Epigenetic reprogramming in mammalian cell differentiation, transdifferentiation and dedifferentiation.

Accepted for publication in CAB Reviews as of 23 March 2015. The only accredited archive of the content that has been certified and accepted after peer review.

Epigenetic reprogramming in mammalian cell differentiation, transdifferentiation and dedifferentiation

Tuempong Wongtawan[1]*, Cristina Aguilar-Sanchez[2], Busabun Wongtawan[2§] and Sari Pennings[2]

[1]Laboratory of Cellular Biomedicine and Veterinary Medicine, Department of Pre-clinic and Applied Animal Science, Mahidol University, Salaya, Puthamonthon, Nakhonprathom 73170, Thailand.

[2]Centre for Cardiovascular Science, Queen's Medical Research Institute, the University of Edinburgh, 47 Little France Crescent, Edinburgh, EH16 4TJ, UK.

*Corresponding author: tuempong.wan@mahidol.edu

[§]Deceased

Abstract

Epigenetic and chromatin modifications have important roles in governing gene activity and nuclear architecture. They are also necessary for normal embryonic development and cell differentiation. Early epigenetic programming events during mouse embryogenesis are believed to be essential for normal growth and development. Aberrant epigenetic profiles are associated

with the conversion of normal cell phenotypes into cancer cells. Because epigenetic alterations are potentially reversible, experimental progress in this area may offer great promise for new cancer therapy. Nuclear epigenetic profiles can be manipulated using techniques such as somatic cell reprogramming, genetic engineering and small molecules, which can reprogramme the cell towards dedifferentiation and transdifferentiation. Advances into the mechanisms will improve the potential for regenerative medicine. In this review, we describe the principles of epigenetics and its relation to cell reprogramming, differentiation, dedifferentiation and transdifferentiation.

Keywords: Epigenetics, Reprogramming, Differentiation, Dedifferentiation, Transdifferentiation, Cancer

Review methodology

Literature was sourced from PubMed, Google Scholar and Web of Science; journal publishers; meeting reports and communications from colleagues. In addition to these articles, we checked references cited by the authors for additional relevant material.

Epigenetic definitions

Epigenetics describes the phenomena between genotype and phenotype that can alter the phenotypic outcome associated with genomic loci in the absence of changes to the underlying DNA sequence [1]. For example, the majority of cells in our body share an identical genotype originally derived from the first single cell after fertilisation, the zygote, yet these cells can have different morphologies and functions. During development, cells eventually generate a diversity

of disparate and stable cell types in a process called cellular differentiation. These transitions were first envisioned by Waddington as being governed by changes in trajectory across a conceptual 'epigenetic landscape', rather than by alterations in genetic inheritance [2]. In molecular terms, epigenetics is defined as the study of any potentially stable and heritable change in gene expression or cellular phenotype that occurs without altering the DNA sequence of the cell lineage [1]. The mechanisms can involve covalent modification marks on histones and DNA or non-coding RNAs (ncRNAs) [3-5]. ncRNAs are transcribed from DNA but are not translated into proteins; those ncRNAs that appear to be involved in epigenetic processes [6] can mediate non-mendelian inheritance of an epigenetic change [7].

Epigenetic modifications include the methylation states of cytosine residues of DNA and posttranslational methylation groups on the histone proteins associated with the DNA. Co-regulator proteins with binding domains for these chemical groups may associate with these epigenetic marks and affect the activity of nearby genes [8, 9]. The specific combination of epigenetic modifications may furthermore determine the conformation of the chromatin fibre into which the DNA and histones are packaged, and can thereby regulate the transcriptional potential of the underlying genes [4, 10]. This is based on the notion that repression of gene expression is caused by a lack of accessibility to the gene by the RNA polymerase [11], as well as its recruitment [12].

During development as well as in adult life, an interplay exists between the environment and genome; however, the currently known framework of gene–environment interactions is not sufficient to fully explain the risks of common diseases, some of which appear modulated by epigenetic mechanisms [13]. Many environmental factors have been implicated in aberrant epigenetic changes both in experimental and epidemiological studies [14]. These environmental epigenetic modulators include nutrients, oxygen, temperature, radiation, pollution, chemicals and

toxins [13-17]. Specific epigenetic modifications and transcriptional profiles have been shown to have a dynamic potential for rapidly adapting to culture conditions [17, 18]

DNA methylation

DNA methylation involves the addition of a methyl group to CpG sequences at the 5' position of the cytosine ring (5-methylcytosine; 5mC). This modification, which occurs in the DNA of most but not all eukaryotes, is catalysed by DNA methyltransferases (Dnmt) and is generally associated with gene repression [3, 9, 11]. The repression mechanisms can act through direct interference by the methyl group or involve a family of methyl binding proteins and associated complexes in vertebrates [9]. DNA methylation can occur in two ways: de novo methylation relies on Dnmt3a and Dnmt3b enzymes that add new methyl groups to CpG sequences; whereas methylation maintenance requires Dnmt1 to restore methyl groups to hemi-methylated CpG sequences following DNA replication [3, 12]. DNA methylation can be further modified, as part of a presumed active demethylation mechanism, by the Tet family of enzymes converting 5mC to 5-hydroxymethylcytosine (5hmC) and its higher oxidative products 5-formylcytosine (5fC) and 5-carboxylcytosine (5caC) [19-21].

Histone methylation

Post-translational modifications can be found on the histone protein globular core regions, around which DNA is wrapped [22]. However, the majority of histone modifications occur on the lysine-rich N-terminal amino acid "tails" extending from the nucleosome structure [8]. These include: acetylation, phosphorylation, sumoylation, ubiquitination and methylation [23]. Methylation of histones is an epigenetically heritable histone modification found on lysine (K) or arginine (R) residues, produced by a family of histone methyltransferases (HMTs). Conversely, histone demethylases work to remove methyl groups from these residues [8]. Histone lysine residues can be mono- (me), di- (me2), or tri-methylated (me3); each of these posttranslational

modifications can have a decisive influence on gene and chromatin functions [24]. For instance, H3K9me3 represses gene transcription and assists in the formation of constitutive heterochromatin, while H3K9me2 represses genes in euchromatin as well as forming facultative heterochromatin [25]. Modifications of histone lysine can act as either repressive or active marks. For example, methylations of H3K4, H3K36 and H3K79 have been highly correlated with transcriptional activation, whereas methylations of H3K9, H3K27 and H4K20 are associated with repressive chromatin states [26, 27]. The repression mechanisms typically involve protein complexes with binding modules for these methyl groups [8]. This has led to a model describing the proteins involved in histone modification management as 'writers, erasers and readers', in an analogy with other signalling pathways [28].

Methylation of histone arginine residues by arginine methyltransferases (PRMTs) is less extensively studied but it has been found to play significant roles in gene regulation, development and cancer [29]. Histone arginine methylation can be transcriptionally activating [30] or repressive [31] depending on the target residue, and on whether the methylation is symmetric or asymmetric. In mammals, PRMT1- and CARM1-catalysed histone asymmetric histone dimethylation at arginine is involved in gene activation [30] while PRMT5-catalyzed symmetric histone dimethylated arginine is associated with gene repression [31].

Epigenetics and differentiation.

In developmental biology, cellular differentiation is the process by which a less specialized cell (stem cell or progenitor) becomes a more specialized cell type. Differentiation can dramatically change a cell's morphology and function, as a result of alterations in gene expression with the involvement of epigenetic modifications [32, 33]. Differentiation occurs numerous times during development and continues into adulthood, as adult stem cells divide and create fully differentiated daughter cells during tissue repair and during normal cell turnover [34]. In cancer,

the differentiation state (sometimes referred as redifferentiation) is used in grading tumours to assess cancer progression, by comparing the genotype and phenotype of cancer tissue to normal tissue. Well-differentiated cancer cells are comparable to normal cells, in that they grow and spread more slowly than poorly differentiated or undifferentiated cancer cells [35, 36].

Each cell population is thought to have its own characteristic epigenetic signature, which correlates with its differentiation potential. Mammalian development is a unidirectional process during which there is a progressive loss of developmental potential. It begins with the formation of a unicellular zygote and ends with the establishment of more than 200 specialized cell types of the mammalian body [37]. According to this diminishing differentiation potential, specific terms have been assigned to the individual cell populations that arise during development, such as: totipotency (ability to differentiate into intraembryonic tissue and extraembryonic tissue), pluripotency (ability to differentiate into intraembryonic tissue; ectoderm, mesoderm and endoderm), multipotency (ability to differentiate into two or more lineages) and unipotency (ability to differentiate to one lineage).

It is thought that at specific stages in development and differentiation, biologically important differences in the 'openness' of chromatin occur. For example, chromatin in preimplantation embryos is more open than in postimplantation cells, while stem cell chromatin is less compact and more transcription-permissive than that of differentiated cells [18, 38]. Open chromatin structure, characterized by relatively few condensed heterochromatin areas, has a higher proportion of active epigenetic marks (i.e., H3K4me3, H3K39me and H3K79me) compared to repressive epigenetic marks (i.e., H3K9me, H4K20me and DNA methylation) [39]. In addition, developmental genes can be 'bivalent', marked by both the active epigenetic mark H3K4me3 and the repressive epigenetic mark H3K27me3, which signifies genes that are silent but transcriptionally poised for activation [40, 41]. The bivalent histone modification patterns

disappear after cell differentiation, when most stemness genes are repressed in association with repressive epigenetic marks while specific differentiated genes become activated [40, 42]. At the same time, heterochromatin spreading takes place and chromatin plasticity is diminished [38, 43].

Reprogramming, dedifferentiation and transdifferentiation.

Unlike in lower vertebrates, reprogramming, dedifferentiation and transdifferentiation rarely occur naturally in mammals. However, under certain experimental conditions, differentiated cells can revert into a less differentiated state, in a dedifferentiation process induced by nuclear/cell reprogramming. Examples include the generation of induced pluripotent stem cells (iPSC) [44], or the creation of a totipotent embryo derived from somatic cell nuclear transfer (SCNT) [45]. Reprogramming also describes the conversion of one differentiated cell type into another, for instance of a B lymphocyte into a macrophage [46], or a fibroblast into a cardiac muscle cell [47], following the induced expression of defined transcription factors. Because these two examples of cell fate change may not involve a gain in differentiation potential, the term `lineage conversion' or `transdifferentiation' is currently used to describe these processes. Moreover, cellular dedifferentiation has also been implicated in cancer. As cancer can only be established from cells that have the potential to divide, and not terminally differentiated cells, one theory suggests that tumours may arise from the unrestrained growth of dedifferentiated cells that resemble embryonic or stem cells [48].

In molecular terms, cell reprogramming describes the molecular changes that cells undergo as their fate changes. Epigenetic reprogramming has been used to describe certain nuclear epigenetic changes that occur irrespective of changes to the differentiation state of cells, such as the DNA and histone methylation changes after fertilisation [49, 50], during germ cell maturation [51], dedifferentiation [37] and transdifferentiation [52].

Epigenetic patterns can be inherited within cell lineages, as well as being dynamic during early development. Most somatic DNA and histone methylation modifications are erased during germ cell development [53, 54] and preimplantation stages [55], and are subsequently reinstated during pre and postimplantation [18, 32, 50]. It is thought that the erasure of 'epigenetic memory' is required for proper development, while incomplete and aberrant epigenetic reprogramming may cause developmental arrest and abnormalities [56-58].

Manipulation of epigenetic profiles.

Mechanisms of endogenous origin, as well as exogenous factors can be used to manipulate nuclear epigenetic profiles, and can in this way alter cell fate. Techniques include nuclear transfer [59], cell fusion [60], cell treatment with other cell extracts [61] or small molecules [62], and over expression of specific genes [63]. Such epigenetic reprogramming strategies may be useful for future therapies, for example in the treatment of cancers and mental retardation which have epigenetic abnormalities [64, 65]. Cell fate reprogramming strategies are already employed in disease modelling and have potential for regenerative medicine approaches aimed at tissue renewal [66]. Veterinary applications extend further into transgenic animal generation, drug development, and the preservation of biological diversity [67].

Somatic cell nuclear transfer (SCNT) experiments in amphibians, and subsequently in sheep and other mammals, first demonstrated that it is possible to generate an adult cloned animal from a differentiated cell, albeit at low efficiency. [45, 68, 69]. Studies in different species using the nuclear transfer technique have shown that eggs or oocytes have the ability to erase somatic epigenetic patterns (epigenetic memory) of the donor nucleus and replace these with embryonic marks, leading to the development of pluripotent stem cells that are functionally equivalent to those derived from fertilized embryos. However, incomplete reprogramming by nuclear transfer may result in failure of full term development [58, 69-71].

Epigenetics in iPSC reprogramming.

In a major advance demonstrating that cell reprogramming capability is not restricted to oocytes, ectopic expression or introduction of recombinant proteins of the pluripotency transcription factors (Oct4, Sox2, Klf4, Myc, Nanog, Lin28) was shown to be sufficient for reprogramming of a small proportion of somatic cells into a pluripotent state in mouse [44] and human cells [68]. These iPSCs are also in many respects similar to natural pluripotent embryonic stem cells (ESCs), such as the expression of certain stem cell genes and proteins, chromatin methylation patterns, doubling time, embryoid body formation, teratoma formation, and viable chimera formation, as well as potency and differentiability. Genomic mapping studies show that iPSC techniques can induce global epigenetic reprogramming of differentiated cells (fibroblasts) towards a pluripotent cell epigenome [63, 68]. The iPSC methodology permits the derivation of either patient-specific or disease-specific pluripotent cells. These cells can be used for drug screening, and as a model for the pathogenesis of degenerative diseases such as Alzheimer's, Parkinson's or multiple sclerosis, as well as having potential for cell therapy [72]. The study of iPS cells that are corrected for a gene mutation to rescue sickle cell anaemia and thalassemia in mouse models has demonstrated 'proof of principle' for the use of iPSC combined with gene therapy for disease treatment [73, 74]. Nevertheless, analysis of human iPSC lines suggests that variability in differentiation potential and the epigenetic control of cancer dedifferentiation during cell reprogramming need to be better understood prior to application in regenerative medicine [75, 76].

Cell reprogramming in veterinary pre-clinical models and agriculture.

Mouse models suggest treatment of a number of common degenerative diseases is possible using transplanted induced pluripotent stem cells. Mice lack physiological similarity with humans, however; while targeted gene mutation in mouse often fails to reproduce human phenotypes [77].

Interest in the use of iPSCs in large animal pre-clinical models for disease modelling has ranged from rhesus monkey (pancreatic insulin-producing cells for diabetes), pig (rod photoreceptor cells for retinal disease; endothelial cells for cardiovascular disease), dog (endothelial cells), to macaque (dopaminergic neurons for Parkinsons disease). By filling the gaps between laboratory findings in the mouse and clinical trials in humans, domestic animal models are therefore invaluable for testing the safety and potential of iPSCs [67]. Interestingly, while somatic cell reprogramming to iPSCs in many species has relied on over-expression of the conserved Yamanaka set of transcription factors, additional steps are likely needed here to achieve a true pluripotent state with competence for germ-line transmission [67, 78]. Epigenetic modifications are evolutionary conserved but some variation exists between species in the modifying enzymes and binding protein homologues involved [9]. Overall, iPSC and ES cell technology have been mainly limited to rodents and humans. Instead, SCNT cell reprogramming technology has continued to deliver live births in a range of species including transgenic production in farm animals for potential agricultural applications [77].

Epigenetic inhibitors.

In the last decade, a variety of small molecules have been created and discovered, some of which have the potential to alter epigenetic marks resulting in cell differentiation, transdifferentiation and dedifferentiation. Early examples include DNA demethylating agents such as 5-azacytidine (5-AzaC), which is a cytosine analogue that can cause extensive global DNA demethylation and reduce DNA methyltransferase activity in the cells [79, 80]. It was originally developed as an antitumor agent, and has been useful in the treatment of leukaemia and myelodysplastic syndrome [79, 81]. The effect of 5-AzaC is unpredictable, as it may cause dedifferentiation [82], differentiation [83] or transdifferentiation [84]. Other types of modifiers include histone deacetylase (HDAC) inhibitors such as valproic acid (VPA) and trichostatin (TSA). VPA has

been utilised for decades as a treatment for epilepsy, as a mood stabiliser and in migraine therapy, while TSA is currently applied as an anticancer medicine [85, 86]. It has been shown that both VPA and TSA can inhibit HDACs and then trigger active global demethylation of the mammalian epigenome, causing reprogramming of gene expression [87]. VPA and TSA induce dedifferentiation by enhancing epigenetic reprogramming in iPSC and SCNT technologies [88-90]. Moreover, VPA and TSA can induce redifferentiation in cancer, causing growth inhibition and apoptosis [91, 92].

In addition, histone methylation inhibitors such as BIX-01294 (a diazepin-quinazolin-amine derivative) have been demonstrated to selectively impair G9a (Ehmt2) HMTs and levels of H3K9me2 [93]. A combination of BIX-01294 with defined factors (chromatin remodellers) could increase the cellular and epigenetic reprogramming rate of iPSC methodology [94].

Epigenetic modifier enzyme roles in differentiation in development and disease.

Gene knockdown and knockout technologies in both in vivo and in vitro studies have revealed that mammalian development and differentiation requires both DNA/histone methylation (see table 1) and demethylation (see table 2). Most of the DNA and histone methyltransferases are important for normal embryonic development and differentiation. Conversely, most demethylase knockout embryos can survive until birth but cell differentiation is affected.

Epigenetic modifiers are therefore essential and their defects are strongly linked to dedifferentiation towards stem cells or cancer (see table 1 and 2). The tables show that modifiers related to formation of heterochromatin, such as Suv39h, Suv420h, Dmnt1 and Dnmt3l, tend to act as repressors for dedifferentiation (table 1), whereas histone demethylases Jmjd1 and Jmjd2 act as activators (table 2). H3K4 histone methyl transferases tend to activate cell reprogramming towards stem cells, but repress cancer (table 1). The important roles played in various

differentiation aspects identify these enzymes as potential drug targets for treating disease phenotypes and in regenerative reprogramming.

Conclusion/Summary.

In this review, we conclude that epigenetic marks are important for development, differentiation and that their dysregulation can cause dedifferentiation. Each cell phenotype has a unique epigenetic signature, which undergoes alteration when the cells are differentiated, transdifferentiated or dedifferentiated. Manipulation of epigenetic mechanisms can help control cell phenotypic outcomes in disease, and in this capacity can be useful for medicine and veterinary medicine, while animal production from reprogrammed somatic cells can find use in agriculture and animal conservation. The detailed information that is now available on the epigenomic maps (http://www.roadmapepigenomics.org/) from different adult and embryonic tissues, cross-referenced with disease states will provide the roadmap to these goals, as well as advancing our understanding of underlying epigenetic processes [95-97].

References

[1] Goldberg AD, Allis CD, Bernstein E. Epigenetics: a landscape takes shape. Cell. 2007;128:635-8.

[2] Waddington CH. The Strategy of the Genes,. London: Geo Allen and Unwin; 1957.

[3] Reddington JP, Pennings S, Meehan RR. Non-canonical functions of the DNA methylome in gene regulation. Biochemical Journal. 2013;451:13-23.

278 [4] Zhou VW, Goren A, Bernstein BE. Charting histone modifications and the functional
279 organization of mammalian genomes. Nature Reviews Genetics. 2011;12:7-18.

280 [5] Moazed D. Small RNAs in transcriptional gene silencing and genome defence. Nature.
281 2009;457:413-20.

282 [6] Andersen AA, Panning B. Epigenetic gene regulation by noncoding RNAs. Current Opinion
283 in Cell Biology. 2003;15:281-9.

284 [7] Rassoulzadegan M, Grandjean V, Gounon P, Vincent S, Gillot I, Cuzin F. RNA-mediated
285 non-mendelian inheritance of an epigenetic change in the mouse. Nature. 2006;441:469-74.

286 [8] Ruthenburg AJ, Li H, Patel DJ, Allis CD. Multivalent engagement of chromatin
287 modifications by linked binding modules. Nature Reviews. 2007;8:983-94.

288 [9] Moffat M, Reddington JP, Pennings S, Meehan R. DNA Methylation in Mammalian and
289 Non-Mammalian Organism. In: Tatarinova T, editor. DNA Methylation - From Genomics to
290 Technology: Intech; 2012. DOI:5772/38181.

291 [10] Felsenfeld G, Groudine M. Controlling the double helix. Nature. 2003;421:448-53.

292 [11] Boyes J, Bird A. DNA methylation inhibits transcription indirectly via a methyl-CpG
293 binding protein. Cell. 1991;64:1123-34.

294 [12] Klose RJ, Bird AP. Genomic DNA methylation: the mark and its mediators. Trends in
295 Biochemical Sciences. 2006;31:89-97.

296 [13] Bollati V, Baccarelli A. Environmental epigenetics. Heredity. 2010;105:105-12.

297 [14] Baccarelli A, Bollati V. Epigenetics and environmental chemicals. Current Opinion in
298 Pediatrics. 2009;21:243-51.

299 [15] Cortessis VK, Thomas DC, Levine AJ, Breton CV, Mack TM, Siegmund KD, et al.
300 Environmental epigenetics: prospects for studying epigenetic mediation of exposure-response
301 relationships. Human Genetics. 2012;131:1565-89.

302 [16] Feil R, Fraga MF. Epigenetics and the environment: emerging patterns and implications.
303 Nature reviews Genetics. 2011;13:97-109.

304 [17] Nestor CE, Ottaviano R, Reinhardt D, Cruickshanks HA, Mjoseng HK, McPherson RC, et
305 al. Rapid reprogramming of epigenetic and transcriptional profiles in mammalian culture
306 systems. Genome Biology. 2015;16:11.

307 [18] Wongtawan T, Taylor JE, Lawson KA, Wilmut I, Pennings S. Histone H4K20me3 and
308 HP1alpha are late heterochromatin markers in development, but present in undifferentiated
309 embryonic stem cells. Journal of Cell Science. 2011;124:1878-90.

310 [19] Kriaucionis S, Heintz N. The nuclear DNA base 5-hydroxymethylcytosine is present in
311 Purkinje neurons and the brain. Science. 2009;324:929-30.

312 [20] Tahiliani M, Koh KP, Shen Y, Pastor WA, Bandukwala H, Brudno Y, et al. Conversion of
313 5-methylcytosine to 5-hydroxymethylcytosine in mammalian DNA by MLL partner TET1.
314 Science. 2009;324:930-5.

315 [21] Ito S, Shen L, Dai Q, Wu SC, Collins LB, Swenberg JA, et al. Tet proteins can convert 5-
316 methylcytosine to 5-formylcytosine and 5-carboxylcytosine. Science. 2011;333:1300-3.

317 [22] Cosgrove MS, Boeke JD, Wolberger C. Regulated nucleosome mobility and the histone
318 code. Nature Structural & Molecular Biology. 2004;11:1037-43.

319 [23] Portela A, Esteller M. Epigenetic modifications and human disease. Nature Biotechnology.
320 2010;28:1057-68.

321 [24] Li B, Carey M, Workman JL. The role of chromatin during transcription. Cell.
322 2007;128:707-19.

323 [25] Lachner M, Jenuwein T. The many faces of histone lysine methylation. Current Opinion in
324 Cell Biology. 2002;14:286-98.

325 [26] Vakoc CR, Sachdeva MM, Wang H, Blobel GA. Profile of histone lysine methylation
326 across transcribed mammalian chromatin. Molecular and Cellular Biology. 2006;26:9185-95.

327 [27] Schotta G, Lachner M, Peters AH, Jenuwein T.The Indexing Potential of Histone Lysine
328 Methylation. In: Bock G, Goode J, editors. Reversible Protein Acetylation: Novartis Foundation
329 Symposium 259. Chichester, UK: John Wiley & Sons, Ltd; 2004.
330 DOI:10.1002/0470862637.ch3.

331 [28] Baker LA, Allis CD, Wang GG. PHD fingers in human diseases: disorders arising from
332 misinterpreting epigenetic marks. Mutation Research. 2008;647:3-12.

333 [29] Stopa N, Krebs JE, Shechter D. The PRMT5 arginine methyltransferase: many roles in
334 development, cancer and beyond. Cellular and Molecular Life Science. 2015. DOI:
335 10.1007/s00018-015-1847-9

336 [30] Chen D, Ma H, Hong H, Koh SS, Huang SM, Schurter BT, et al. Regulation of transcription
337 by a protein methyltransferase. Science. 1999;284:2174-7.

[31] Pal S, Vishwanath SN, Erdjument-Bromage H, Tempst P, Sif S. Human SWI/SNF-associated PRMT5 methylates histone H3 arginine 8 and negatively regulates expression of ST7 and NM23 tumor suppressor genes. Molecular and Cellular Biology. 2004;24:9630-45.

[32] Meehan RR, Dunican DS, Ruzov A, Pennings S. Epigenetic silencing in embryogenesis. Experimental Cell Research. 2005;309:241-9.

[33] Feng S, Jacobsen SE, Reik W. Epigenetic reprogramming in plant and animal development. Science. 2010;330:622-7.

[34] Sugimoto K, Gordon SP, Meyerowitz EM. Regeneration in plants and animals: dedifferentiation, transdifferentiation, or just differentiation? Trends in Cell Biology. 2011;21:212-8.

[35] Ben-Porath I, Thomson MW, Carey VJ, Ge R, Bell GW, Regev A, et al. An embryonic stem cell-like gene expression signature in poorly differentiated aggressive human tumors. Nature Genetics. 2008;40:499-507.

[36] Coindre JM, Trojani M, Contesso G, David M, Rouesse J, Bui NB, et al. Reproducibility of a histopathologic grading system for adult soft tissue sarcoma. Cancer. 1986;58:306-9.

[37] Hochedlinger K, Plath K. Epigenetic reprogramming and induced pluripotency. Development. 2009;136:509-23.

[38] Meshorer E, Misteli T. Chromatin in pluripotent embryonic stem cells and differentiation. Nature Reviews. 2006;7:540-6.

[39] Gaspar-Maia A, Alajem A, Meshorer E, Ramalho-Santos M. Open chromatin in pluripotency and reprogramming. Nature Reviews. 2011;12:36-47.

[40] Bernstein BE, Mikkelsen TS, Xie X, Kamal M, Huebert DJ, Cuff J, et al. A bivalent chromatin structure marks key developmental genes in embryonic stem cells. Cell. 2006;125:315-26.

[41] Vastenhouw NL, Schier AF. Bivalent histone modifications in early embryogenesis. Current Opinion in Cell Biology. 2012;24:374-86.

[42] De Gobbi M, Garrick D, Lynch M, Vernimmen D, Hughes JR, Goardon N, et al. Generation of bivalent chromatin domains during cell fate decisions. Epigenetics & Chromatin. 2011;4:9.

[43] Grigoryev SA, Bulynko YA, Popova EY. The end adjusts the means: heterochromatin remodelling during terminal cell differentiation. Chromosome Research. 2006;14:53-69.

[44] Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell. 2006;126:663-76.

[45] Wilmut I, Schnieke AE, McWhir J, Kind AJ, Campbell KH. Viable offspring derived from fetal and adult mammalian cells. Nature. 1997;385:810-3.

[46] Xie H, Ye M, Feng R, Graf T. Stepwise reprogramming of B cells into macrophages. Cell. 2004;117:663-76.

[47] Ieda M, Fu JD, Delgado-Olguin P, Vedantham V, Hayashi Y, Bruneau BG, et al. Direct reprogramming of fibroblasts into functional cardiomyocytes by defined factors. Cell. 2010;142:375-86.

[48] Sell S. Cellular origin of cancer: dedifferentiation or stem cell maturation arrest? Environmental Health Perspectives. 1993;101 Suppl 5:15-26.

[49] Santos F, Dean W. Epigenetic reprogramming during early development in mammals. Reproduction. 2004;127:643-51.

[50] Wongtawan T. The importance of epigenetics in embryonic development and reproductive biotechnology. Journal of Applied Animal Science. 2012;5:9-26.

[51] Surani MA, Ancelin K, Hajkova P, Lange UC, Payer B, Western P, et al. Mechanism of mouse germ cell specification: a genetic program regulating epigenetic reprogramming. Cold Spring Harbor Symposia on Quantitative Biology. 2004;69:1-9.

[52] Graf T. Historical origins of transdifferentiation and reprogramming. Cell Stem Cell. 2011;9:504-16.

[53] Hajkova P, Ancelin K, Waldmann T, Lacoste N, Lange UC, Cesari F, et al. Chromatin dynamics during epigenetic reprogramming in the mouse germ line. Nature. 2008;452:877-81.

[54] Hajkova P, el-Maarri O, Engemann S, Oswald J, Olek A, Walter J. DNA-methylation analysis by the bisulfite-assisted genomic sequencing method. Methods in Molecular Biology. 2002;200:143-54.

[55] Arand J, Wossidlo M, Lepikhov K, Peat JR, Reik W, Walter J. Selective impairment of methylation maintenance is the major cause of DNA methylation reprogramming in the early embryo. Epigenetics & Chromatin. 2015;8:1.

[56] Taylor J, Moore H, Beaujean N, Gardner J, Wilmut I, Meehan R, et al. Cloning and expression of sheep DNA methyltransferase 1 and its development-specific isoform. Molecular Reproduction and Development. 2009;76:501-13.

[57] Beaujean N, Hartshorne G, Cavilla J, Taylor J, Gardner J, Wilmut I, et al. Non-conservation of mammalian preimplantation methylation dynamics. Current Biology. 2004;14:R266-7.

[58] Beaujean N, Taylor J, Gardner J, Wilmut I, Meehan R, Young L. Effect of limited DNA methylation reprogramming in the normal sheep embryo on somatic cell nuclear transfer. Biology of Reproduction. 2004;71:185-93.

[59] Rideout WM, 3rd, Eggan K, Jaenisch R. Nuclear cloning and epigenetic reprogramming of the genome. Science. 2001;293:1093-8.

[60] Cowan CA, Atienza J, Melton DA, Eggan K. Nuclear reprogramming of somatic cells after fusion with human embryonic stem cells. Science. 2005;309:1369-73.

[61] Freberg CT, Dahl JA, Timoskainen S, Collas P. Epigenetic reprogramming of OCT4 and NANOG regulatory regions by embryonal carcinoma cell extract. Molecular Biology of the Cell. 2007;18:1543-53.

[62] Szyf M. Epigenetics, DNA methylation, and chromatin modifying drugs. Annual Review of Pharmacology and Toxicology. 2009;49:243-63.

[63] Maherali N, Sridharan R, Xie W, Utikal J, Eminli S, Arnold K, et al. Directly reprogrammed fibroblasts show global epigenetic remodeling and widespread tissue contribution. Cell Stem Cell. 2007;1:55-70.

[64] Yoo CB, Jones PA. Epigenetic therapy of cancer: past, present and future. Nature Reviews Drug Discovery. 2006;5:37-50.

[65] Egger G, Liang G, Aparicio A, Jones PA. Epigenetics in human disease and prospects for epigenetic therapy. Nature. 2004;429:457-63.

[66] Xu Y, Shi Y, Ding S. A chemical approach to stem-cell biology and regenerative medicine. Nature. 2008;453:338-44.

[67] Cebrian-Serrano A, Stout T, Dinnyes A. Veterinary applications of induced pluripotent stem cells: regenerative medicine and models for disease? Veterinary Journal. 2013;198:34-42.

[68] Takahashi K, Tanabe K, Ohnuki M, Narita M, Ichisaka T, Tomoda K, et al. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. Cell. 2007;131:861-72.

[69] Ng RK, Gurdon JB. Epigenetic memory of active gene transcription is inherited through somatic cell nuclear transfer. Proceedings of the National Academy of Sciences of the United States of America. 2005;102:1957-62.

[70] Yang J, Yang S, Beaujean N, Niu Y, He X, Xie Y, et al. Epigenetic marks in cloned rhesus monkey embryos: comparison with counterparts produced in vitro. Biology of Reproduction. 2007;76:36-42.

[71] Martin C, Beaujean N, Brochard V, Audouard C, Zink D, Debey P. Genome restructuring in mouse embryos during reprogramming and early development. Developmental Biology. 2006;292:317-32.

[72] Park IH, Arora N, Huo H, Maherali N, Ahfeldt T, Shimamura A, et al. Disease-specific induced pluripotent stem cells. Cell. 2008;134:877-86.

[73] Hanna J, Wernig M, Markoulaki S, Sun CW, Meissner A, Cassady JP, et al. Treatment of sickle cell anemia mouse model with iPS cells generated from autologous skin. Science. 2007;318:1920-3.

[74] Wang Y, Zheng CG, Jiang Y, Zhang J, Chen J, Yao C, et al. Genetic correction of beta-thalassemia patient-specific iPS cells and its use in improving hemoglobin production in irradiated SCID mice. Cell Research. 2012;22:637-48.

[75] Koyanagi-Aoi M, Ohnuki M, Takahashi K, Okita K, Noma H, Sawamura Y, et al. Differentiation-defective phenotypes revealed by large-scale analyses of human pluripotent stem cells. Proceedings of the National Academy of Sciences of the United States of America. 2013;110:20569-74.

[76] Ohnishi K, Semi K, Yamamoto T, Shimizu M, Tanaka A, Mitsunaga K, et al. Premature termination of reprogramming in vivo leads to cancer development through altered epigenetic regulation. Cell. 2014;156:663-77.

[77] Koh S, Piedrahita JA. From "ES-like" cells to induced pluripotent stem cells: a historical perspective in domestic animals. Theriogenology. 2014;81:103-11.

[78] Nowak-Imialek M, Niemann H. Pluripotent cells in farm animals: state of the art and future perspectives. Reproduction Fertility and Development. 2012;25:103-28.

[79] Taylor SM. 5-Aza-2'-deoxycytidine: cell differentiation and DNA methylation. Leukemia. 1993;7 Suppl 1:3-8.

[80] Jones PA, Taylor SM. Hemimethylated duplex DNAs prepared from 5-azacytidine-treated cells. Nucleic Acids Research. 1981;9:2933-47.

[81] Silverman LR, Mufti GJ. Methylation inhibitor therapy in the treatment of myelodysplastic syndrome. Nature Clinical Practice Oncology. 2005;2 Suppl 1:S12-23.

[82] Tsuji-Takayama K, Inoue T, Ijiri Y, Otani T, Motoda R, Nakamura S, et al. Demethylating agent, 5-azacytidine, reverses differentiation of embryonic stem cells. Biochemical and Biophysical Research Communications. 2004;323:86-90.

[83] Jones PA, Taylor SM. Cellular differentiation, cytidine analogs and DNA methylation. Cell. 1980;20:85-93.

[84] Xu W, Zhang X, Qian H, Zhu W, Sun X, Hu J, et al. Mesenchymal stem cells from adult human bone marrow differentiate into a cardiomyocyte phenotype in vitro. Experimental Biology and Medicine (Maywood). 2004;229:623-31.

[85] Butler R, Bates GP. Histone deacetylase inhibitors as therapeutics for polyglutamine disorders. Nature Reviews Neuroscience. 2006;7:784-96.

[86] Marks PA, Jiang X. Histone deacetylase inhibitors in programmed cell death and cancer therapy. Cell cycle (Georgetown, Tex). 2005;4:549-51.

[87] Milutinovic S, D'Alessio AC, Detich N, Szyf M. Valproate induces widespread epigenetic reprogramming which involves demethylation of specific genes. Carcinogenesis. 2007; 28:560-71.

[88] Huangfu D, Maehr R, Guo W, Eijkelenboom A, Snitow M, Chen AE, et al. Induction of pluripotent stem cells by defined factors is greatly improved by small-molecule compounds. Nature Biotechnology. 2008;26:795-7.

[89] Miyoshi K, Mori H, Mizobe Y, Akasaka E, Ozawa A, Yoshida M, et al. Valproic acid enhances in vitro development and Oct-3/4 expression of miniature pig somatic cell nuclear transfer embryos. Cellular Reprogramming. 2010;12:67-74.

[90] Kishigami S, Mizutani E, Ohta H, Hikichi T, Thuan NV, Wakayama S, et al. Significant improvement of mouse cloning technique by treatment with trichostatin A after somatic nuclear transfer. Biochemical and Biophysical Research Communications. 2006;340:183-9.

[91] Gottlicher M, Minucci S, Zhu P, Kramer OH, Schimpf A, Giavara S, et al. Valproic acid defines a novel class of HDAC inhibitors inducing differentiation of transformed cells. The EMBO Journal. 2001;20:6969-78.

[92] Marks PA, Richon VM, Rifkind RA. Histone deacetylase inhibitors: inducers of differentiation or apoptosis of transformed cells. Journal of the National Cancer Institute. 2000;92:1210-6.

[93] Kubicek S, O'Sullivan RJ, August EM, Hickey ER, Zhang Q, Teodoro ML, et al. Reversal of H3K9me2 by a small-molecule inhibitor for the G9a histone methyltransferase. Molecular Cell. 2007;25:473-81.

[94] Shi Y, Do JT, Desponts C, Hahm HS, Scholer HR, Ding S. A combined chemical and genetic approach for the generation of induced pluripotent stem cells. Cell Stem Cell. 2008;2:525-8.

[95] Gjoneska E, Pfenning AR, Mathys H, Quon G, Kundaje A, Tsai LH, et al. Conserved epigenomic signals in mice and humans reveal immune basis of Alzheimer's disease. Nature. 2015;518:365-9.

[96] Zhou X, Li D, Zhang B, Lowdon RF, Rockweiler NB, Sears RL, et al. Epigenomic annotation of genetic variants using the Roadmap Epigenome Browser. Nature Biotechnology. 2015;DOI:10.1038/nbt.3158.

[97] Ernst J, Kellis M. Large-scale imputation of epigenomic datasets for systematic annotation of diverse human tissues. Nature biotechnology. 2015;DOI:10.1038/nbt.3157

[98] Bledau AS, Schmidt K, Neumann K, Hill U, Ciotta G, Gupta A, et al. The H3K4 methyltransferase Setd1a is first required at the epiblast stage, whereas Setd1b becomes essential after gastrulation. Development. 2014;141:1022-35.

[99] Salz T, Li G, Kaye F, Zhou L, Qiu Y, Huang S. hSETD1A regulates Wnt target genes and controls tumor growth of colorectal cancer cells. Cancer Research. 2014;74:775-86.

[100] Song Y, Li L, Ou Y, Gao Z, Li E, Li X, et al. Identification of genomic alterations in oesophageal squamous cell cancer. Nature. 2014;509:91-5.

[101] Yu BD, Hess JL, Horning SE, Brown GA, Korsmeyer SJ. Altered Hox expression and segmental identity in Mll-mutant mice. Nature. 1995;378:505-8.

[102] McMahon KA, Hiew SY, Hadjur S, Veiga-Fernandes H, Menzel U, Price AJ, et al. Mll has a critical role in fetal and adult hematopoietic stem cell self-renewal. Cell Stem Cell. 2007;1:338-45.

[103] Vieira FQ, Costa-Pinheiro P, Ramalho-Carvalho J, Pereira A, Menezes FD, Antunes L, et al. Deregulated expression of selected histone methylases and demethylases in prostate carcinoma. Endocrine-Related Cancer. 2014;21:51-61.

[104] Liu Y, Cheng H, Gao S, Lu X, He F, Hu L, et al. Reprogramming of MLL-AF9 leukemia cells into pluripotent stem cells. Leukemia. 2014;28:1071-80.

[105] Huang YC, Shih HY, Lin SJ, Chiu CC, Ma TL, Yeh TH, et al. The epigenetic factor Kmt2a/Mll1 regulates neural progenitor proliferation and neuronal and glial differentiation. Developmental Neurobiology. 2014; DOI: 10.1002/dneu.22235.

[106] Glaser S, Schaft J, Lubitz S, Vintersten K, van der Hoeven F, Tufteland KR, et al. Multiple epigenetic maintenance factors implicated by the loss of Mll2 in mouse development. Development. 2006;133:1423-32.

[107] Lin DC, Hao JJ, Nagata Y, Xu L, Shang L, Meng X, et al. Genomic and molecular characterization of esophageal squamous cell carcinoma. Nature Genetics. 2014;46:467-73.

[108] Wan X, Liu L, Ding X, Zhou P, Yuan X, Zhou Z, et al. Mll2 Controls Cardiac Lineage Differentiation of Mouse Embryonic Stem Cells by Promoting H3K4me3 Deposition at Cardiac-Specific Genes. Stem Cell Reviews. 2014;10:643-52.

[109] Kandoth C, McLellan MD, Vandin F, Ye K, Niu B, Lu C, et al. Mutational landscape and significance across 12 major cancer types. Nature. 2013;502:333-9.

[110] Chen C, Liu Y, Rappaport AR, Kitzing T, Schultz N, Zhao Z, et al. MLL3 is a haploinsufficient 7q tumor suppressor in acute myeloid leukemia. Cancer Cell. 2014;25:652-65.

[111] Lee S, Lee DK, Dou Y, Lee J, Lee B, Kwak E, et al. Coactivator as a target gene specificity determinant for histone H3 lysine 4 methyltransferases. Proceedings of the National Academy of Sciences of the United States of America. 2006;103:15392-7.

[112] Smith SL, Everts RE, Tian XC, Du F, Sung LY, Rodriguez-Zas SL, et al. Global gene expression profiles reveal significant nuclear reprogramming by the blastocyst stage after

cloning. Proceedings of the National Academy of Sciences of the United States of America. 2005;102:17582-7.

[113] Takeda S, Chen DY, Westergard TD, Fisher JK, Rubens JA, Sasagawa S, et al. Proteolysis of MLL family proteins is essential for taspase1-orchestrated cell cycle progression. Genes & Development. 2006;20:2397-409.

[114] Baek S, Quan X, Kim S, Lengner C, Park JK, Kim J. Electromagnetic Fields Mediate Efficient Cell Reprogramming into a Pluripotent State. ACS Nano. 2014;8:10125-38.

[115] Heuser M, Yap DB, Leung M, de Algara TR, Tafech A, McKinney S, et al. Loss of MLL5 results in pleiotropic hematopoietic defects, reduced neutrophil immune function, and extreme sensitivity to DNA demethylation. Blood. 2009;113:1432-43.

[116] Sebastian S, Sreenivas P, Sambasivan R, Cheedipudi S, Kandalla P, Pavlath GK, et al. MLL5, a trithorax homolog, indirectly regulates H3K4 methylation, represses cyclin A2 expression, and promotes myogenic differentiation. Proceedings of the National Academy of Sciences of the United States of America. 2009;106:4719-24.

[117] Goyal A, Chavez SL, Reijo Pera RA. Generation of human induced pluripotent stem cells using epigenetic regulators reveals a germ cell-like identity in partially reprogrammed colonies. PLOS ONE. 2013;8:e82838.

[118] Sowalsky AG, Xia Z, Wang L, Zhao H, Chen S, Bubley GJ, et al. Whole Transcriptome Sequencing Reveals Extensive Unspliced mRNA in Metastatic Castration-Resistant Prostate Cancer. Molecular Cancer Research. 2015;13:98-106.

561 [119] Campaner S, Spreafico F, Burgold T, Doni M, Rosato U, Amati B, et al. The
562 methyltransferase Set7/9 (Setd7) is dispensable for the p53-mediated DNA damage response in
563 vivo. Molecular Cell. 2011;43:681-8.

564 [120] Dai JP, Zhang Y, Shen YF. Histone lysine methyltransferase Setd7 enhances Ngn 1 gene
565 expression. Zhongguo yi xue ke xue yuan xue bao Acta Academiae Medicinae Sinicae.
566 2009;31:692-5.

567 [121] Proserpio V, Fittipaldi R, Ryall JG, Sartorelli V, Caretti G. The methyltransferase SMYD3
568 mediates the recruitment of transcriptional cofactors at the myostatin and c-Met genes and
569 regulates skeletal muscle atrophy. Genes & Development. 2013;27:1299-312.

570 [122] Hamamoto R, Furukawa Y, Morita M, Iimura Y, Silva FP, Li M, et al. SMYD3 encodes a
571 histone methyltransferase involved in the proliferation of cancer cells. Nature Cell Biology.
572 2004;6:731-40.

573 [123] Nagamatsu G, Saito S, Kosaka T, Takubo K, Kinoshita T, Oya M, et al. Optimal ratio of
574 transcription factors for somatic cell reprogramming. The Journal of Biological Chemistry.
575 2012;287:36273-82.

576 [124] Tachibana M, Ueda J, Fukuda M, Takeda N, Ohta T, Iwanari H, et al. Histone
577 methyltransferases G9a and GLP form heteromeric complexes and are both crucial for
578 methylation of euchromatin at H3-K9. Genes & Development. 2005;19:815-26.

579 [125] Ohno H, Shinoda K, Ohyama K, Sharp LZ, Kajimura S. EHMT1 controls brown adipose
580 cell fate and thermogenesis through the PRDM16 complex. Nature. 2013;504:163-7.

[126] Onder TT, Kara N, Cherry A, Sinha AU, Zhu N, Bernt KM, et al. Chromatin-modifying enzymes as modulators of reprogramming. Nature. 2012;483:598-602.

[127] Aniello F, Colella G, Muscariello G, Lanza A, Ferrara D, Branno M, et al. Expression of four histone lysine-methyltransferases in parotid gland tumors. Anticancer Research. 2006;26:2063-7.

[128] Wagschal A, Sutherland HG, Woodfine K, Henckel A, Chebli K, Schulz R, et al. G9a histone methyltransferase contributes to imprinting in the mouse placenta. Molecular and Cellular Biology. 2008;28:1104-13.

[129] Antignano F, Burrows K, Hughes MR, Han JM, Kron KJ, Penrod NM, et al. Methyltransferase G9A regulates T cell differentiation during murine intestinal inflammation. The Journal of Clinical Investigation. 2014;124:1945-55.

[130] Chen MW, Hua KT, Kao HJ, Chi CC, Wei LH, Johansson G, et al. H3K9 histone methyltransferase G9a promotes lung cancer invasion and metastasis by silencing the cell adhesion molecule Ep-CAM. Cancer Research. 2010;70:7830-40.

[131] Dodge JE, Kang YK, Beppu H, Lei H, Li E. Histone H3-K9 methyltransferase ESET is essential for early development. Molecular and Cellular Biology. 2004;24:2478-86.

[132] Lawson KA, Teteak CJ, Gao J, Li N, Hacquebord J, Ghatan A, et al. ESET histone methyltransferase regulates osteoblastic differentiation of mesenchymal stem cells during postnatal bone development. FEBS Letters. 2013;587:3961-7.

[133] Peters AH, O'Carroll D, Scherthan H, Mechtler K, Sauer S, Schofer C, et al. Loss of the Suv39h histone methyltransferases impairs mammalian heterochromatin and genome stability. Cell. 2001;107:323-37.

[134] Ait-Si-Ali S, Guasconi V, Fritsch L, Yahi H, Sekhri R, Naguibneva I, et al. A Suv39h-dependent mechanism for silencing S-phase genes in differentiating but not in cycling cells. The EMBO Journal. 2004;23:605-15.

[135] Lee MH, Jothi M, Gudkov AV, Mal AK. Histone methyltransferase KMT1A restrains entry of alveolar rhabdomyosarcoma cells into a myogenic differentiated state. Cancer Research. 2011;71:3921-31.

[136] Chen J, Liu H, Liu J, Qi J, Wei B, Yang J, et al. H3K9 methylation is a barrier during somatic cell reprogramming into iPSCs. Nature Genetics. 2013;45:34-42.

[137] Fang W, Piao Z, Simon D, Sheu JC, Huang S. Mapping of a minimal deleted region in human hepatocellular carcinoma to 1p36.13-p36.23 and mutational analysis of the RIZ (PRDM2) gene localized to the region. Genes, Chromosomes & Cancer. 2000;28:269-75.

[138] Steele-Perkins G, Fang W, Yang XH, Van Gele M, Carling T, Gu J, et al. Tumor formation and inactivation of RIZ1, an Rb-binding member of a nuclear protein-methyltransferase superfamily. Genes & Development. 2001;15:2250-62.

[139] Varambally S, Dhanasekaran SM, Zhou M, Barrette TR, Kumar-Sinha C, Sanda MG, et al. The polycomb group protein EZH2 is involved in progression of prostate cancer. Nature. 2002;419:624-9.

620 [140] Puschendorf M, Terranova R, Boutsma E, Mao X, Isono K, Brykczynska U, et al. PRC1
621 and Suv39h specify parental asymmetry at constitutive heterochromatin in early mouse embryos.
622 Nature Genetics. 2008;40:411-20.

623 [141] Caretti G, Di Padova M, Micales B, Lyons GE, Sartorelli V. The Polycomb Ezh2
624 methyltransferase regulates muscle gene expression and skeletal muscle differentiation. Genes &
625 Development. 2004;18:2627-38.

626 [142] Ezhkova E, Lien WH, Stokes N, Pasolli HA, Silva JM, Fuchs E. EZH1 and EZH2
627 cogovern histone H3K27 trimethylation and are essential for hair follicle homeostasis and wound
628 repair. Genes & Development. 2011;25:485-98.

629 [143] Bardot ES, Valdes VJ, Zhang J, Perdigoto CN, Nicolis S, Hearn SA, et al. Polycomb
630 subunits Ezh1 and Ezh2 regulate the Merkel cell differentiation program in skin stem cells. The
631 EMBO Journal. 2013;32:1990-2000.

632 [144] Schotta G, Sengupta R, Kubicek S, Malin S, Kauer M, Callen E, et al. A chromatin-wide
633 transition to H4K20 monomethylation impairs genome integrity and programmed DNA
634 rearrangements in the mouse. Genes & Development. 2008;22:2048-61.

635 [145] Nicetto D, Hahn M, Jung J, Schneider TD, Straub T, David R, et al. Suv4-20h histone
636 methyltransferases promote neuroectodermal differentiation by silencing the pluripotency-
637 associated Oct-25 gene. PLOS Genetics. 2013;9:e1003188.

638 [146] Marion RM, Schotta G, Ortega S, Blasco MA. Suv4-20h abrogation enhances telomere
639 elongation during reprogramming and confers a higher tumorigenic potential to iPS cells. PLOS
640 ONE. 2011;6:e25680.

[147] Fraga MF, Ballestar E, Villar-Garea A, Boix-Chornet M, Espada J, Schotta G, et al. Loss of acetylation at Lys16 and trimethylation at Lys20 of histone H4 is a common hallmark of human cancer. Nature Genetics. 2005;37:391-400.

[148] Takawa M, Cho HS, Hayami S, Toyokawa G, Kogure M, Yamane Y, et al. Histone lysine methyltransferase SETD8 promotes carcinogenesis by deregulating PCNA expression. Cancer Research. 2012;72:3217-27.

[149] Oda H, Okamoto I, Murphy N, Chu J, Price SM, Shen MM, et al. Monomethylation of histone H4-lysine 20 is involved in chromosome structure and stability and is essential for mouse development. Molecular and Cellular Biology. 2009;29:2278-95.

[150] Driskell I, Oda H, Blanco S, Nascimento E, Humphreys P, Frye M. The histone methyltransferase Setd8 acts in concert with c-Myc and is required to maintain skin. The EMBO Journal. 2012;31:616-29.

[151] Rayasam GV, Wendling O, Angrand PO, Mark M, Niederreither K, Song L, et al. NSD1 is essential for early post-implantation development and has a catalytically active SET domain. The EMBO Journal. 2003;22:3153-63.

[152] Wang GG, Cai L, Pasillas MP, Kamps MP. NUP98-NSD1 links H3K36 methylation to Hox-A gene activation and leukaemogenesis. Nature Cell Biology. 2007;9:804-12.

[153] Wang L, Zheng A, Yi L, Xu C, Ding M, Deng H. Identification of potential nuclear reprogramming and differentiation factors by a novel selection method for cloning chromatin-binding proteins. Biochemical and Biophysical Research Communications. 2004;325:302-7.

[154] Berdasco M, Ropero S, Setien F, Fraga MF, Lapunzina P, Losson R, et al. Epigenetic inactivation of the Sotos overgrowth syndrome gene histone methyltransferase NSD1 in human neuroblastoma and glioma. Proceedings of the National Academy of Sciences of the United States of America. 2009;106:21830-5.

[155] Hu M, Sun XJ, Zhang YL, Kuang Y, Hu CQ, Wu WL, et al. Histone H3 lysine 36 methyltransferase Hypb/Setd2 is required for embryonic vascular remodeling. Proceedings of the National Academy of Sciences of the United States of America. 2010;107:2956-61.

[156] Zhang Y, Xie S, Zhou Y, Xie Y, Liu P, Sun M, et al. H3K36 Histone Methyltransferase Setd2 Is Required for Murine Embryonic Stem Cell Differentiation toward Endoderm. Cell Reports. 2014;8:1989-2002.

[157] Al Sarakbi W, Sasi W, Jiang WG, Roberts T, Newbold RF, Mokbel K. The mRNA expression of SETD2 in human breast cancer: correlation with clinico-pathological parameters. BMC Cancer. 2009;9:290.

[158] Yang P, Guo L, Duan ZJ, Tepper CG, Xue L, Chen X, et al. Histone methyltransferase NSD2/MMSET mediates constitutive NF-kappaB signaling for cancer cell proliferation, survival, and tumor growth via a feed-forward loop. Molecular and Cellular Biology. 2012;32:3121-31.

[159] Nimura K, Ura K, Shiratori H, Ikawa M, Okabe M, Schwartz RJ, et al. A histone H3 lysine 36 trimethyltransferase links Nkx2-5 to Wolf-Hirschhorn syndrome. Nature. 2009;460:287-91.

[160] Lee YF, Nimura K, Lo WN, Saga K, Kaneda Y. Histone H3 Lysine 36 Methyltransferase Whsc1 Promotes the Association of Runx2 and p300 in the Activation of Bone-Related Genes. PLOS ONE. 2014;9:e106661.

683 [161] Diehl F, Brown MA, van Amerongen MJ, Novoyatleva T, Wietelmann A, Harriss J, et al.
684 Cardiac deletion of Smyd2 is dispensable for mouse heart development. PLOS ONE.
685 2010;5:e9748.

686 [162] Sese B, Barrero MJ, Fabregat MC, Sander V, Izpisua Belmonte JC. SMYD2 is induced
687 during cell differentiation and participates in early development. The International Journal of
688 Developmental Biology. 2013;57:357-64.

689 [163] Komatsu S, Imoto I, Tsuda H, Kozaki KI, Muramatsu T, Shimada Y, et al. Overexpression
690 of SMYD2 relates to tumor cell proliferation and malignant outcome of esophageal squamous
691 cell carcinoma. Carcinogenesis. 2009;30:1139-46.

692 [164] Institute WTS. Alleles produced for the EUCOMM and EUCOMMTools projects by the
693 Wellcome Trust Sanger Institute. MGI Direct Data Submission. 2010.

694 [165] Wray J, Williamson EA, Sheema S, Lee SH, Libby E, Willman CL, et al. Metnase
695 mediates chromosome decatenation in acute leukemia cells. Blood. 2009;114:1852-8.

696 [166] Miyazaki H, Higashimoto K, Yada Y, Endo TA, Sharif J, Komori T, et al. Ash1l
697 methylates Lys36 of histone H3 independently of transcriptional elongation to counteract
698 polycomb silencing. PLOS Genetics. 2013;9:e1003897.

699 [167] Jones B, Su H, Bhat A, Lei H, Bajko J, Hevi S, et al. The histone H3K79 methyltransferase
700 Dot1L is essential for mammalian development and heterochromatin structure. PLOS Genetics.
701 2008;4:e1000190.

[168] Barry ER, Krueger W, Jakuba CM, Veilleux E, Ambrosi DJ, Nelson CE, et al. ES cell cycle progression and differentiation require the action of the histone methyltransferase Dot1L. Stem Cells. 2009;27:1538-47.

[169] Nguyen AT, Taranova O, He J, Zhang Y. DOT1L, the H3K79 methyltransferase, is required for MLL-AF9-mediated leukemogenesis. Blood. 2011;117:6912-22.

[170] Li E, Bestor TH, Jaenisch R. Targeted mutation of the DNA methyltransferase gene results in embryonic lethality. Cell. 1992;69:915-26.

[171] Rhee KD, Yu J, Zhao CY, Fan G, Yang XJ. Dnmt1-dependent DNA methylation is essential for photoreceptor terminal differentiation and retinal neuron survival. Cell Death & Disease. 2012;3:e427.

[172] Rhee I, Bachman KE, Park BH, Jair KW, Yen RW, Schuebel KE, et al. DNMT1 and DNMT3b cooperate to silence genes in human cancer cells. Nature. 2002;416:552-6.

[173] Arima T, Hata K, Tanaka S, Kusumi M, Li E, Kato K, et al. Loss of the maternal imprint in Dnmt3Lmat-/- mice leads to a differentiation defect in the extraembryonic tissue. Developmental Biology. 2006;297:361-73.

[174] Neri F, Krepelova A, Incarnato D, Maldotti M, Parlato C, Galvagni F, et al. Dnmt3L antagonizes DNA methylation at bivalent promoters and favors DNA methylation at gene bodies in ESCs. Cell. 2013;155:121-34.

[175] Gokul G, Ramakrishna G, Khosla S. Reprogramming of HeLa cells upon DNMT3L overexpression mimics carcinogenesis. Epigenetics (official journal of the DNA Methylation Society). 2009;4:322-9.

[176] Eilertsen KJ, Power RA, Harkins LL, Misica P. Targeting cellular memory to reprogram the epigenome, restore potential, and improve somatic cell nuclear transfer. Animal Reproduction Science. 2007;98:129-46.

[177] Okano M, Bell DW, Haber DA, Li E. DNA methyltransferases Dnmt3a and Dnmt3b are essential for de novo methylation and mammalian development. Cell. 1999;99:247-57.

[178] Challen GA, Sun D, Jeong M, Luo M, Jelinek J, Berg JS, et al. Dnmt3a is essential for hematopoietic stem cell differentiation. Nature Genetics. 2012;44:23-31.

[179] Li H, Rauch T, Chen ZX, Szabo PE, Riggs AD, Pfeifer GP. The histone methyltransferase SETDB1 and the DNA methyltransferase DNMT3A interact directly and localize to promoters silenced in cancer cells. The Journal of Biological Chemistry. 2006;281:19489-500.

[180] Wongtrakoongate P, Li J, Andrews PW. DNMT3B inhibits the re-expression of genes associated with induced pluripotency. Experimental Cell Research. 2014;321:231-9.

[181] Zhang RR, Cui QY, Murai K, Lim YC, Smith ZD, Jin S, et al. Tet1 regulates adult hippocampal neurogenesis and cognition. Cell Stem Cell. 2013;13:237-45.

[182] Dawlaty MM, Ganz K, Powell BE, Hu YC, Markoulaki S, Cheng AW, et al. Tet1 is dispensable for maintaining pluripotency and its loss is compatible with embryonic and postnatal development. Cell Stem Cell. 2011;9:166-75.

[183] Koh KP, Yabuuchi A, Rao S, Huang Y, Cunniff K, Nardone J, et al. Tet1 and Tet2 regulate 5-hydroxymethylcytosine production and cell lineage specification in mouse embryonic stem cells. Cell Stem Cell. 2011;8:200-13.

743 [184] Hsu CH, Peng KL, Kang ML, Chen YR, Yang YC, Tsai CH, et al. TET1 suppresses cancer
744 invasion by activating the tissue inhibitors of metalloproteinases. Cell Reports. 2012;2:568-79.

745 [185] Langlois T, da Costa Reis Monte-Mor B, Lenglet G, Droin N, Marty C, Le Couedic JP, et
746 al. TET2 deficiency inhibits mesoderm and hematopoietic differentiation in human embryonic
747 stem cells. Stem Cells. 2014;32:2084-97.

748 [186] Moran-Crusio K, Reavie L, Shih A, Abdel-Wahab O, Ndiaye-Lobry D, Lobry C, et al.
749 Tet2 loss leads to increased hematopoietic stem cell self-renewal and myeloid transformation.
750 Cancer Cell. 2011;20:11-24.

751 [187] Li Z, Cai X, Cai CL, Wang J, Zhang W, Petersen BE, et al. Deletion of Tet2 in mice leads
752 to dysregulated hematopoietic stem cells and subsequent development of myeloid malignancies.
753 Blood. 2011;118:4509-18.

754 [188] Doege CA, Inoue K, Yamashita T, Rhee DB, Travis S, Fujita R, et al. Early-stage
755 epigenetic modification during somatic cell reprogramming by Parp1 and Tet2. Nature.
756 2012;488:652-5.

757 [189] Solary E, Bernard OA, Tefferi A, Fuks F, Vainchenker W. The Ten-Eleven Translocation-
758 2 (TET2) gene in hematopoiesis and hematopoietic diseases. Leukemia. 2014;28:485-96.

759 [190] Gu TP, Guo F, Yang H, Wu HP, Xu GF, Liu W, et al. The role of Tet3 DNA dioxygenase
760 in epigenetic reprogramming by oocytes. Nature. 2011;477:606-10.

761 [191] Li T, Yang D, Li J, Tang Y, Yang J, Le W. Critical Role of Tet3 in Neural Progenitor Cell
762 Maintenance and Terminal Differentiation. Molecular Neurobiology. 2014.

763 [192] Du C, Kurabe N, Matsushima Y, Suzuki M, Kahyo T, Ohnishi I, et al. Robust quantitative
764 assessments of cytosine modifications and changes in the expressions of related enzymes in
765 gastric cancer. Gastric cancer (official journal of the International Gastric Cancer Association
766 and the Japanese Gastric Cancer Association). 2014; DOI: 10.1007/s10120-014-0409-4.

767 [193] Qiu J, Shi G, Jia Y, Li J, Wu M, Li J, et al. The X-linked mental retardation gene PHF8 is
768 a histone demethylase involved in neuronal differentiation. Cell Research. 2010;20:908-18.

769 [194] Bjorkman M, Ostling P, Harma V, Virtanen J, Mpindi JP, Rantala J, et al. Systematic
770 knockdown of epigenetic enzymes identifies a novel histone demethylase PHF8 overexpressed in
771 prostate cancer with an impact on cell proliferation, migration and invasion. Oncogene.
772 2012;31:3444-56.

773 [195] Zhou Z, Thomsen R, Kahns S, Nielsen AL. The NSD3L histone methyltransferase
774 regulates cell cycle and cell invasion in breast cancer cells. Biochemical and Biophysical
775 Research Communications. 2010;398:565-70.

776 [196] Dong R, Yao R, Du J, Wang S, Fan Z. Depletion of histone demethylase KDM2A
777 enhanced the adipogenic and chondrogenic differentiation potentials of stem cells from apical
778 papilla. Experimental Cell Research. 2013;319:2874-82.

779 [197] Wagner KW, Alam H, Dhar SS, Giri U, Li N, Wei Y, et al. KDM2A promotes lung
780 tumorigenesis by epigenetically enhancing ERK1/2 signaling. The Journal of Clinical
781 Investigation. 2013;123:5231-46.

782 [198] Wang T, Chen K, Zeng X, Yang J, Wu Y, Shi X, et al. The histone demethylases
783 Jhdm1a/1b enhance somatic cell reprogramming in a vitamin-C-dependent manner. Cell Stem
784 Cell. 2011;9:575-87.

785 [199] Ishimura A, Minehata K, Terashima M, Kondoh G, Hara T, Suzuki T. Jmjd5, an
786 H3K36me2 histone demethylase, modulates embryonic cell proliferation through the regulation
787 of Cdkn1a expression. Development. 2012;139:749-59.

788 [200] Youn MY, Yokoyama A, Fujiyama-Nakamura S, Ohtake F, Minehata K, Yasuda H, et al.
789 JMJD5, a Jumonji C (JmjC) domain-containing protein, negatively regulates osteoclastogenesis
790 by facilitating NFATc1 protein degradation. The Journal of Biological Chemistry.
791 2012;287:12994-3004.

792 [201] Hsia DA, Tepper CG, Pochampalli MR, Hsia EY, Izumiya C, Huerta SB, et al. KDM8, a
793 H3K36me2 histone demethylase that acts in the cyclin A1 coding region to regulate cancer cell
794 proliferation. Proceedings of the National Academy of Sciences of the United States of America.
795 2010;107:9671-6.

796 [202] Brien GL, Gambero G, O'Connell DJ, Jerman E, Turner SA, Egan CM, et al. Polycomb
797 PHF19 binds H3K36me3 and recruits PRC2 and demethylase NO66 to embryonic stem cell
798 genes during differentiation. Nature Structural & Molecular Biology. 2012;19:1273-81.

799 [203] Suzuki C, Takahashi K, Hayama S, Ishikawa N, Kato T, Ito T, et al. Identification of Myc-
800 associated protein with JmjC domain as a novel therapeutic target oncogene for lung cancer.
801 Molecular Cancer Therapeutics. 2007;6:542-51.

802 [204] Fukuda T, Tokunaga A, Sakamoto R, Yoshida N. Fbxl10/Kdm2b deficiency accelerates
803 neural progenitor cell death and leads to exencephaly. Molecular and Cellular Neurosciences.
804 2011;46:614-24.

805 [205] Liang G, He J, Zhang Y. Kdm2b promotes induced pluripotent stem cell generation by
806 facilitating gene activation early in reprogramming. Nature Cell Biology. 2012;14:457-66.

[206] Tzatsos A, Paskaleva P, Ferrari F, Deshpande V, Stoykova S, Contino G, et al. KDM2B promotes pancreatic cancer via Polycomb-dependent and -independent transcriptional programs. The Journal of Clinical Investigation. 2013;123:727-39.

[207] Wang Y, Zhang H, Chen Y, Sun Y, Yang F, Yu W, et al. LSD1 is a subunit of the NuRD complex and targets the metastasis programs in breast cancer. Cell. 2009;138:660-72.

[208] Lin SL, Chang DC, Lin CH, Ying SY, Leu D, Wu DT. Regulation of somatic cell reprogramming through inducible mir-302 expression. Nucleic Acids Research. 2011;39:1054-65.

[209] Wang J, Scully K, Zhu X, Cai L, Zhang J, Prefontaine GG, et al. Opposing LSD1 complexes function in developmental gene activation and repression programmes. Nature. 2007;446:882-7.

[210] Amente S, Lania L, Majello B. The histone LSD1 demethylase in stemness and cancer transcription programs. Biochimica et Biophysica Acta (BBA) - Gene Regulatory Mechanisms. 2013;1829:981-6.

[211] Weiss J, Hurley LA, Harris RM, Finlayson C, Tong M, Fisher LA, et al. ENU mutagenesis in mice identifies candidate genes for hypogonadism. Mammalian Genome. 2012;23:346-55.

[212] Fog CK, Galli GG, Lund AH. PRDM proteins: important players in differentiation and disease. Bioessays. 2012;34:50-60.

[213] Feichtinger J, Aldeailej I, Anderson R, Almutairi M, Almatrafi A, Alsiwiehri N, et al. Meta-analysis of clinical data using human meiotic genes identifies a novel cohort of highly restricted cancer-specific marker genes. Oncotarget. 2012;3:843-53.

828 [214] Klose RJ, Yan Q, Tothova Z, Yamane K, Erdjument-Bromage H, Tempst P, et al. The
829 retinoblastoma binding protein RBP2 is an H3K4 demethylase. Cell. 2007;128:889-900.

830 [215] Benevolenskaya EV, Murray HL, Branton P, Young RA, Kaelin WG, Jr. Binding of pRB
831 to the PHD protein RBP2 promotes cellular differentiation. Molecular Cell. 2005;18:623-35.

832 [216] Hou J, Wu J, Dombkowski A, Zhang K, Holowatyj A, Boerner JL, et al. Genomic
833 amplification and a role in drug-resistance for the KDM5A histone demethylase in breast cancer.
834 American Journal of Translational Research. 2012;4:247-56.

835 [217] Wang WP, Tzeng TY, Wang JY, Lee DC, Lin YH, Wu PC, et al. The EP300, KDM5A,
836 KDM6A and KDM6B chromatin regulators cooperate with KLF4 in the transcriptional
837 activation of POU5F1. PLOS ONE. 2012;7:e52556.

838 [218] Albert M, Schmitz SU, Kooistra SM, Malatesta M, Morales Torres C, Rekling JC, et al.
839 The histone demethylase Jarid1b ensures faithful mouse development by protecting
840 developmental genes from aberrant H3K4me3. PLOS genetics. 2013;9:e1003461.

841 [219] Schmitz SU, Albert M, Malatesta M, Morey L, Johansen JV, Bak M, et al. Jarid1b targets
842 genes regulating development and is involved in neural differentiation. The EMBO Journal.
843 2011;30:4586-600.

844 [220] Cellot S, Hope KJ, Chagraoui J, Sauvageau M, Deneault E, MacRae T, et al. RNAi screen
845 identifies Jarid1b as a major regulator of mouse HSC activity. Blood. 2013;122:1545-55.

846 [221] Kidder BL, Hu G, Yu ZX, Liu C, Zhao K. Extended self-renewal and accelerated
847 reprogramming in the absence of Kdm5b. Molecular and Cellular Biology. 2013;33:4793-810.

[222] Xu J, Deng X, Disteche CM. Sex-specific expression of the X-linked histone demethylase gene Jarid1c in brain. PLOS ONE. 2008;3:e2553.

[223] Cloos PA, Christensen J, Agger K, Helin K. Erasing the methyl mark: histone demethylases at the center of cellular differentiation and disease. Genes & Development. 2008;22:1115-40.

[224] Stein J, Majores M, Rohde M, Lim S, Schneider S, Krappe E, et al. KDM5C is overexpressed in prostate cancer and is a prognostic marker for prostate-specific antigen-relapse following radical prostatectomy. The American Journal of Pathology. 2014;184:2430-7.

[225] Perinchery G, Sasaki M, Angan A, Kumar V, Carroll P, Dahiya R. Deletion of Y-chromosome specific genes in human prostate cancer. The Journal of Urology. 2000;163:1339-42.

[226] Liu Z, Zhou S, Liao L, Chen X, Meistrich M, Xu J. Jmjd1a demethylase-regulated histone modification is essential for cAMP-response element modulator-regulated gene expression and spermatogenesis. The Journal of Biological Chemistry. 2010;285:2758-70.

[227] Tateishi K, Okada Y, Kallin EM, Zhang Y. Role of Jhdm2a in regulating metabolic gene expression and obesity resistance. Nature. 2009;458:757-61.

[228] Herzog M, Josseaux E, Dedeurwaerder S, Calonne E, Volkmar M, Fuks F. The histone demethylase Kdm3a is essential to progression through differentiation. Nucleic Acids Research. 2012;40:7219-32.

867 [229] Lockman K, Taylor JM, Mack CP. The histone demethylase, Jmjd1a, interacts with the
868 myocardin factors to regulate SMC differentiation marker gene expression. Circulation Research.
869 2007;101:e115-23.

870 [230] Wongtawan T. Epigenetic and chromatin reprogramming in mouse development and
871 embryonic stem cell (PhD dissertation). Edinburgh, U.K.: the University of Edinburgh; 2010.

872 [231] Zhang QJ, Chen HZ, Wang L, Liu DP, Hill JA, Liu ZP. The histone trimethyllysine
873 demethylase JMJD2A promotes cardiac hypertrophy in response to hypertrophic stimuli in mice.
874 The Journal of Clinical Investigation. 2011;121:2447-56.

875 [232] Ye L, Fan Z, Yu B, Chang J, Al Hezaimi K, Zhou X, et al. Histone demethylases KDM4B
876 and KDM6B promotes osteogenic differentiation of human MSCs. Cell Stem Cell. 2012;11:50-
877 61.

878 [233] Fu L, Chen L, Yang J, Ye T, Chen Y, Fang J. HIF-1alpha-induced histone demethylase
879 JMJD2B contributes to the malignant phenotype of colorectal cancer cells via an epigenetic
880 mechanism. Carcinogenesis. 2012;33:1664-73.

881 [234] Wang J, Zhang M, Zhang Y, Kou Z, Han Z, Chen DY, et al. The histone demethylase
882 JMJD2C is stage-specifically expressed in preimplantation mouse embryos and is required for
883 embryonic development. Biology of Reproduction. 2010;82:105-11.

884 [235] Loh YH, Zhang W, Chen X, George J, Ng HH. Jmjd1a and Jmjd2c histone H3 Lys 9
885 demethylases regulate self-renewal in embryonic stem cells. Genes & Development.
886 2007;21:2545-57.

887 [236] Luo W, Chang R, Zhong J, Pandey A, Semenza GL. Histone demethylase JMJD2C is a
888 coactivator for hypoxia-inducible factor 1 that is required for breast cancer progression.
889 Proceedings of the National Academy of Sciences of the United States of America.
890 2012;109:E3367-76.

891 [237] Iwamori N, Zhao M, Meistrich ML, Matzuk MM. The testis-enriched histone demethylase,
892 KDM4D, regulates methylation of histone H3 lysine 9 during spermatogenesis in the mouse but
893 is dispensable for fertility. Biology of Reproduction. 2011;84:1225-34.

894 [238] Kim TD, Oh S, Shin S, Janknecht R. Regulation of tumor suppressor p53 and HCT116 cell
895 physiology by histone demethylase JMJD2D/KDM4D. PLOS ONE. 2012;7:e34618.

896 [239] Ciccone DN, Su H, Hevi S, Gay F, Lei H, Bajko J, et al. KDM1B is a histone H3K4
897 demethylase required to establish maternal genomic imprints. Nature. 2009;461:415-8.

898 [240] Crea F, Sun L, Mai A, Chiang YT, Farrar WL, Danesi R, et al. The emerging role of
899 histone lysine demethylases in prostate cancer. Molecular Cancer. 2012;11:52.

900 [241] Huang C, Xiang Y, Wang Y, Li X, Xu L, Zhu Z, et al. Dual-specificity histone
901 demethylase KIAA1718 (KDM7A) regulates neural differentiation through FGF4. Cell research.
902 2010;20:154-65.

903 [242] Osawa T, Muramatsu M, Wang F, Tsuchida R, Kodama T, Minami T, et al. Increased
904 expression of histone demethylase JHDM1D under nutrient starvation suppresses tumor growth
905 via down-regulating angiogenesis. Proceedings of the National Academy of Sciences of the
906 United States of America. 2011;108:20725-9.

[243] Jiang W, Wang J, Zhang Y. Histone H3K27me3 demethylases KDM6A and KDM6B modulate definitive endoderm differentiation from human ESCs by regulating WNT signaling pathway. Cell Research. 2013;23:122-30.

[244] Wang C, Lee JE, Cho YW, Xiao Y, Jin Q, Liu C, et al. UTX regulates mesoderm differentiation of embryonic stem cells independent of H3K27 demethylase activity. Proceedings of the National Academy of Sciences of the United States of America. 2012;109:15324-9.

[245] van Haaften G, Dalgliesh GL, Davies H, Chen L, Bignell G, Greenman C, et al. Somatic mutations of the histone H3K27 demethylase gene UTX in human cancer. Nature Genetics. 2009;41:521-3.

[246] Burgold T, Voituron N, Caganova M, Tripathi PP, Menuet C, Tusi BK, et al. The H3K27 demethylase JMJD3 is required for maintenance of the embryonic respiratory neuronal network, neonatal breathing, and survival. Cell Reports. 2012;2:1244-58.

[247] Yang D, Okamura H, Nakashima Y, Haneji T. Histone demethylase Jmjd3 regulates osteoblast differentiation via transcription factors Runx2 and osterix. The Journal of Biological Chemistry. 2013;288:33530-41.

[248] Ene CI, Edwards L, Riddick G, Baysan M, Woolard K, Kotliarova S, et al. Histone demethylase Jumonji D3 (JMJD3) as a tumor suppressor by regulating p53 protein nuclear stabilization. PLOS ONE. 2012;7:e51407.

Acknowledgements

We dedicate this review to the memory of Busabun Chaisalee Wongtawan (1975-2011), who contributed to the literature study for this review. Research in the Wongtawan lab on epigenetic dedifferentiation and transdiferentiation is funded by a grant from Mahidol University. Research in the Pennings lab is funded by the Biotechnology & Biological Sciences Research Council and the British Heart Foundation.

Table 1 – 2. Legend

Reported activating roles in cancer include: the protein was observed to be overexpressed in cancer tissues and/or loss-of-function experiments reduced cancer phenotypes, or overexpression enhanced cancer phenotypes. Reported repressive roles in cancer include: the protein was observed to be underexpressed in cancer tissues and/or loss-of-function was observed to result in cancer phenotypes, or overexpression reduced cancer phenotypes.

941 **Table 1** The importance of histone lysine methyltransferase and DNA methyltransferase for development,
942 differentiation, cell reprogramming (SCNT and iPSC) and cancer.

Site	Enzyme	Embryonic Lethality	Abnormal differentiation	Cell reprogramming	Cancer	Reference
H3K4	Setd1a/ Kmt2f	Yes (E7.5)	No	-	Activating (leukaemia)	[98, 99]
	Setd1b/ Kmt2g	Yes (E11.5)	No	-	Repressive (squamous cell carcinoma)	[98, 100]
	Mll/ Kmt2a	Yes (E11.5)	Yes (blood)	Enhance	Repressive (prostate carcinoma)	[101-105]
	Kmt2b/ Mll4	Yes (E10.5)	Yes (heart)	Enhance	Repressive (squamous cell carcinoma)	[103, 106-109]
	Mll3/ Kmt2c	No	Yes (blood)	Enhance	Repressive (myeloid leukemia)	[103, 110-112]
	Kmt2d/ Mll2	No	Yes (heart)	Enhance	Repressive (lung cancer)	[108, 109, 113, 114]
	Kmt2e/ Mll5	No	Yes (heart)	-	Repressive (prostate carcinoma)	[103, 115, 116]
	Setd7/ Kmt7	No	Yes (neuron)	Inhibit	Repressive (prostate cancer)	[117-120]
	Smyd3/ Kmt3e	-	Yes (muscle)	Enhance	Activating (hepatocellular carcinomas)	[121-123]
H3K9	Ehmt1/ Kmt1d	Yes (E9.5)	Yes (fat)	Enhance	Activating (parotid gland tumour)	[124-127]
	Ehmt2/ Kmt1c	Yes (E9.5)	Yes (blood)	Enhance	Activating (lung cancer)	[124, 126, 128-130]
	Eset/ Kmt1e	Yes (E8.5)	Yes (bone)	Enhance	Activating (parotid gland tumour)	[126, 127, 131, 132]
	Suv39h1,2/ Kmt1a,b	Yes (E14.5)	Yes (muscle)	Inhibit	Repressive (alveolar rhabdomyosarcoma)	[126, 133-136]
	Prdm2/ Kmt8/	No	Yes (blood)	-	Repressive (B-cell lymphoma)	[137, 138]
	Setdb2/ Kmt1f/	-	-	Enhance	-	[123]
H3K27	Ezh2/ Kmt6a	Yes (E6.5)	Yes (neuron)	Enhance	Activating (prostate cancer)	[126, 139-141]
	Ezh1/ Kmt6b	No	Yes (skin)	-	-	[142, 143]
H4K20	Suv420h1,2/ /Kmt5b,5c	Yes (E18)	Yes (neuron)	Inhibit	Repressive (skin cancer)	[144-147]
	Setd8/ Kmt5a	Yes (E2)	Yes (skin)	-	Activating (bladder cancer)	[148-150]
H3K36	Nsd1/ Kmt3b	Yes (E10.5)	Yes (blood)	Enhance	Activating (leukaemia)	[151-154]
	Setd2/ Kmt3a	Yes (E11.5)	Yes (endoderm)	-	Activating (breast cancer)	[155-157]
	Whsc1/ Nsd2	No	Yes (bone)	Enhance	Activating (prostate cancer)	[123, 158-160]
	Smyd2/ Kmt3c	No	Yes (endoderm)	-	Activating (squamous cell carcinoma)	[161-163]
	Setmar/ Metnase	No	-	-	Activating (leukaemia)	[164, 165]
	Ash1l/ Kmt2h	No	Yes (endoderm)	-	-	[166]
H3K79	Dot1L/ Kmt4	Yes (E9.5)	Yes (ectoderm)	Inhibit	Repressive (leukaemia)	[126, 127, 167-169]
DNA	Dnmt1	Yes (E9.5)	Yes (neuron)	Inhibit	Repressive (colorectal carcinoma)	[126, 170-172]
	Dnmt3L	Yes (E15.5)	Yes (germ cell)	Enhance	Activating (squamous cell carcinoma)	[173-176]
	Dnmt3a	No	Yes (blood)	Inhibit	Repressive (breast cancer)	[126, 177-179]
	Dnmt3b	Yes (E15.5)	Yes (neuron)	-	Repressive (colorectal carcinoma)	[172, 177, 180]

943

944

945 **Table 2.** The importance of histone histone (lysine) demethylase and DNA demethylases for development,
946 differentiation, cell reprogramming (SCNT and iPSC), and cancer.

Site	Enzyme	Embryonic lethality	Abnormal differentiation	Cell reprogramming	Cancer	Reference
DNA	Tet1	No	Yes (neuron)	Enhance	Repressive (prostate cancer)	[181-184]
	Tet2	No	Yes (blood)	Enhance	Repressive (leukaemia)	[185-189]
	Tet3	No	Yes (neuron)	Enhance	Repressive (breast cancer)	[190-192]
	Tet1-3	No	Yes (three germ layers)	-	-	[182, 183]
H3K9 H3K4 H4K20 H3K27	Phf8/ Jhdm1f	-	Yes (neuron)	-	Activating (prostate cancer)	[193, 194]
H3K4 H3K27	Nsd3/ Whsc1l1	-	-	-	Repressive (breast cancer)	[195]
H3K36	Kdm2a/ Jhdm1a	-	Yes (fat)	Enhance	Activating (lung tumour)	[196-198]
	Jmjd5/ Kdm8	Yes (E11)	Yes (bone)	-	Activating (breast cancer)	[199-201]
H3K4 H3K36	C14orf169/ No66	-	Yes (three germ layers)	-	Activating (lung cancer)	[202, 203]
	Kdm2b/ Jhdm1b	Yes (E19)	Yes (neuron)	Enhance	Activating (pancreatic cancer)	[204-206]
	Kdm1a/ Lsd1	Yes (E10.5)	Yes (three germ layers)	Inhibit	Activating (breast cancer)	[207-210]
H3K4	Prdm9	No	No	-	Activating (ovarian cancer)	[211-213]
	Kdm5a/ Jarid1a	No	Yes (pancreas)	Enhance	Activating (leukaemia)	[214-217]
	Kdm5b/ Jarid1b	No	Yes (blood)	Inhibit	Activating (prostate cancer)	[194, 218-221]
	Kdm5c/ Jarid1c	Yes (E15.5)	Yes (neuron)	-	Activating (prostate cancer)	[222-224]
	Kdm5d/ Jarid1d	-	No	-	Repressive (prostate cancer)	[223, 225]
H3K9	Kdm3a/ Jmjd1a	Yes	Yes (endoderm)	Enhance	Activating (prostate cancer)	[136, 194, 226-230]
	Kdm3b/ Jmjd1b	-	-	Enhance	Activating (prostate cancer)	[136, 194]
	Kdm4a/ Jmjd2a	Yes	Yes (heart)	No effect	Activating (prostate cancer)	[136, 194, 230, 231]
	Kdm4b/ Jmjd2b	-	Yes (bone)	Enhance	Activating (colorectal cancer)	[136, 232, 233]
	Kdm4c/ Jmjd2c	Yes (E2)	No	Enhance	Activating (breast cancer)	[136, 230, 234-236]
	Kdm4d/ Jmjd2d	No	No	No effect	Activating (colorectal cancer)	[136, 237, 238]
	Kdm1b/ Lsd2	No	No	Inhibit	Activating (prostate cancer)	[239, 240]
H3K9 H3K27	Kdm7a/ Jhdm1d	-	Yes (neuron)	-	Repressive (uterine cancer)	[241, 242]
H3K27	Kdm6a/ Utx	Yes (E12.5)	Yes (mesoderm)	Enhance	Repressive (myeloma)	[217, 243-245]
	Kdm6b/ Jmjd3	No	Yes (bone)	Enhance	Repressive (Glioblastoma)	[217, 232, 246-248]

947

948