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# Epigenetic Reprogramming in Early Mammalian Embryogenesis: Comparative Insights from Human and Model Systems

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**ABSTRACT**

*Erasure and reinstatement of the epigenetic effects of totipotency and lineage specifications is the main event in early mammalian embryonic differentiation and entails epigenetic reprogramming. Two large-scale DNA demethylation waves of the world, global chromatin remodelling, histone dynamics of change, genomic imprint reinstatement, and X-chromosome reactivation, are also characteristic of it. Although our knowledge of the mechanics is largely based on the murine models, the growing availability of the single cell and multi omics technology has shown that there are species and conservation regulatory properties in human embryos. It may also be added that timing, maintenance of the imprint, access to the chromatin and control of transposable elements is also varied and this aspect explains why direct extrapolation cannot be carried out on human beings using the mouse models. In addition, the imprinting disorders have been linked to the epigenetic reprogramming perturbations and assisted reproductive technologies can have an effect on it. The provided review is a comparative examination in specifics of the epigenetic reprogramming in the first mammalian growth that attempts to discover the common mechanisms, species peculiarities, technological progress, and more recent clinical applications. Other questions/ directions that have not been addressed include translational reproductive medicine and epigenome editing.*

**Keywords: DNA methylation, Epigenetic reprogramming, Human embryogenesis, Histone modifications.**

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## INTRODUCTION

One can refer to epigenetic reprogramming as one of the most radical reprogramming during the evolution of mammals. After fertilization, the two highly specialized forms of gametic genomes that have been combined in different epigenetic landscapes are to be rearranged so as to create totipotency and developmental plasticity. It does not involve the erasure of epigenetic marks but an organisation of a global scale yet an arrangement of DNA methylation, histone modifications, chromatin accessibility as well as higher order genome organisation in a co-ordinated as well as a selective manner. It was found that the context-dependent and dynamic epigenetic reprogramming is fixed on the principles and highly inter-species diverse [1,2] . Two waves of epigenetic reprogramming have traditionally been defined to occur in mammals. The former wave happens during the preimplantation phase between the zygote and the blastocyst formation stage and is characterized by enormous DNA demethylation, chromatin restructuring, and histone mark relocation. The second wave is found in primordial germ cells (PGCs), where the genome-wide epigenetic demethylation of the cells is reset to permit the development of patterns of sex in the offspring


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[3,4] . Although this two step model has been rather widely accepted, recent high resolution studies have demonstrated that the dynamics, the regulation processes, and the degree of epigenetic stability of human embryos and mouse embryos differ significantly.

We have long historically done much with our mechanistic knowledge with mice. The original studies had discovered three active DNA demethylation by TET enzymes, passive replication that depended on dilution of methylation, and Polycomb-related chromatin repression as the main control systems [5,6]. However, a growing concern is that it is not possible to make a direct extrapolation of mouse to human embryogenesis. It involves another dynamics and maintenance of imprinted loci as well as species-specific patterns of chromatin accessibility of human embryos [7,8] . The differences are what bring out the significance of a comparative approach in relation to universal conservation.

This has been transformed by the single cell and multi omics technologies. Integrative studies of single cell RNA sequencing and DNA methylome profiling combined with chromatin accessibility mapping have shown that the epigenetics reorganization of early development is not temporally homogenous and homogenous between blastomeres [9,10] . Rather, the epigenetic heterogeneity can be identified at the early stage of embryos, it means that the bias in the lineage can be revealed sooner than expected. More to the point, spatial epigenomic profiling already has started to detect lineage-specific signatures of chromatin in early human embryos and provides another tier of the developmental regulatory [11,12].

The progress in the classical understanding of reprogramming is still lengthened. In addition to **global DNA methylation** erasure, 3D genome architecture and restructuring regulatory circuits of species communities are now the topics of study of interest. These types of comparative studies show that these processes of methylation and repeats elements activation and chromatin topology are the most interacting aspects, and in the human and murine system, the difference is significant [13,14,15]. According to these findings, the need to consider epigenetic reprogramming as a complete re-arrangement of regulatory genome, and not individual demethylation exists.

Epigenome Translational analysis The feeling of species-specific regulation of the epigenome is critical. Developmental windows of increased epigenetic plasticity are associated with **assisted reproductive technologies (ART),** culture of in vitro embryo and manipulation of the germline. Long-term disturbances of such critical periods have been linked to the imprinting disorders and the developmental effects [16]. This creates the need to have a sophisticated comparative knowledge whereby the model systems are properly perceived and improvement is applied in clinical reproductive plans.

As the high resolution epigenomic data becomes rapidly extended and the importance of interspecies divergence is recognized, the time to reconsider epigenomic reprogramming in a comparative mammalian system has come and the demand has been fulfilled. In this case, we examine the current literature of the dynamics of DNA methylation, histone modification remodelling, genomic imprint regulation, and X-chromosome reactivation during early embryonic development in mammals. Having a mixture of nature-conserved processes and species-specific variations, we would strive to expound on conceptual vagueness and refer to emergent trends in essential and applied research of embryology.

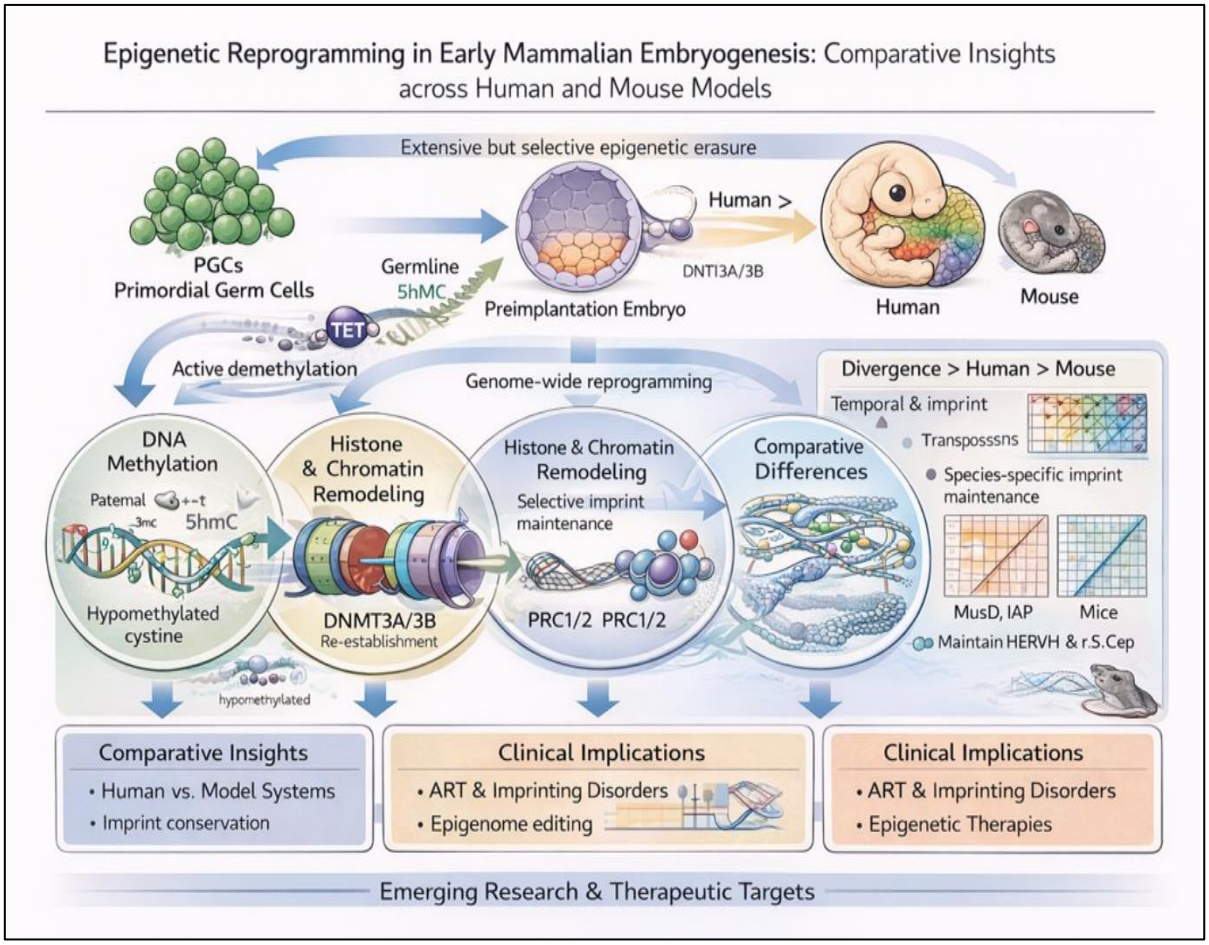


**Figure 1. Conceptual framework of germline and embryonic epigenetic reprogramming in early mammalian development.**

*The schematic illustrates extensive but selective DNA demethylation, histone remodeling, imprint maintenance, and species-specific divergence between human and mouse models, highlighting clinical implications in assisted reproduction and imprinting disorders.*

## DNA Methylation Reprogramming in Early Mammalian Embryogenesis

### 2.1 First Wave: Post-fertilization Demethylation

The mammalian embryo is known to undergo a genome wide rearrangement of DNA methylation syntactically after fertilization. Paternal genome undergoes rapid and active process of paternal genome demethylation in the mouse followed by initial demethylcytosine replication process that is meditated by TET3-dependent 5-methylcytosine oxidation [5,6]. Instead, the maternal genome is diluted out through repenting distortion during further cleavages during replication.

This form of asymmetric demethylation is extensively established in mice, but other demethylation dynamics were observed in embryos of human beings. The genome wide methylome results indicated that the human process of demethylation of the zygote is not polarized and gradual between the maternal and male genomes,[7,8]. Along with this, these single cell methylome data suggest that there is a big cell to cell variation at cleavage stages indicating that not all the demethylation is performed concurrently and synchronously on the blastomeres.

The degree of the loss of methylation has also been found to vary species-specifically as a result of comparative analysis. As the degree of global CpG methylation of the mouse

embryos diminishes to approximately 20 %.[17] Even in the blastocyst stage, human embryos retain significantly higher levels of residual methylation in some of the genomic sites, including repetitive and imprinted loci [18]. These outcomes are contradictory to the concept of complete loss of epigenetics and suggest that selective protection mechanisms species-specific may exist.

**2.2 Protection and Selective Maintenance of Genomic Regions**

Although the genome-wide demethylation is commonplace, there are areas in the genome that have been resistant to resetting. The imprinting control regions (ICRs) are regions of the genome that allow the parent of origin specific methylations to be maintained in both mouse and human embryo that are required to allow the monoallelic expression of certain genes [16]. These regions have been found to be controlled by ZFP 57 and associates in mice and how regulation is done with human beings has not yet been well defined. Species-specific regulatory dynamics of transposable elements (TEs) also contribute to early reprogramming as the majority of recent studies assert. Retrotransposons are retrotransposon-like structures that are transiently expressed in zygotic genome activation (ZGA) in mice but which are more a part of early development-regulatory networks in humans [13,15,19]. The implication of such a deviation is that DNA methylation reprogramming has a direct association with the regulation of repeats elements in a species-specific way.

**2.3 The Second Wave: Germ line Epigenetic Resetting**

The second wave of reprogramming in DNA methylation occurs in the primordial germ cells (PGCs) during which the epigenetic ground state is restored by the almost complete genome-wide demethylation preceding sex specific remethylation. This is done both in E 6.5-E 13.5 embryonic mice and in both active and passive demethylation [3].

The same pattern in human PGC reprogramming is generally similar except at other times and with diverse sensitivities of the genome. The methylome profiling of human PGCs indicates that there is extensive silencing of CpG methylation, covering imprinted loci, although a few repetitive components are seemingly resistant [4]. It has been compared with other studies that the human germline is capable of having a longer demethylation kinetic compared to that of mouse and this may be possibly attributed to disparities in developmental rate and limits of the regulation[20].

It is noteworthy that in recent studies, the emphasis is made on the fact that germline reprogramming course occurs not only due to the loss of methylation but also due to ordered changes in chromatins, the replacement of histones, and the global reorganization of the nuclear framework [13,20.] Thus, the erasure of DNA methylation is worth being viewed in a broader context of epigenomics.

**2.4 Mechanistic Drivers of Demethylation**

That is called active demethylation and is carried out in a mechanistic manner where 5-methylcytosine is oxidized by TET to 5-hydroxymethylcytosine and additional derivatives and that the process is carried out in series of pathways that are on the basis of base excision repair [5]. The passive demethylation is not maintained by maintenance methylation via DNMT 1, and this process is only active during replication. However, recent multi omics data suggest that chromatin accessibility, histone modification landscapes, and transcriptional activation states strongly influence regional demethylation efficiency[11,15]. In this context, DNA methylation reprogramming is not merely enzyme-driven but is modulated by chromatin environment and 3D genome organization.

### 2.5 Comparative Synthesis: Conserved Principles and Divergent Features

In mammals, there are a number of conserved principles:

- Biphasic reprogramming (preimplantation and germline)
- Combination of active and passive demethylation
- Protection of imprinting control regions
- Coupling with chromatin remodeling

However, the critical divergences between human and mouse systems are (Table1):

**Table 1: Critical divergences between human and mouse systems.**

| Feature | Mouse | Human |
|---|---|---|
| Paternal demethylation | Rapid, TET3-dependent | More gradual |
| Residual methylation at blastocyst | Very low global levels | Higher at selected loci |
| TE regulation | Transient activation | Broader regulatory contribution |
| Germline timing | Rapid embryonic window | Extended developmental window |

*These differences underscore the importance of cautious interpretation when extrapolating murine findings to human embryology.*

**Table 2. Comparative DNA Methylation Reprogramming in Early Mammalian Development.**

| Feature | Mouse (Mus musculus) | Human (Homo sapiens) | Key References |
|---|---|---|---|
| **First Wave Timing** | Zygote to blastocyst (E0.5–E3.5) | Zygote to blastocyst (Day 1–5/6) | 5, 7 |
| **Paternal Genome Demethylation** | Rapid, active TET3-mediated | More gradual, less asymmetric | 21, 8 |
| **Maternal Genome Demethylation** | Passive, replication-dependent | Predominantly passive | 7 |
| **Global CpG Levels at Blastocyst** | ~20% residual methylation | Higher residual methylation at specific loci | 7, 20 |
| **Imprinting Control Regions (ICRs)** | Protected via ZFP57 complex | Generally protected, mechanisms less defined | 16 |
| **Transposable Elements (TEs)** | Transient activation during ZGA | Broader regulatory integration | 13,22 |
| **Second Wave (PGCs)** | E6.5–E13.5 embryonic window | Weeks 2-9 post-fertilization | 3,4 |
| **Extent of Germline Demethylation** | Near-complete genome-wide erasure | Extensive but regionally variable | 3,4 |
| **Chromatin Coupling** | Strong linkage with histone remodeling | Increasing evidence of 3D genome involvement | 15 , 19 |

### 2.6 Critical Perspective and Conceptual Challenges

Although much has been done so far in mapping the dynamics of the DNA methylation during the early development of mammals, there are still a number of conceptual and methodological needs that must be addressed. To begin with, most part of the mechanistic framework that denotes the murine origin characterizes the active and passive demethylation.

First, Despite the fact that mouse models are an inevitable approach, the emerging comparative data suggest that human embryos have stronger temporal kinetics, regulatory interactions, and chromatin[4,22] . Perhaps, it

should also be known that the supposition of the cross species conservation simplifies too much the biologically important diversification.

Second, in spite of most prevalent definitions of genome-wide loss of methylation stating that it is (global), mounting evidence is indicating that reprogramming can be extremely selective and region-specific. Some of the repetitive elements that are more prone to erasure include imprinted loci and regulatory domains[16,20]. A few basic questions are also on such selective preservation as to the presence of protective mechanisms, and the similarity of these mechanisms to the protective mechanisms in the species of mammals.

Third, most of the current models have been on the enzymatic pathways namely TET mediated oxidation and DNMT1 exclusion as the primary drivers of the demethylation [5]. However, recent multi omics reports indicate that the that chromatin accessibility, transcriptional activation state, and the higher order organization of the genome have a significant role in the action of regional methylation dynamics [15,20.] It is this reprogramming of DNA methylation that should be reconsidered in a system level rather than being considered another biochemical process.

Finally, there are technical and ethical limitations that limit direct experimental manipulation of human embryos such that even then there remains a need to either use model organisms or embryo models based on stem cell derivatives.

Though these systems are useful factors of estimates, they may be necessary to represent the regulatory complexity of n in vivo human development. The limitations will be overcome using integrative comparative approaches of single cell multi omics, spatial epigenomics and highly validated model systems. All these considerations combined suggest that future research would need to transcend a descriptive methylation profiling to an analysis of species specific regulatory networks on a mechanistic basis. Developmental biology and even translational applications of developmental biology in reproductive medicine and in intervention of the germline would be impossible without a polished sense of comparison.

## 3. Histone Modification Remodeling During Early Mammalian Embryogenesis

### 3.1 Histone Remodeling as a Parallel Reprogramming Axis

Though the dynamics of DNA methylation have long been the central focus of debate about epigenetic reprogramming, it is emerging that histone modification remodelling is also a fundamentally simple regulatory route. This is an extensive redistribution of histone marks which is both activating (H 3 K 4 me 3) and repressive (H 3 K 27 me 3 and H 3 K 9 me 3). Changes regulate the chromatin accessibility, transcriptional competency, and lineage specification [20, 23].

It is important to mention that histone remodeling is not the second effect of DNA demethylation. Instead, there is accumulating evidence to suggest that regional susceptibility to methylation erasure may be instructed by chromatin states and that process of transcriptional activation during zygotic genome activation (ZGA) may be regulated by chromatin states [24]

### 3.2 H3K4me3 Dynamics: Broad Domains and Species-Specific Patterns

The formation of wide non-canonical (H 3 K 4 me 3) domains in the mouse oocytes and early embryos before fertilization and later rearrangement during cleavage events is observed. These rough domains are associated with transcriptional priming and to a degree transformed into canonical promoter related peaks in the course of development [25]

The patterns of human embryos have been maintained slightly, but they are not

 

homogenous regarding time and genome distribution. According to the data that is introduced in the article by the single cell chromatin profiling, the remodelling of human (H 3 K 4 me 3) appears to be slower and it may also be closely linked to species-specific transcriptional programs [22]. These dissimilarities are further differentiation of regulation between species.

### 3.3 H3K27me3 and Polycomb-Mediated Repression

The polycomb repressive complex 2 (PRC2) knock out the repressive histone mark H3K27me3, which plays a critical role in development regulation of gene expression in early embryo. Maternal H3K27me3 further assists in the regulation of non-canonical imprinting in mouse embryos that do not rely on the influence of DNA methylation [16].

However, the maintenance and localization of H3K27me3 of human embryos is dissimilar. It has been demonstrated through comparative studies that not all the Polycomb-mediated imprinting systems that occur in mice are completely conserved in humans [22]. Such findings refute the use of Polycomb-dependent imprinting models in murine models.

Furthermore, the recent experiments are additionally highlighting that the presence of the rearrangement of H3K27me3 is closely linked to the interventions of the chromatin structure and 3D genome in the lineage distribution [15,19] . Thus, the histone remodelling must be considered within a larger order chromatin context.

### 3.4 H3K9me3 and Transposable Element Regulation

H3K9me3 is an essential repressive chromosomal marker of transposable factors (TEs) and heterochromatic locations. Some retrotransposon families of ZGA are stabilised through the relaxation of Brief H3K9me3 in mouse embryos and its activation [6].

TE on the other hand has more regulatory networks in human embryos. It is also appearing that specific endogenous retroviral components assist in the intensification of the landscapes of stimulators in early human progress and possibly provide enhanced concerted control [22]. The difference in the mechanisms of the epigenetic regulation is also brought into the limelight as of this species-specific TE is involved.

### 3.5 Germline Histone Remodeling

Germline reprogramming also involves a strong reorganization of histone changes along with DNA demethylation. Both global H3K9me2 depletion and redistribution of H3K27me3 in mouse PGCs occur with erasure of methylation [3]. The overall trends of human PGCs are also rather close, although the differences in time and chromatin compaction have been reported [4,22,24] .

Interestingly, it appears that histone variant exchange and chromatin decompaction help in facilitating the accessibility of demethylation machinery which means that histone remodeling and the loss of DNA methylation is orchestrated to play.

### 3.6 Integrative Perspective: Beyond Individual Marks

The last multi omics methods reveal that histone modification, chromatin access, transcriptional activity, and 3 D genome organization dynamics are very dependent during the early development stages [15,19,24]. Rather than autonomous epigenetic changes, histone changes form part of orchestrated regulatory cells of lineage competence.

Compared to the other mammals, the greatest principle that needs to be maintained is the vast chromatin plasticity. However, regulatory circuitry, imprinting pathways and TE - associated chromatin state are different in human beings and mice. These differences have enormous implications to the developmental models of translation and translational implementation to reproductive medicine.

### 4.1 Classical DNA Methylation- Dependent Imprinting

This particular type of the epigenetic process is known as genomic imprinting and the process assumes special expression of genes of one parent of the origin or the other. The major operation of this monoallelic expression is facilitated by the regions of differentially methylated DNA (DMRs) or imprinting control regions (ICRs) that are formed during gametogenesis and are maintained after fertilization.

The overall tendency of the initial wave of epigenetic reprogramming is the monumental erosion of the DNA methylation in a relatively bigger portion of the genome; the imprinted DMRs are exceptionally resistant to the erosion [24]. This defense and detection of the methylated hexanucleotide motifs in the ICRs to cause maintenance machinery necessitates the activity of ZPF 57, TRIM 28 (KAP1) and other complexes in mice.

Preimplantation demethylation in human beings also involves imprinted loci, however, regulation of such process appears to be less evident. Based on the Methylome analyses of the human embryos, a subset of the classical ICRs are more stable and maintain the methylation, some of them are a little less stable [22]

. It means that the imprint protection may have species-specific variations.

### 4.2 Non-Canonical Imprinting and Polycomb-Dependent Regulation

In addition to classical form of imprinting with the help of DNA methylation, the new mice findings have also revealed non-canonical imprinting with the help of maternal H3K 27me3 marks instead of DNA methylation [16,24]. This model enables the temporary formation of parent specific gene silencing and out-of-oocyte inherited repression through Polycomb.

The outcome has widened the intellectualization of imprinting and this implies that the procedures of histone can persist even in the absence of CpG methylation. Although, the relative stability and the prevalence of Polycomb dependent imprinting could vary across species.

As it has been demonstrated so far, H3K27me3- Only imprinting in human beings is less stable, though transient maternal histone asymmetries have been observed [22,24]. Such results fail to reflect the assumption of the universally inherent nature of the principles of murine imprinting and stress on cross species extrapolation.

### 4.3 Germline Reprogramming and Imprint Erasure

The second wave of reprogramming of primordial germ cells (PGCs) leads to the erasure of the parental epigenetic memory through the demethylation of imprinted DMRs in the genome [24,26]. It is a very important resetting in the recovery of sex specific imprinting during gametogenesis. By comparing studies, it is found that both mouse and human PGCs differ in the timing and regional dynamics of these cells even though both cells are subjected to the vast erasure of imprints. Human PGC demethylation appears to be a long-term and developmental process in several weeks, whereas the mouse germline embryonic reprogramming occurs in a shorter span of embryonic time [20,26]. Such temporal division may impact on the imprint stability and susceptibility to distortion of the environment.

### 4.4 Imprinting, Transposable Elements, and Chromatin Context

Recent observations reveal that the process of regulating imprint is not entirely dependent on the CpG methylation but this is dependent on the local chromatin and the localization of transposable elements. The repeats are associated with the imprinted someloci that can be used in regulatory insulation in the mice.

There is likely a possibility that the insertion of species-specific TE into regulatory landscapes will alter the imprinting structure, and enhancer contacts in humans [19,22]. These disparities point out the fact that imprinting should be considered within the context of chromatin topology and 3D genome organization and not as an independent maintenance of DMR.

### 4.5 Clinical and Translational Implications

The developmental syndromes of Angelman syndrome and Silver Russell syndrome as well as Beckwith Wiedemann syndrome have been associated with interferons with imprinting. The assisted reproductive technologies (ART) have been addressed since the preservation of imprinting is also linked to the period at which the system of epigenetics is more prone to alterations [16].

The regulation of species specific imprinting has great implications in translation. In the absence of similarity between the imprinting maintenance systems in the human and mouse systems, the ART safety data in human beings may not be well represented by murine systems to reveal the human risk profiles. Comparative epigenomic studies, therefore, are indispensable in the idealization of clinical guidelines.

### 4.6 Critical Perspective: Rethinking Imprinting Universality

The growing awareness of the non-canonical imprinting and species-specific divergence requires the exploration of the familiar models. Although the paradigm of DNA methylation dependency still takes centre stage, the intricacy of imprint regulation is no longer explainable. This is further regulatory subtlety induced by the polycomb dependent imprinting, chromatin topology and integration of transposable elements.

It is worth mentioning that to a large part of the mechanism of histone based imprinting, the support is murine. It has not yet been clarified to what extent such mechanisms can be stable and functional in human beings [15,22]. These ambiguities would warrant future integrative multi omics especially to human embryos and known embryo models to solve them.

## 5. Integration of Multi-Omics and 3D Genome Architecture

### 5.1 From Single-Layer Epigenetics to Systems-Level Regulation

The classical epigenetic reprogramming models have mostly incorporated separate analysis of one regulatory stratum DNA methylation, histone modification or imprinting. But due to the latest technological advancements, it is proved that there are strong multi-layered epigenomic networks, which are involved in the regulation of the early mammalian development. Now, it is possible to study transcriptome, methylome, chromatin accessibility, and, most recently, chromatin conformation of single cells through multi omics [27,28,29]. The converging studies lead to the fact that reprogram of the epigenetic process cannot be a list of independent molecular events but is the reorganization of the regulatory genome.

### 5.2 Single Cell Multi Omics Reveals Epigenetic Heterogeneity

By use of a combination of DNA methylome or ATAC-seq analysis and single cell RNA sequencing, this is demonstrated to be the case and that there is a considerable amount of heterogeneity at early stages of cleavage across blastomeres. Zygotic genome activation (ZGA) is associated with both dynamic accessibility of chromatin and selective loss of methylation, which are both attributed to transcriptional activation in mouse and human embryos [27,29].

Interestingly, comparative studies assume that the process of epigenetics transition in human embryos is superior and uncoordinated, in relation to the murine embryos. This difference in species time can be indicative of species-specific regulation time and

developmental time difference [27]. It is discovered that the intra embryonic heterogeneity contradicts the previous models expecting that the epigenetic resetting of the cells is homogenous.

### 5.3 3D Genome Architecture During Reprogramming

In combination with the linear epigenetic residues, during the early embryonic stage, rearrangement of the higher order chromatin is immense. Plans that engage chromosome conformation capture have defined that massive remodelling of topologically interacting domains (TADs) and chromatin compartments happens in preimplantation development.

The postfertilisation mouse embryos stabilize TAD insulation which is subsequently replenished in the cleavage stages. The general parallels are observed in the human embryo, but the compartment strength and time changes have been reported [30,31]. Changes are accompanied by DNA demethylation and histone remodelling to demonstrate that the changes are coordinated.

It should be mentioned that repeats and species-specific enhancers seem to play a role in the active process of looping of chromatin in early development, and species-specific regulatory networks are gained in the course of ZGA [31] .

### 5.4 Coupling Between DNA Methylation and 3D Genome Organization

The most recent integrative analysis has shown that the loss of DNA methylation is not randomly distributed in the genome, but is instead characterized by the availability of chromatin and the geographical location on the nucleus. The regions of open chromatin and transcriptional activities but not the regions of heterochromatin are usually subjected to the demethylation process (before a certain time) [30,31].

Compartmental switching A/B chromatin segments is associated with the development of lineage-specific transcriptional programs other than that. These changes seem to be slightly different in human and mouse embryos that prefers the notion of the idea of species-specific reorganization of the regulatory genome [31].

Thus the concept of epigenetic reprogramming needs to be referred to as a process of multidimensional restructuring which suggests:

- Linear DNA methylation changes
- Histone modification redistribution
- Chromatin accessibility shifts
- 3D architectural reconfiguration

### 5.5 Emerging Technologies and Conceptual Implications

Spatial transcriptomics with single-cell sequencing of the methylome and chromatin conformation profiling have set out to bridge the gap between the molecular biology of epigenetics and morphogenesis development. According to the Spatial epigenomic techniques, the early distribution of the lineage and the microenvironment was correlated with the epigenetic statuses [32].

Such observations need to be conceptually redefined: the transcription of epigenetic reprogramming is not an apparent straightforward biochemical resetting reaction but instead it is an organisational re-structuring of the embryonic regulation milieu per se. Coincidentally, comparative analysis has shown that core principles are not just being maintained but the topology of regulatory networks and time coordination vice versa is divergent across species[27,31].

### 5.6 Critical Perspective: Toward a Multidimensional Model of Reprogramming

With all the improvement, the existing multi omics data remains limited as it has technical limitations such as a low input material, low coverage, and the lack of ethics on the use of human embryos. In addition to

 

these, cross platform integration and normalization are also methodological issues.[33]

However, the emergence of integrative systems level frameworks of single layer epigenetic model may be considered incumbent revolution within the sphere of developmental biology. The studies in this field must aim at balancing the multi omics data, seeking more efficient ways of refining the spatial resolution and conducting a direct comparison of human and model systems in standardized pipelines.[33,34]

It is only under such integrative modes of approaches that the field can manage to accomplish complete demystification of the species specific logic governing early mammalian epigenetic reprogramming.[34] .

## 6. Clinical and Translational Implications

### 6.1 Assisted Reproductive Technologies (ART) and Epigenetic Vulnerability

Early embryogenesis is an early developmental plasticity in which the levels of epigenetic plasticity increase. The patterns of global DNA demethylation, histone remodelling and chromatin remodelling occur simultaneously during preimplantation as embryos are typically manipulated in vitro during assisted reproductive technologies (ART). This delay has led to a current study of whether the ART procedures can have any influence on epigenetic stability or not.

The first experimental works on mice have already shown that levels of methylation at imprinted loci and repetitive elements can be changed by the condition of superovulation, in vitro fertilization (IVF) and embryo culture [35]. Nevertheless, such extrapolations should be done with caution on human beings because there are species-specific variations in the reprogramming kinetics and maintenance of imprints [31,36]

The conceived people in ART develop normally but there has been a reduced augment of imprinting related disorders in some groups in humans. Notwithstanding a disputed causality, biological defensibility of ART interventions is offensive with regards to timing of development since the ART interventions coincide with the periods of imprint protection and methylation erasure [37].

### 6.2 Imprinting Disorders and Epigenetic Dysregulation

Disruption of imprinting control regions (ICRs) has been attributed to several congenital syndromes such as:

Beckwith Wiedemann syndrome (BWS): It is a developmental disorder that occurs at an early age and is associated with short stature, heart defects, and oligophrenia [15].

- Angelman syndrome
- Silver Russell syndrome
- Prader Willi syndrome

The causes of such disorders are typically an abnormal methylation at DMRs or uniparental disomy. Because such process of erasing and restoring imprints can be observed during the germline reprogramming process, any error that occurs during the process can have transgenerational implications [38].

Interestingly, the interpretation of diagnosis is even harder since non-canonical imprinting processes mediated by H3K27me3 complicate the situation. Provided the imprint regulation of human beings can be subjected to control of the histone-based processes to a lesser extent than in the mice, the human peculiar susceptibility can be concealed by the murine imprinting paradigms [39].

### 6.3 Epigenetic Instability and Long-Term Health Outcomes

Along with the classical syndromes of imprinting, new research has been conducted on whether small-scale manipulations of early epigenetic reprogramming can have long-term health effects, e.g. a metabolic disease or an alternative developmental pathway. Although definitive causal relationships are being

studied, the Developmental Origins of Health and Disease (DOHaD) paradigm provides a conceptual basis of causal relationship.

The multi omics profiling denotes that initial exposure to the environment may influence the preservation of the methylation at the chosen areas of the genome, particularly the maintenance of the methylation of the metabolic control and growth factor signaling [32]. The variations in species regarding the imprint stability and the control of transposable elements also contribute to the impossibility of translation modeling even further.

### 6.4 Implications for Embryo Selection and Epigenetic Biomarkers

The emergence of single cell and non invasive embryo assessment methodology provides a possibility of the integration of epigenetic biomarkers, becoming a component of embryo selection processes. However, the intrinsic heterogeneity of the reprogramming of the epigenetics in the early stages of cleavage has complications.

The single cell analyses show that the traces of the methylation or chromatin accessibility may vary in blastomeres of the same embryo [29,40]. Whether such variability is normal developmental plasticity or pathological instability is, nevertheless, still unknown.

Besides this, the fact that it is also evident that species specific variations to the dynamics of methylation are warning enough to the fact that the application of murine thresholds are the only measures that should be used to define epigenetic (normality) in embryos of a human being [36].

### 6.5 Germline Editing and Ethical Considerations

The situation is even more complex when epigenetics reprogramming conflicts with the emerging technologies in the area of germline editing. Epigenetic resetting is a germ line development process, so any unintentional alteration of the chromatin structure or the methylation patterns can be intergenerational. Despite the recent regulations that constrained the scope of the germ line editing of human beings, comparative analysis of epigenetics reveals that before such implementation can be considered in its translational format, it is imperative to first understand the species specificity of the reprogramming information.

### 6.6 Critical Perspective: Translational Caution in a Comparative Context

The epigenetic knowledge of interspecies divergence should be taken into consideration when the findings are used in clinical practice. Mechanical precision of mouse models has been incredibly useful, but differences in mouse imprint maintenance, TE regulation and rate of reprogramming point to the possibility that the simple extrapolation will streamline human developmental biology [41,42].

Future translational research should be aimed at:

- Multi omics datasets of human nature.
- There are protocols of embryo culture.
- Cohort longitudinal studies.
- Clinical interpretation of genome architecture 3D.

Only through their stringent approach to comparative and systems level research does epigenetic research stand to contribute a significant contribution to reproductive medicine without having to run unnecessary risks[42, 43]

## 7. Future Directions and Emerging Frontiers

### 7.1 Toward High-Resolution Integrative Epigenomics

However, the existing data sets are poorly covered, comprehensive, and combined through regulatory layers, even with tremendous advancements in single cell methylome and chromatin accessibility profiling. Simultaneous multi-modal profiling

 

of the DNA methylation, histone modifications, chromatin accessibility, transcription, and 3D genome architecture of individual cells are one of the frontiers in the discipline.[32]

The methodological innovations must strive to come up with improved:

- Sensitivity Multi omic co-assay sensitivity.
- Time resolution between the stages of development.
- Pipeline harmonization across species.

Such approaches will enable a direct, human to model organism comparison of regulatory network architecture by avoiding the necessity to extrapolate the findings to other organisms [32,36] .

### 7.2 Spatial Epigenomics and Lineage-Resolved Reprogramming

Space transcriptomic technologies and space epigenetic technologies that are in place have provided the unprecedented possibility to relate molecular reprogramming to embryonic space organization. Future research should be considered to take into account micro environmental factors and lineage-depending chromatin landscapes instead of focusing on early embryos as a cell population of equal homogeneity.

It is possible to comprehend the stochastic or deterministic lineage priming of epigenetic heterogeneity using single cells through the use of high resolution spatial mapping [44]. Another implication of these analyses to comparative human-mouse systems will be used in an attempt to explain the meaning of conserved and species-specific developmental strategies.[45]

### 7.3 Revisiting Imprinting Paradigms

Recent findings of non-canonical, Polycomb mediated imprinting in mice cast basic doubt on its evolutionary conservation. There is need to test the stability, prevalence and functional importance of histone based imprinting in human embryos in a systematic manner in the future.

To clarify the question of the universal applicability of murine imprinting paradigms, it will be necessary to perform integrative epigenetic profiling of imprinting control regions including methylation and distribution of H3K27me3, chromatin conformation, and allele-specific expression [46].

### 7.4 Transposable Elements as Regulatory Innovators

Transposable elements (TEs) are currently being recognized as active agents to work as early embryonic regulators instead of the passively residing relics of genomes. Comparative analyses have revealed that TE families have been co-opted across species of mammals and this has led to species-specific enhancer landscapes and transcription factor binding positions [47]. .

The research to be conducted in future ought to investigate:

- TE chromatin communication at ZGA[48]
- Activation of human embryos TE associated.
- Development of regulatory evolution in epigenetics.

Such a work can demonstrate that the reprogramming of the epigenetics is a correlative process with the evolution of the genome.[47,48]

### 7.5 Epigenome Editing and Functional Validation

CRISPR-based epigenome editing tools offer a new avenue of discovery of similar causes and effects of definite epigenetic signatures and development. This could be due to the targeted manipulation of DNA methylation or histone modification of reprogramming cascade functional hierarchies in the reprogramming control regions or lineage controlled areas.[43]

This kind of experimentation is however being limited today by the consideration of

ethics and technical limitation in the human embryos. The systems of embryos and the stem cells systems may result in the development of the intermediate levels of functioning testing.[43]

### 7.6 Translational Precision in Reproductive Medicine

One of the key future directions is the process of incorporating the knowledge of epigenetics in clinical reproductive practice. Mechanistic clarity of windows of epigenetic vulnerability will be needed to standardize the conditions of embryo culture, optimize the procedures of ART, and generate non-invasive biomarkers.[41] Comparative epigenomic information can be used to identify which mechanisms are conserved, and which are species-specific and can be more precisely translated into animal models into human clinical scenarios.[41,43]

### 7.7 Conceptual Outlook: From Erasure to Reorganization

A conceptual change that might be the most important to arise out of recent research is that instead of viewing of epigenetic reprogramming as global erasure, it can be viewed as multidimensional reorganization. The loss of DNA methylation, histone redistribution, restructuring of chromatin topology and transcriptional activation are interdependent events in an ever-changing regulatory environment[42].Future studies should thus be open to systems level frameworks, which put forward molecular, spatial, temporal, and evolutionary views. It is only in this way that the field can be able to fully explain the logic of early mammalian development.[44,32].

## CONCLUSION

One of the major biological processes that directly developmental plasticity, localization of lineage differentiation and intergenerational stability are based on is the original embryonic reprogramming of the epigenome. As a worldwide operating lift and substitute DNA methylation mechanism, it is no longer as multidimensional and multifaceted as it was historically. Time-coordination and organization of DNA methylation, histone remodeling, regulation of genomic imprints, activity and genome dynamics reorganization of transposable elements is orchestrated.

It has been established that though the essential principles of biphasic reprogramming are generally conserved, demethylation, imprint stability, Polycomb dependent regulation, and utilization of transposable components and chromatin structure has been observed to be highly heterogeneous depending on species. This would render it difficult to see an overall mechanistic homology of mammals, and would demonstrate that a person should proceed with caution in extrapolating the results of model organism studies to human embryology.

Single-cell multi-omics and spatial epigenetic technologies have transformed the approaches to the previous concept of developmental regulation. Epigenetic reprogramming is context dependent process that is heterogeneous and depends on chromatin accessibility, nuclear organization and lineage specific regulation circuits as it is known today. Such perspective of systems level transformation changes the field that it no longer relies on reductionist models, but on integrative models which are more relevant in describing biological complexity.

Translational perspective for the interpretation of how the epigenetic reprogramming mechanism is executed has direct implications to the assisted reproductive technologies, imprinting diseases, successfulness of the germline and generational implication. The increased sensitivity is associated with the periods of restructuring of the epigenetic (periods of growth), and the role of mechanistic accuracy in reproductive medicine can hardly be overoverestimated.

The future research must be centered on high resolution integrative epigenomics, inter-species comparisons, which are normalized and the validation of the functions in ethically sustainable model systems. A correlation among the DNA methylation and histone modification to the genome topology will be very essential in clearing the conceptual grey zones over its ages.

Lastly, the early mammalian reprogramming of the epigenetics can no longer be viewed as an erasing and resetting but an organizing reorganizing of the embryonic regulatory genome. The species-conserved and species-specific measures of adaptation determination will render the developmental models easier to implement and it will enhance translational utility and it will dictate the future of the applied embryology research.

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