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Review

Refurbishing the germline epigenome: Out with the old, in with the new

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ABSTRACT

Mammalian germline reprogramming involves the erasure and re-establishment of epigenetic information critical for germ cell function and inheritance in offspring. The bi-faceted nature of such reprogramming ensures germline repression of somatic programmes and the establishment of a carefully constructed epigenome essential for fertilisation and embryonic development in the next generation. While the majority of the germline epigenome is erased in preparation for embryonic development, certain genomic sequences remain resistant to this and may represent routes for transmission of epigenetic changes through the germline. Epigenetic reprogramming is regulated by highly conserved epigenetic modifiers, which function to establish, maintain and remove DNA methylation and chromatin modifications. In this review, we discuss recent findings from a considerable body of work illustrating the critical requirement of epigenetic modifiers that influence the epigenetic signature present in mature gametes, and have the potential to affect developmental outcomes in the offspring. We also briefly discuss the similarities of these mechanisms in the human germline and consider the potential for inheritance of epigenetically induced germline genetic errors that could impact on offspring phenotypes.

Contents

Abbreviations: AID, activation induced deaminase; BER, base excision repair; CGI, CpG island; DNMT, DNA methyltransferase; EED, embryonic ectoderm development; ERV, endogenous retrovirus; EZH, enhancer of zeste; GV, germinal vesicle; HDAC, histone deacetylase; IAP, intracisternal A-particle; LTR, long terminal repeat; PGCs, primordial germ cells; PRC, polycomb repressive complex; REs, repetitive elements; RNF, ring finger protein; TET, ten-eleven translocation; TDG, thymidine; DNA, glycosylase; 5-mC, 5-methylcytosine; 5-hmC, 5-hydroxymethylcytosine.

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1. Introduction

Germ cells transmit genetic and epigenetic information to the offspring. Although genetic inheritance is well understood and the DNA sequence provides the underlying material on which natural selection acts, the role of epigenetic inheritance in biology and evolution is relatively poorly understood. Moreover, epigenetic mechanisms perform fundamental roles in regulating genome stability and the possibility that altered germline epigenetics may mediate genetic changes that affect inheritance, remains poorly understood.

Epigenetic mechanisms regulate chromatin structure, allowing the DNA to be properly organised and compacted into the nucleus in a way that permits accurate gene transcription and gene silencing [1]. This is mediated primarily through DNA methylation and an array of chemical modifications to the histone proteins (histone modifications). These modifications are flexible in that they can be removed or added, providing a myriad of chromatin formats that profoundly affect developmental processes. However, epigenetic modifications are also heritable across cell generations and thereby provide cells with the ability to stabilise lineage identity and somatic gene expression profiles throughout life [2].

Similarly, heritability of some epigenetic modifications from the parent significantly affects behaviour, development and health in the offspring [3]. The best understood example of epigenetic inheritance is genomic imprinting, which involves differential methylation of genomic regions that confers allele or parent-specific gene expression important for offspring growth, development and behaviour. Germ cells perform a critical role in removing existing epigenetic information from the genome and establishing new epigenetic information in the forming gametes, a process known as *epigenetic reprogramming*. In most cases this process underpins normal outcomes in the offspring. However, the plasticity of epigenetic modifications also leaves the germline susceptible to environmental influences that potentially alter epigenetic state in the parental germline and may have consequences in the offspring.

In this review, we outline the role of the germline in regulating the epigenetic signature of the gametes and the potential for altered epigenetic states to be inherited by the next generation. Although most existing models focus on identifying epigenetic changes in the germline that alter outcomes in the offspring, we briefly raise the possibility that epigenetic change in the germline leads to secondary genetic changes that could be transmitted to the offspring. As most of what we know is derived from studies in mice, this review will primarily focus on the mouse model. However, recent advances in deriving human germline cells from pluripotent stem cells and from studies of *in vivo* germline development have significantly progressed our understanding of human germline epigenetics.

2. Epigenetic reprogramming in the germline

In the mouse, primordial germ cells (PGCs) are specified *via* BMP signalling in the posterior extra-embryonic mesoderm at embryonic day (E) 6.25 [4–6] (Fig. 1). The newly specified PGCs migrate from the base of the allantois, along the hindgut to reach the genital ridge by E11.0. Although there is a short period of mitotic arrest at E8.5, the PGCs are highly proliferative during migration and for around two days after colonising the gonad [7–9]. At ~E12.0 the bipotential gonad differentiates down the testis or ovarian pathway and germ cells initiate differentiation through sex-specific signalling from supporting somatic cells (Fig. 1) [10,11]. By E14.5 male germ cells exit the cell cycle and enter a period of mitotic arrest, which is not resumed until after birth [12]. In contrast,

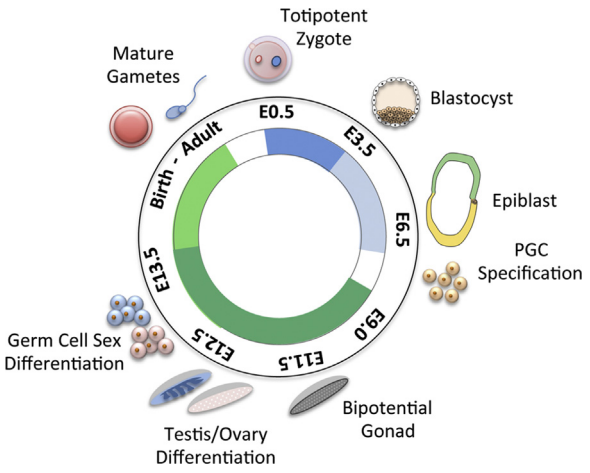

Fig. 1. Germline cycle and epigenetic reprogramming waves. Primordial germ cells (PGCs) are specified from the mouse epiblast at embryonic day (E)6.5. PGCs migrate and enter the bipotential gonad at E11.0, followed shortly after by gonad differentiation and germ cell sex determination. Germ cells subsequently follow sex-specific developmental trajectories; female germ cells enter meiosis and male germ cells enter mitotic arrest between E13.5–E14.5. In the adult, gametes mature through folliculogenesis in the ovary and spermatogenesis in the testis to produce mature gametes capable of fertilisation. After specification widespread epigenetic reprogramming occurs in the germline (wave 1: green bar) with an initial phase of epigenetic erasure (dark green) that removes parent-specific information, following by establishment of new sex-specific epigenetic information (light green). A second round of epigenetic reprogramming (wave 2: blue bar) occurs in the embryo (erasure/re-methylation: darker/lighter blue), but inherited epigenetic modifications survive this phase.

female germ cells cease to proliferate, enter meiosis and become arrested in prophase I by E14.5 [13], thus representing a finite gametogenic store for female individuals.

2.1. DNA methylation dynamics in the developing germline

During mammalian development there are two waves of extensive epigenetic reprogramming; the first occurring in the newly specified PGCs during migration and colonisation of the gonad, and the second taking place in the early preimplantation embryo shortly after fertilisation (Fig. 2). The first round of epigenetic reprogramming permits the removal of existing epigenetic information and establishment of an epigenome that is distinct to that of somatic lineages, a process that is essential for germline identity and function. Furthermore, epigenetic reprogramming in the germline establishes a chromatin signature that permits a return to totipotency (the ability to form all cell types in the body), which is essential for formation of a viable zygote, and that carries sex-specific epigenetic information critical for health and development in the offspring. Hence male and female germ cells represent specialised cell types that must acquire epigenetic patterning suitable for directing gametogenic function and the ability to support development.

Genome-wide DNA demethylation is a major event characterising germline and preimplantation epigenetic reprogramming (Fig. 2). DNA methylation is a biochemical modification occurring primarily at cytosine residues within cytosine-guanidine (CpG) dinucleotides. DNA methylation has established roles in gene and retrotransposon silencing, genomic imprinting, X-chromosome inactivation and chromosomal stability [14–16]. Upon specification, the germline undergoes widespread global DNA demethylation [17], primarily at introns, intergenic regions and repeats, with more modest losses occurring within exons and promoters [18]. Germline DNA demethylation takes place in two discernible stages; the first prior to E9.5 when up to 70% of DNA methylation is lost, and another during the final stages of

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