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proÞling reveals signiÞcant variation in the degree of demethylation across different element classes, and even within their component families [8]. These differences may reßect the need to ensure correct transcriptional activation in the early embryo while maintaining repression of potentially dangerous retrotransposition activity. Other regions have a more evident requirement for maintenance of methylation in the face of global erasure Ñ such as the imprinting control regions (ICRs) crucial to parental imprinting, which are protected against both active demethylation in the zygote and the ensuing passive loss [6,25] (Figure 1).

Methylation proÞling of the hypomethylated blastocyst led to the surprising Þnding that ICRs are not the only regions to resist DNA methylation erasure in the early embryo: the majority of oocyte-speciÞc CGIs along with a subset of sperm-speciÞc CGIs retain higher than predicted methylation [4,5,6,8]. In addition, repetitive elements such as the intracisternal A particles (IAPs) class (the most recent and still potentially active retrotransposons in the rodent

methylation at these regions is only lost completely in the second demethylation phase from E11.5 [7,10,11,19]. This is in line with previous reports describing methylation erasure at ICRs and promoters of germ line specific genes from E11.5 [27–31]. DNA methylation erasure in PGCs is completed in the gonadal stage and results in a globally hypomethylated state at E13.5 [1,2].

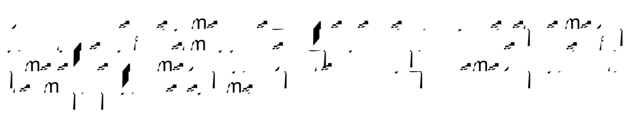
Few regions escape DNA methylation erasure in PGCs and these mostly include IAPs. Other repetitive elements such as the long interspersed element 1 (LINE1) and short interspersed element (SINE) groups are largely reprogrammed; these contrasting dynamics mirror the complex demethylation patterns of retrotransposons in the zygote [7,10,24]. A number of studies have identified regions that escape methylation erasure in PGCs and there seems to be a positive correlation between likelihood of resistance and proximity to an IAP [7,10,11]. However there is also a limited number (a couple of hundred) of CGIs not linked to IAPs, which show variable resistance to reprogramming and may thus contribute to transgenerational epigenetic inheritance [10,1110

embryonic cells. While this accounts for the loss of methylation contributed by the oocyte, active mechanisms also act to remove methylation from the paternal genome in the zygote [as described above]. Both the elongator complex and the base excision repair (BER) pathway (see Box 1) have been implicated in this process [14,33], but their precise role has yet to be dissected. Recent work has uncovered that Tet3 plays a crucial role in active erasure by oxidizing

vivo analysis is needed to study the role of these factors in targeted methylation maintenance in PGCs, however it seems that before the gonadal stage of erasure the dynamics of demethylation and maintenance of speciÞc regions share striking similarities with those in the early embryo.

by the non-canonical maintenance mechanism and thus, ICRs and promoters of germ line specific genes become sensitive to passive demethylation upon hydroxymethylation from around E10.5 [19]. Indeed Zfp57 prefers to bind to its target sequence when methylated, but not when hydroxymethylated [47], providing a potential mechanism for such a switch.

It seems paradoxical that certain methylation marks are maintained in migrating PGCs if they are destined to be erased in gonadal PGCs. It is possible that this paradox is simply a consequence of the non-canonical methylation maintenance mechanism that these regions have evolved, and which seems to be universally in place in early PGCs, ESCs, and cells of the early embryo to ensure robust maintenance even when global methylation erasure occurs. In PGCs, where imprints have to be reset and



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