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5 **Epigenetic reprogramming in mammalian cell differentiation, transdifferentiation and**  
6 **dedifferentiation**

7 Tuempong Wongtawan<sup>1\*</sup>, Cristina Aguilar-Sanchez<sup>2</sup>, Busabun Wongtawan<sup>2§</sup> and Sari Pennings<sup>2</sup>

8

9 <sup>1</sup>Laboratory of Cellular Biomedicine and Veterinary Medicine, Department of Pre-clinic and Applied  
10 Animal Science, Mahidol University, Salaya, Puthamonthon, Nakhonprathom 73170, Thailand.

11 <sup>2</sup>Centre for Cardiovascular Science, Queen's Medical Research Institute, the University of Edinburgh, 47  
12 Little France Crescent, Edinburgh, EH16 4TJ, UK.

13 \*Corresponding author: [tuempong.wan@mahidol.edu](mailto:tuempong.wan@mahidol.edu)

14 §Deceased

15

16 **Abstract**

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

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

28 **Keywords:** Epigenetics, Reprogramming, Differentiation, Dedifferentiation,  
29 Transdifferentiation, Cancer

30

### 31 **Review methodology**

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

35

### 36 **Epigenetic definitions**

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

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

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

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

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

## 68 **DNA methylation**

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

## 81 **Histone methylation**

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

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

100 Methylation of histone arginine residues by arginine methyltransferases (PRMTs) is less  
101 extensively studied but it has been found to play significant roles in gene regulation,  
102 development and cancer [29]. Histone arginine methylation can be transcriptionally activating  
103 [30] or repressive [31] depending on the target residue, and on whether the methylation is  
104 symmetric or asymmetric. In mammals, PRMT1- and CARM1-catalysed histone asymmetric  
105 histone dimethylation at arginine is involved in gene activation [30] while PRMT5-catalysed  
106 symmetric histone dimethylated arginine is associated with gene repression [31].

### 107 **Epigenetics and differentiation.**

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

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

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

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

138 disappear after cell differentiation, when most stemness genes are repressed in association with  
139 repressive epigenetic marks while specific differentiated genes become activated [40, 42]. At the  
140 same time, heterochromatin spreading takes place and chromatin plasticity is diminished [38,  
141 43].

### 142 **Reprogramming, dedifferentiation and transdifferentiation.**

143 Unlike in lower vertebrates, reprogramming, dedifferentiation and transdifferentiation rarely  
144 occur naturally in mammals. However, under certain experimental conditions, differentiated cells  
145 can revert into a less differentiated state, in a dedifferentiation process induced by nuclear/cell  
146 reprogramming. Examples include the generation of induced pluripotent stem cells (iPSC) [44],  
147 or the creation of a totipotent embryo derived from somatic cell nuclear transfer (SCNT) [45].  
148 Reprogramming also describes the conversion of one differentiated cell type into another, for  
149 instance of a B lymphocyte into a macrophage [46], or a fibroblast into a cardiac muscle cell  
150 [47], following the induced expression of defined transcription factors. Because these two  
151 examples of cell fate change may not involve a gain in differentiation potential, the term 'lineage  
152 conversion' or 'transdifferentiation' is currently used to describe these processes. Moreover,  
153 cellular dedifferentiation has also been implicated in cancer. As cancer can only be established  
154 from cells that have the potential to divide, and not terminally differentiated cells, one theory  
155 suggests that tumours may arise from the unrestrained growth of dedifferentiated cells that  
156 resemble embryonic or stem cells [48].

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



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

### 168 **Manipulation of epigenetic profiles.**

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

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

**186 Epigenetics in iPSC reprogramming.**

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

**206 Cell reprogramming in veterinary pre-clinical models and agriculture.**

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

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

#### 224 **Epigenetic inhibitors.**

225 In the last decade, a variety of small molecules have been created and discovered, some of which  
226 have the potential to alter epigenetic marks resulting in cell differentiation, transdifferentiation  
227 and dedifferentiation. Early examples include DNA demethylating agents such as 5-azacytidine  
228 (5-AzaC), which is a cytosine analogue that can cause extensive global DNA demethylation and  
229 reduce DNA methyltransferase activity in the cells [79, 80]. It was originally developed as an  
230 antitumor agent, and has been useful in the treatment of leukaemia and myelodysplastic  
231 syndrome [79, 81]. The effect of 5-AzaC is unpredictable, as it may cause dedifferentiation [82],  
232 differentiation [83] or transdifferentiation [84]. Other types of modifiers include histone  
233 deacetylase (HDAC) inhibitors such as valproic acid (VPA) and trichostatin (TSA). VPA has

234 been utilised for decades as a treatment for epilepsy, as a mood stabiliser and in migraine  
235 therapy, while TSA is currently applied as an anticancer medicine [85, 86]. It has been shown  
236 that both VPA and TSA can inhibit HDACs and then trigger active global demethylation of the  
237 mammalian epigenome, causing reprogramming of gene expression [87]. VPA and TSA induce  
238 dedifferentiation by enhancing epigenetic reprogramming in iPSC and SCNT technologies [88-  
239 90]. Moreover, VPA and TSA can induce redifferentiation in cancer, causing growth inhibition  
240 and apoptosis [91, 92].

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

#### 245 **Epigenetic modifier enzyme roles in differentiation in development and disease.**

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

251 Epigenetic modifiers are therefore essential and their defects are strongly linked to  
252 dedifferentiation towards stem cells or cancer (see table 1 and 2). The tables show that modifiers  
253 related to formation of heterochromatin, such as Suv39h, Suv420h, Dmmt1 and Dnmt3l, tend to  
254 act as repressors for dedifferentiation (table 1), whereas histone demethylases Jmjd1 and Jmjd2  
255 act as activators (table 2). H3K4 histone methyl transferases tend to activate cell reprogramming  
256 towards stem cells, but repress cancer (table 1). The important roles played in various

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

### 259 **Conclusion/Summary.**

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

270

271

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925

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932

933 **Table 1 – 2. Legend**

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

939

940

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]
	Ash1/ 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]

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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/ Whsc111	-	-	-	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]

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