Essays in Biochemistry (2019) **63** 691–705
://d /10.1042/EBC20190043

Review Article

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Epigenetic information in the mammalian oocyte has the potential to be transmitted to the next generation and in uence gene expression; this occurs naturally in the case of imprinted genes. Therefore, it is important to understand how epigenetic information is patterned during oocyte development and growth. Here, we review the current state of knowledge of

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transcript species [26,55,56]. Transcriptional activity of these LTRs contributes to the generation of hypermethylated domains found downstream (Figure 1B) [26]. A recent study in mouse, rat and human oocytes identified that approximately one-sixth of all DNA methylation is linked to transcription initiated at LTRs [31]. LTR-dependent DNA methylation shows strong species specificity, and can be inherited to blastocyst or extraembryonic tissues [31]. Moreover, LTRs are suggested to be drivers of species-specific imprint establishment in humans and mice (https://www.biorxiv.org/content/biorxiv/early/2019/08/07/723254.full.pdf).

Local chromatin environment

As noted above, not all sites gain methylation simultaneously during oocyte growth [24,27,29]. The timing of DNA methylation of specific genes and genomic features is not linked to the underlying sequence but could rather be assigned to local chromatin environment, histone PTMs and nucleosome density. Although the oocyte is in a non-replicative state, nucleosome turnover, an inherent process during transcription, is required to aid oocyte maturation. Deletion of HIRA, a histone chaperone responsible for non-canonical histone deposition in quiescent cells [57], in the oocyte results in increased accessibility and loss of landmark histone modifications, which in turn leads to genome-wide hypomethylation [58]. At the same time, nucleosome depletion at certain sites increases accessibility and could allow easier access for DNMTs. Genes showing high accessibility at TSSs or across the gene body during oocyte development are associated with higher transcription and DNA methylation levels [53]. Genes that remain highly compacted throughout oocyte growth tend to remain silent and are not subjected to *de n* methylation. Similarly, precocious expression of the *de n* methyltransferases DNMT3A and DNMT3L accelerates imprint establishment at only a selection of loci and others appear to be protected by a restrictive chromatin environment [59].

Loci that acquire methylation late in oocyte growth are often CGI-rich, and require removal of H3K4me2 or H3K4me3, active chromatin marks that inhibit binding and activity of the DNMT3A/L complex [29,46]. The H3K4 demethylases KDM1A and KDM1B are expressed throughout oocyte growth or from mid-growth phase, respectively. Ablation of KDM1B, and to some extent KDM1A, in the oocyte resulted in failure to establish full DNA methylation over most imprinted genes and led to focal hypomethylation [46,48,60,61]. Similarly, histone deacetylase 1 and 2 (HDAC1/2) are expressed in early oocytes, with the former subsequently decreasing as growth progresses. Loss of HDAC1/2 results in altered chromatin environment and perturbed transcription, leading to both global and imprint-specific DNA methylation loss in the oocyte [62,63]. As noted above, 10% of DNA methylation in the oocyte is transcription-independent and these loci tend to be methylated quite late in oocyte growth. DNMT targeting to those sites is likely to involve histone modifications, remodellers or other chromatin-interacting proteins that would

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ADD-catalytic domain interaction, allowing activation of DNMT3A enzymatic function [85]. Thus, DNA methylation and H3K4me3 are mutually exclusive in the genome. Engineering of the ADD domain to lose sensitivity to

6 I , R.S., G , U., W , S., K , A.R.W., J , K.D., T , D.J. (2010) O C G I L N C P M G *PLos Genet.* **6**, 1001134, ://. /10.1371/ .1001134
7 S , D. (2015) F DNA . *Nature* **517**, 321 326,

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https://doi.org/10.1042/EBC20190043

35 K , M., H , R., C , H., O , M., L , E. , S , H. (2010) G D 3 - D 3 . *Genes Cells* **15**, 169 179, ://. /10.1111/.1365-2443.2009.01374.

36 B , D., X , G.-L., L , C.-S., B , B. B , T.H. (2001) D 3L E M G I . *Science* **294**, 2536 2539, ://. /10.1126/ 1065848

37 H , K., O , M., L , H. L , E. (2002) D 3L D 3 DNA . *Development* **129**, 1983 1993

38 B , M.R., K , M., P -G , V., B , A.B., C , M., F , E. (2016) M DNA M R E T D . *Dev. Cell* **36**, 152 163, ://. /10.1016/.2015.12.027

39 C , M., S , S.A., R , N., D , C., L , D., F , M. (2009) T . *Genes Dev.* **23**, 105 117, ://. /10.1101/.495809

40 L , X., I , M., Z , F., Y , N., Z , X., L , P. (2008) A M -Z E G Z , 57, M B M P I . *Dev Cell.* **15**, 547 557, ://. /10.1016/.2008.08.014

41 Q S., V G., C , A., K , A., J , J., O , S. (2011) I E S C , ZFP57/KAP1 R M H A C DNA M I C R . *Mol Cell.* **44**, 361 372, ://. /10.1016/.2011.08.032

42 L , Y. L , J. (2019) T . *PLos Genet.* **15**, 1008151, ://. /10.1371/.1008151

43 P , C., D , R., A , S., C , M., I , J., C , G. (2012) P D N M I M P -O M I G . *Mol. Cell* **47**, 909 920, ://. /10.1016/.2012.07.010

44 R C.E., T , A., O'N , K.M., I , R.E., S , S., H , K. (2014) O , .

P

120 X , K., C , X., Y , H., X , Y., H Y., W , C. (2017) M S 4 I , E , M M O . *J. Biol. Chem.* **292**, 1798 1807, ://_ . /10.1074/ .M116.767061
121 H , C.W., D , H. K , G. (2018) E , : ? *Hum. Reprod. Update.* **24**, 556 576, ://_ . /10.1093/ _/_ 021
122 G , H., Z , P., Y , L., L , R., H , B., L , Y. (2014) T DNA . *Nature* **511**, 606 610, ://_ . /10.1038/ 13544
123 S , Z.D., C , M.M., H , K.C., K , R., M , S., R , A. (2014) DNA . *Nature* **511**, 611 615, ://_ . /10.1038/ 13581
124 X , W., X , J., Y , G., Y , G., X , K., M , X. (2019) R . *Science* **365**, 353 360, ://_ . /10.1126/ 5118
125 H , J., H , M., O , B., H , S.E., B , J.C., R , A.J. (2004) E RNA DNA -C G- . *Mol. Reprod. Dev.* **67**, 323 336, ://_ . /10.1002/ .20030
126 N , R., N , O., M , T., S , N., I T., Y , K. (2018) L F 60 , S 3 , . *eLife* **7**, 36435, ://_ . /10.7554/ 36435
127 J , R., M , E.O., D , O., M , J., M , M., F V. (2015) M SIN3A R R G E D M P D . *Biol. Reprod.* **93**, 89, ://_ . /10.1095/ .115.133504
128 Z , J.J., B , M., W , F.C., H , Y., L C., D , S. (2018) G9 . *eLife* **7**, 33361, ://_ . /10.7554/ 33361