA-2 promoter region revealed that Evi1 directly binds to GATA-2 promoter as an enhancer. Our results reveal that GATA-2 is presumably one of critical targets for Evi1 and that transcription factors regulate the HSC pool hierarchically.

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