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The Epigenetics of Germ-line Immortality: Lessons from an Elegant Model System

Hirofumi Furuhashi[1,*] and **William G. Kelly**[2]

[1]Graduate School of Pharmaceutical Sciences, Tohoku University, Sendai 980-8578, Japan

[2]Biology Department, Emory University, Atlanta, GA 30322, USA

Abstract

Epigenetic mechanisms are thought to help regulate the unique transcription program that is established in germ cell development. During the germline cycle of many organisms, the epigenome undergoes waves of extensive resetting events, while a part of epigenetic modification remains faithful to specific loci. Little is known about the mechanisms underlying these events, how loci are selected for, or avoid, reprogramming, or even why these events are required. In particular, although the significance of genomic imprinting phenomena involving DNA methylation in mammals is now well accepted, the role of histone modification as a transgenerational epigenetic mechanism has been the subject of debate. Such epigenetic mechanisms may help regulate transcription programs and / or the pluripotent status conferred on germ cells, and contribute to germ line continuity across generations. Recent studies provide new evidence for heritability of histone modifications through germ line cells and its potential effects on transcription regulation both in the soma and germ line of subsequent generations. Unraveling transgenerational epigenetic mechanisms involving highly conserved histone modifications in elegant model systems will accelerate the generation of new paradigms and inspire research in a wide variety of fields, including basic developmental studies and clinical stem cell research.

Keywords

chromatin; epigenetics; germ cell; histone modification; transcription

Introduction

The term epigenome refers to the profile of epigenetic modification across any genome, i.e., the genome-wide patterns of DNA and histone modifications within any nucleus. It is becoming clear that the epigenome is a crucial component of the information that is passed through cell division and even across generations besides the genome.

Extensive reprogramming of the epigenome is a conserved feature of germ cell specification in many organisms (Seydoux & Braun 2006; Surani *et al.* 2007; Sasaki & Matsui 2008). Since August Weismann proposed the theory of germline continuity more than a century

*Author to whom all correspondence should be addressed: hfuruha@mail.pharm.tohoku.ac.jp.

ago, the mechanism(s) ensuring germline “immortality” across generations has long been unclear. Recent studies have suggested that this transgenerational continuity can involve epigenetic regulation that includes histone modifications and DNA methylation (Surani *et al.* 2007; Katz *et al.* 2009). However, it is still largely unknown how epigenetic modifications regulated in one generation can directly ensure appropriate control of the specialized gene expression program in germ cells of the next generation. To explore these potential generational effects, genetic, cytological, and epigenomic analyses have been performed in many model systems, and information about this is being accumulated. Some elegant studies regarding these epigenetic mechanisms have been conducted using *Caenorhabditis elegans* as a model system.

This review will mainly describe some previous discoveries in genetic studies using *C. elegans*, in which epigenetic regulators required for germline immortality were elegantly identified, and will focus on “erasure” and maintenance of heritable histone modifications as epigenetic memory, both of which appears to have an impact on germ line continuity.

Epigenetic regulators required for germ-line continuity

The MES proteins

The *maternal effect sterile* (*mes*) genes were identified in screens for “grandchildless” mutants in *C. elegans* 20 years ago (Capowski *et al.* 1991). The *mes* mutations cause maternal-effect sterility, the result of degeneration of the germ line in the F2 generation. The phenotype has always been very interesting, since MES proteins (maternal in origin) are last detected in the primordial germ cells (PGCs) of the F1 mutant animals, yet the PGCs produce approximately 1000 functional descendant germ cells. The germ line only fails when specification is attempted in the absence of maternal MES protein in the following generation, that is, in the PGCs of F2 mutants. The emerging model is that the MES proteins help specify the chromatin organization (e.g., chromatin modification status) that the PGCs inherit, and that participates in specifying the germline transcription program in the nascent germ cells. Indeed, MES proteins are homologues of factors identified as critical epigenetic components. MES-2, MES-3 and MES-6 compose a complex resembling the Polycomb Repressive Complex PRC2, which is highly conserved among multicellular organisms and is involved in chromatin based repression via the histone H3 lysine 27 (H3K27) methyltransferase activity of MES-2 (Paulsen *et al.* 1995; Xu *et al.* 2001; Bender *et al.* 2004). MES-4 is a histone H3 lysine 36 (H3K36) methyltransferase that is homologous to mouse NSD1 (Bender *et al.* 2006) and likely functions with a unique set of partners that have not yet been identified. The MES-mediated histone modifications are detectable in all stages of germline development, while a subset of active chromatin marks are erased and almost undetectable in the PGCs (Fig. 1; discussed below). These MES factors have been shown to play important roles in X chromosome silencing that is observed in adult germ cells, although MES-4’s role in this process is presumably indirect, as MES-4 associates predominantly with autosomal chromatin (Fong *et al.* 2002; Bender *et al.* 2006). In the embryo, the maternally-provided MES proteins are initially found in all cells, but they become restricted to the PGCs in later stages (Fong *et al.* 2002). The function of MES proteins in the embryonic germ line, however, remains unclear. Interestingly, among the *mes*

mutants, *mes-4* mutants display the most severe PGC proliferation defects (Capowski *et al.* 1991). We recently discovered that MES-4 contributes to transgenerational-transcription repression in the PGCs (Furuhashi *et al.* unpubl. data, 2009). Intriguingly, MES-4 has also been shown to be required for ectopic expression of germ line genes in *somatic* cells lacking the NuRD (Nucleosome Remodeling and Deacetylase) complex component MEP-1, suggesting that there is a context-dependent function for MES-4-mediated H3K36 methylation (Unhavaithaya *et al.* 2002).

MRG-1

Mutations in the *mrg-1* gene cause a germline degeneration phenotype that is very similar to that observed in *mes* mutants (Takasaki *et al.* 2007). MRG-1 is the *C. elegans* orthologue of MRG15, a mammalian chromodomain protein related to the mortality factor MORF4, which has been shown to be required for cell proliferation and embryo survival (Tominaga *et al.* 2005a, b). The yeast homologue Eaf3 has been shown to recognize and bind H3K36me. and is required for preventing transcriptional initiation from cryptic promoters within gene bodies (Carrozza *et al.* 2005; Joshi & Struhl 2005; Keogh *et al.* 2005). MRG-1 is required for the repression of genes that are also mis-regulated in *mes-4* mutant animals, and like MES-4 is concentrated on autosomes and excluded from the X chromosome (Takasaki *et al.* 2007). Furthermore, PGCs lacking MRG-1 show a severe proliferation defect and degeneration similar to the phenotypes observed in *mes-4* mutant PGCs, implying that MRG-1 may be a “reader”, but perhaps even an “interpreter” of the MES-4 dependent H3K36me. MRG-1 homologues in other systems associate with both histone acetyltransferase (HAT, also called KAT) and histone deacetylase / demethylase (HDAC/KDM) complexes (Carrozza *et al.* 2005; Joshi & Struhl 2005; Keogh *et al.* 2005; Morillon *et al.* 2005; Martin *et al.* 2006; Taverna *et al.* 2006; Hayakawa *et al.* 2007; Larschan *et al.* 2007; Moshkin *et al.* 2009). This protein may thus function as “reader / interpreter” for both transcription activation and repression. This bifunctional property might contribute to the context dependent function of MES-4-mediated H3K36me described above.

SPR-5 / LSD1

A recent study demonstrated that mutants of *spr-5*, the *C. elegans* orthologue of the H3K4me2 demethylase LSD1 (also called KDM1), exhibit progressive sterility over approximately 20–30 generations (Katz *et al.* 2009). This sterility was shown to correlate with the misregulation of a specific gene set, which is expressed in spermatogenesis, and aberrant transgenerational accumulation of H3K4me2. Details of the exciting discovery are described / discussed below.

Resetting histone modification between generations

H3K4 methylation is a well-characterized, transcription-coupled histone modification that can provide an epigenetic memory for regions of active transcription (Li *et al.* 2007; Shilatifard 2008; Muramoto *et al.* 2010). For example, H3K4 methylation by Trithorax in *Drosophila* is critical for the maintenance of a transcriptionally active state through multiple cell divisions, even in the absence of activating transcription factors (Ringrose & Paro 2004). Ng & Gurdon (2008) recently reported that endoderm genes are inappropriately

expressed in *Xenopus* embryos derived from the transfer of differentiated endoderm nuclei. This effect was correlated with lysine 4 of the histone variant H3.3 that is incorporated during endodermal transcription, implying that the complete reprogramming of a somatic nucleus may require efficient erasure of epigenetic information at H3K4 (Ng & Gurdon 2008). The natural target of erasure mechanisms operating in oocytes during somatic cell nuclear transfer experiments are likely to be epigenetic information arriving in gametes. Inappropriate propagation of epigenetic information acquired during gametogenesis to the next generation could result in the misregulation of gamete- and meiosis-specific genes in the zygote. Therefore, resetting of H3K4me2, and other histone marks, that is acquired during gametogenesis may be required to prevent the inappropriate transmission of epigenetic memory across generations.

DNA methylation does not occur in *C. elegans*, and thus all epigenetic information on chromatin is presumably encoded in histone modifications. In *C. elegans*, a number of conserved epigenetic marks of “active” chromatin, such as H3K4me2, dramatically erased from the *C. elegans* PGCs soon after their birth (Schaner *et al.* 2003; Fig. 2). This event might be analogous to the epigenetic erasure observed in the PGCs of other organisms (Seki *et al.* 2005, 2007; Hajkova *et al.* 2008). One of the candidates that could be involved in such an active epigenetic erasure is histone demethylase activity. Katz *et al.* (2009) tested whether *C. elegans* homologues of LSD1, which catalyzes H3K4me demethylation and is a component of CoREST transcriptional repressor complex (Shi *et al.* 2004), were involved in the H3K4me2 erasure in the worm PGCs. Mutations of all three LSD1 orthologs, alone or in combination, did not initially show apparent defects in the PGC erasure process, indicating the existence of LSD1-independent mechanism(s). However, it was noticed that as lines carrying mutations in one of the orthologs, *spr-5*, were passaged, they produced fewer progeny, that the progeny were often sterile, and that the frequency of sterility increased with each passage. Subsequent careful generational analyses revealed the “germ line mortality” phenotype in the *spr-5* mutant, a phenotype in which the germline becomes progressively dysfunctional in successive generations. In contrast to previously identified mutants displaying this phenotype, no evidence of accumulating genetic defects was obtained during the generational analyses. Instead, Katz *et al.* observed that the above phenotypes could be fully rescued by transient exposure to SPR-5 activity, suggesting that the underlying defects were of an *epigenetic* nature. Expression-profiling analyses comparing samples from multiple generations showed striking and coordinated expression changes in genes expressed during spermatogenesis. The expression of these genes was gradually elevated in early generations and peaked just before the generations that showed a sharp decrease in fertility. At this time point, the expression of these genes was also markedly decreased. However, what was particularly intriguing was that the level of H3K4me2 in the promoter regions of these genes continued to rise. The above observations suggest that aberrant accumulation of epigenetic marks can persist, and even inappropriately accumulate, in successive generations independently of increases in transcription. Moreover, in the later generations, Katz *et al.* observed an increased failure to efficiently erase H3K4me2 from the mutant PGCs. Collectively, these data suggest that SPR-5 / LSD1 is required for removing epigenetic information acquired from the parental germ line, and that defects in the erasure mechanism leads to aberrant accumulation of the epigenetic memory

that becomes increasingly difficult to erase in the PGCs (via the SPR-5 independent mechanisms) in successive generations. The transgenerational accumulation of H3K4me2 leads to defects in gametogenesis in the worms and abolishes germ line immortality. However, many questions remain to be answered. For instance, it is not clear when histone demethylase is required in the germ line cycle. SPR-5 protein is observed in both adult germ cells and in the early embryo, and may be functional in either or both stages. It is also unclear why defects in gametogenesis appear after many generations. The SPR-5 / LSD1-independent mechanism that erases H3K4me in the PGCs is presumed to help "mop up" H3K4me2 erasure that is not removed in *spr-5* mutants, but this is not certain. Inefficiencies in this mechanism may normally and stochastically increase the persistence of H3K4me2 in successive generations, and the loss of SPR-5 function may reveal this stochastisticity. The exact targets of either erasure mechanism are still unknown. Regardless of these current uncertainties, recent studies have shown that histone demethylases are critical for the maintenance of fertility in other organisms (Di Stefano *et al.* 2007; Okada *et al.* 2007; Rudolph *et al.* 2007), suggesting that there is a conserved requirement for "epigenetic erasers" to maintain germline continuity.

Heritability of histone modification across generations

The mechanisms for stability and maintenance of epigenetic information, particularly those involving histone modifications, have been extensively investigated in several model systems. Recent discoveries that modifications such as H3K4me and H3K27me can be inherited through gametes raise new questions about whether the transmitted epigenetic modifications play critical roles in the development of the next generation and, what mechanisms ensure the stable inheritance of these modifications (Hammoud *et al.* 2009). Although the maintenance DNA methyltransferase activity of Dnmt1 in mammals has been well characterized, histone methyltransferase activities predominantly responsible for maintenance, but not *de novo*, methylation have not been described. Existence of such machinery in germ line may be expected to ensure faithful maintenance of the histone modification pattern across generations.

Recently, molecular mechanisms underlying the maintenance of some epigenetic marks after DNA/ chromatin replication have been identified. For example, DNA methylation is maintained via the unique recognition of hemi-methylated CpG sequence by the SRA domain of UHRF1, which recruits Dnmt1 to the DNA (Bostick *et al.* 2007; Sharif *et al.* 2007; Arita *et al.* 2008; Avvakumov *et al.* 2008; Hashimoto *et al.* 2008). Similarly, the PRC2 complex, which catalyzes H3K27me3, specifically binds to pre-existing H3K27me3, and this binding appears to be critical for the heritable transmission of this modification (Hansen *et al.* 2008; Margueron *et al.* 2009). As described above, MES proteins in *C. elegans* are the homologues of the PRC2 components and the NSD-type H3K36 methyltransferases and are critical for germline immortality across generations. Further investigation on the potential transgenerational nature of the MES-mediated epigenetic marks and its maintenance mechanism would provide new insights into the epigenetic/ transgenerational transcription regulation as a critical component in development.

Conclusions

The model system *C. elegans*, which allows a combination of traditional genetic screens, cytological, and next generation genome-wide analyses, has made significant contributions to the field of germ cell research. The studies discussed here are of overlapping interest to scientists involved in both traditional chromatin research, because of its impact on the debate surrounding the “heritability” of histone modifications and the histone code, as well as the wide variety of scientists interested in epigenetic regulation of developmental programs and the establishment and maintenance of the germ line.

An important question that is still largely unclear is exactly how any molecular mechanism determines what information is to be reset and what is to be maintained between generations. Future studies focusing on this will allow us to gain better understanding of the molecular basis of germ line continuity.

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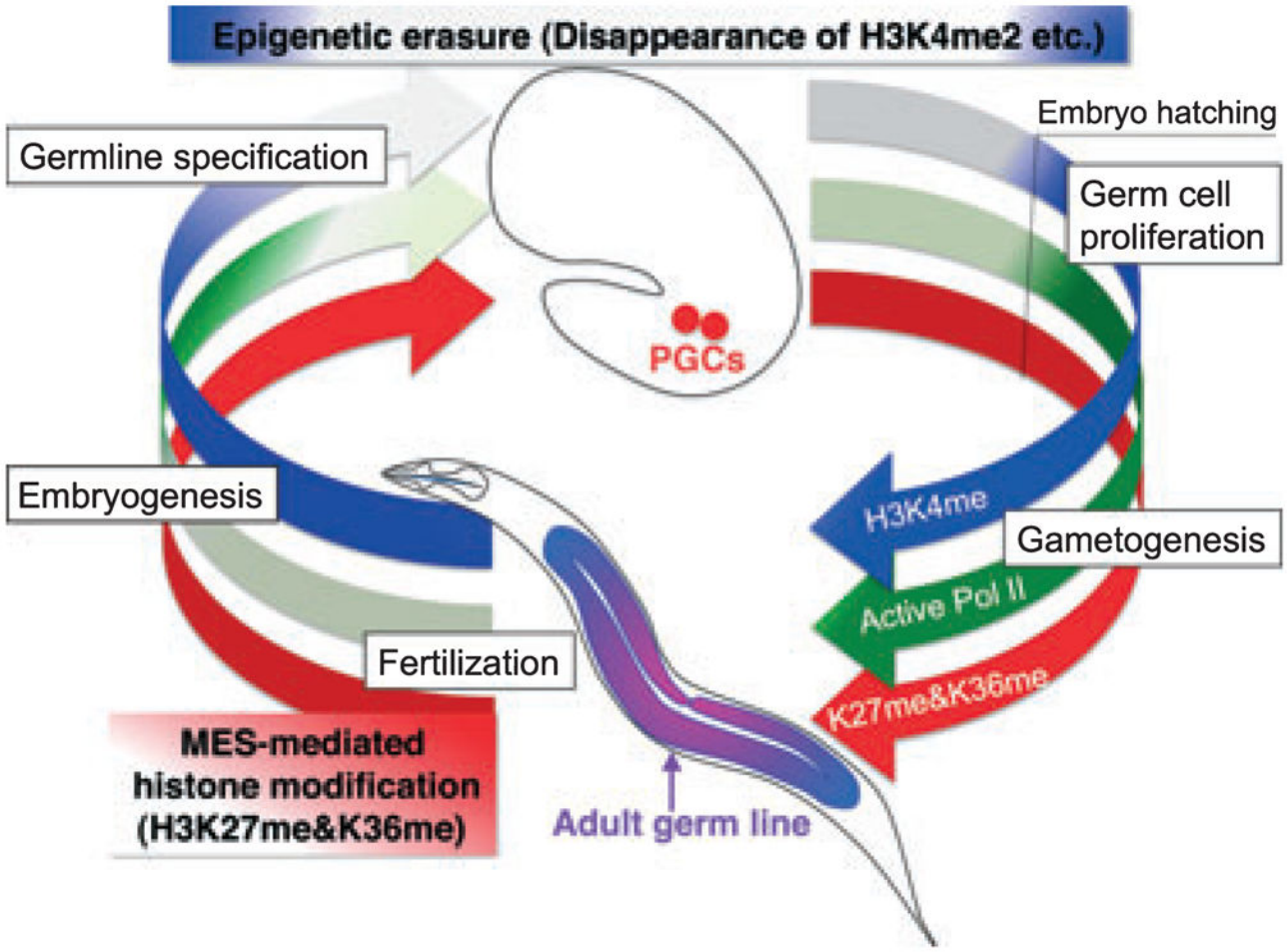

Fig. 1.

Epigenetic erasure/maintenance in *C. elegans* germline cycle. Epigenetic reprogramming involving widespread changes in chromatin is a conserved feature of germ cell specification in many organisms (Schaner *et al.* 2003; Seki *et al.* 2005, 2007; Hajkova *et al.* 2008). In *C. elegans* germline, a subset of conserved epigenetic marks of “active” chromatin, such as H3K4me2, disappears specifically from PGC chromatin soon after the birth of these cells and remains extremely low until hatching. MES-mediated histone modifications, H3K27me and H3K36me, are detectable during the germline cycle (Bender *et al.* 2004, 2006).

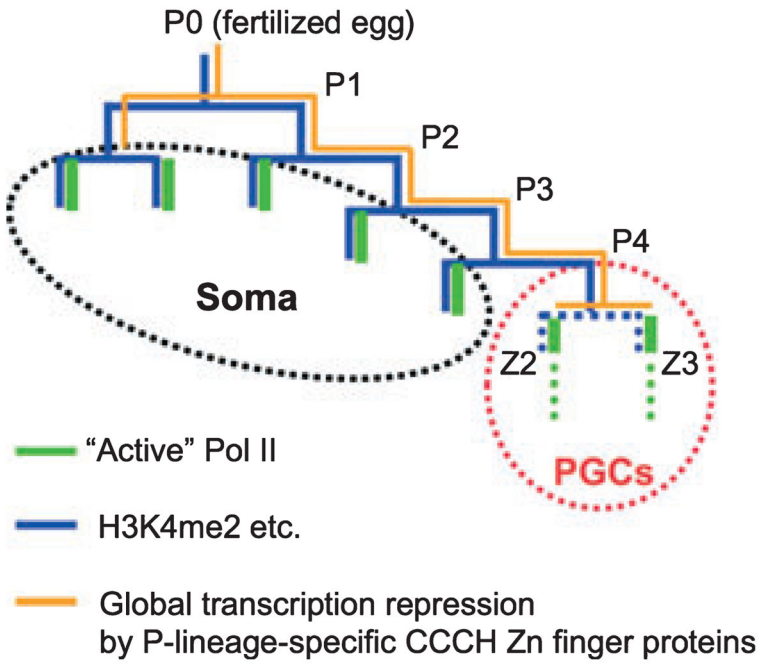

Fig. 2.

Transcription status and histone modification dynamics in *C. elegans* early embryonic blastomeres. During early embryogenesis, the asymmetric divisions of P-lineage cells (P0 to P3) produces germ line precursors and somatic cells. Subsequently, the last P cell (P4) finally makes two germline-committed cells, Z2 and Z3, and they are arrested at G2 phase during the rest of embryogenesis (Fukuyama *et al.* 2006). Throughout P-lineage, CCCH zinc finger proteins, OMA-1/2 and PIE-1, are sequentially acting to maintain transcriptional quiescence independently of the chromatin environment (orange line: Seydoux *et al.* 1996; Seydoux and Dunn, 1997; Guven-Ozkan *et al.* 2008). However, soon after the symmetric cell division of P4, PIE-1 is degraded quickly and "Active Pol II" suddenly appears in the PGCs (green). H3K4me2 (blue) are initially present in both the transcriptionally quiescent P-lineage and their somatic sisters where transcription is activated. H3K4me2 in P-lineage is maintained by unidentified mechanism, but in the PGCs the level of H3K4me2 begin to decrease (indicated by dotted blue lines), and becomes almost undetectable soon after the birth of Z2/Z3 (Schaner *et al.* 2003). Our recent study revealed that the appearance of "active Pol II" in the PGCs is actually transient, and that MES-4 activity is important for the Pol II repression (indicated by dotted green lines) (Furuhashi *et al.* unpubl. data, 2009).