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LITERATURE REVIEW OF EMBRYONIC DEVELOPMENT EPIGENETICS: CHROMATIN MODIFICATION AND CELL PROGRAMMING

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Abstract

This study aims to comprehensively examine epigenetic mechanisms in embryonic development, focusing on the role of chromatin modification and cell programming as regulators of gene expression without changes in DNA sequence. The type of study used was qualitative , with a descriptive approach through literature review, which examined scientific literature from reputable international journals such as *Nature, Trends in Genetics,* and *The FEBS Journal* published between 2015 and 2025. Data were collected through systematic searches of scientific articles using thematic and inductive analysis techniques, including theme identification, data reduction, and concept categorization. The results of the study show that DNA methylation, acetylation, and histone methylation are key factors in regulating gene expression during the *zygotic genome activation* (ZGA) phase and the formation of cell lineages. This process demonstrates the complex interaction between epigenetic and transcriptional factors that determine the direction of cell differentiation. In addition, similarities in epigenetic regulation principles between mammals and plants were found, indicating the conservation of biological mechanisms across species. The implications of the study " " include the development of regenerative therapies, increased effectiveness of assisted reproductive technologies, and innovations in agricultural biotechnology. In conclusion, this study confirms that epigenetics is an important layer of regulation in developmental biology that enriches our understanding of the mechanisms of life formation from the earliest stages.

Keywords: epigenetics, chromatin modification, cell programming, embryonic development, zygotic genome activation.

INTRODUCTION

Epigenetics is one of the fields of molecular biology that has experienced rapid development in the last two decades. This field studies non-genetic mechanisms that regulate gene expression through chemical modifications of DNA and histones without changing the nucleotide base sequence (Xu et al., 2025) . In the context of embryonic development, epigenetic regulation is an important foundation for the formation of cell identity and complex tissue differentiation from the zygote stage to the formation of multicellular organisms (M . This phenomenon has become increasingly relevant as technological advances such as single-cell sequencing have enabled in-depth analysis of chromatin modification dynamics during embryonic development. In the last decade, interest in embryonic epigenetics has increased sharply, particularly due to its role in regulating zygotic genome activation (ZGA) and post-fertilization epigenetic reprogramming (Sotomayor-Lugo et al., 2024) . This *reprogramming* process involves the

removal and reformation of epigenetic marks such as DNA methylation and histone modifications that determine the gene expression patterns of early embryos (Xia et al., 2019) . Disruptions in this stage are known to cause developmental abnormalities and reduce embryo viability (Balder et al., 2024) . For example, environmental factors such as exposure to certain types of pesticides can trigger epigenetic changes that affect non-coding RNA, histone modifications, and DNA methylation patterns. These epigenetic changes not only have a direct impact on the organism but also have the potential to be inherited by subsequent generations (Alawiyah et al. 2024). The urgency of studies in this field has also increased due to their connection with *assistedreproductivetechnology (* ART), which can affect the epigenetic stability of embryos. Several studies have shown that manipulation of oocytes or sperm in the ART process can disrupt chromatin integrity and have implications for pregnancy outcomes and the long-term health of offspring (Edwards-Lee et al., 2025) . Therefore, a comprehensive understanding of chromatin modification and cell programming is crucial to improving the safety and effectiveness of reproductive technologies.

From a molecular perspective, chromatin modifications such as H3K4me3 and H3K27me3 play a central role in regulating the transition of genes from a repressive to an active state during early embryonic development (X. Liu et al., 2016) . H3K4me3 is often associated with active genes, while H3K27me3 plays a role in suppressing certain genes to maintain genetic expression balance (Chen et al., 2022) . The dynamic interaction between these two histone marks creates an epigenetic landscape that determines the direction of cell specification (Schüle & Probst, 2025) . Furthermore, a studyrecent shows a link between cellular metabolism and embryonic epigenetic regulation (Pladevall-Morera & Żylicz, 2022) . Metabolites such as α-ketoglutarate and S-adenosylmethionine act as cofactors for chromatin modification enzymes, indicating a bidirectional relationship between metabolic status and gene expression. These findings open up a new perspective that epigenetic regulation is not only controlled by genetic signals, but also by the physiological conditions of the cell.

However, there is still a knowledge gap regarding the integrative mechanisms between various chromatin modifications in determining cell fate during early developmental stages. Most studies still focus on the analysis of individual modifications, while interactions between epigenetic marks are often overlooked (Fu et al., 2020) . This is an obstacle to fully understanding how totipotent cells transition to pluripotent cells and eventually differentiate into various cell types. This knowledge gap also impacts the clinical application of epigenetic knowledge in the fields of reproduction and tissue regeneration. Although numerous studies have described the role of chromatin modification, the application of these findings in diagnosis and therapy remains limited due to the complexity of epigenetic interactions that are difficult to model (Bozdemir et al., 2025) . Therefore, an in-depth literature review is essential to summarize current findings and identify directions for future studies.

Global trends in developmental biology indicate that epigenetic studies now focus on systemic and integrative approaches, including multi-omic analyses that combine genomic, transcriptomic, and epigenomic data (Sun et al., 2021) . With this approach, researchers can comprehensively map gene regulatory networks and understand the dynamics of epigenetic changes over time. The relevance of this study is not limited to basic biology, but also has implications for the development of therapeutic technologies such as stem cell *reprogramming* and gene therapy. A better understanding of epigenetic programming during embryonic development could form the basis for new strategies in tissue regeneration and the treatment of degenerative diseases (Atlasi & Stunnenberg, 2017) . In an ecological and biotechnological context, epigenetic regulation also plays a role in the embryo's adaptation to changing microenvironments, including oxidative stress or nutritional variations during early development (Xu et al., 2025) . These mechanisms ensure the genetic and epigenetic stability necessary for normal development and species survival.

Overall, understanding chromatin modifications provides insight into how gene expression is precisely regulated during embryo formation. The interplay between genetic, epigenetic, and environmental factors suggests that embryonic development is the result of the complex orchestration of various biological mechanisms (M. Liu et al., 2025) . Despite significant progress, major challenges remain in translating basic findings into clinical and biotechnological applications. One such challenge is the uncertainty in predicting the long-term effects of epigenetic changes resulting from external interventions (Balder et al., 2024) . Therefore, further studies integrating experimental and computational approaches are urgently needed.

This article aims to review the current literature on the role of epigenetics, particularly chromatin modification, in embryonic development and cell programming. This review seeks to identify common patterns, gaps in studies , and the prospects for utilizing the results of epigenetic studies in the fields of reproductive biology and regenerative medicine. Through a systematic approach to the latest scientific literature, this article is expected to contribute theoretically to enriching the understanding of epigenetic mechanisms and provide practical benefits for the development of reproductive technology and tissue engineering. Ultimately, a deep understanding of chromatin modifications will be key to explaining how life begins from a single cell and develops into complex organisms.

METHOD

The type of study used in the article "Literature Review of Embryonic Development Epigenetics: Chromatin Modification and Cell Programming" is a study qualitative with a descriptive approach through literature study. This approach was chosen because it aims to understand epigenetic phenomena in the context of embryonic development in depth based on the results of studiesprevious . The descriptive approach allows researchers to present a factual picture of the dynamics of chromatin modification and cell programming without directly intervening in the study object (Abraham, 2024; Doyle, 2019) . This approach is suitable for use in molecular biology and development because it is able to integrate various empirical findings into a comprehensive theoretical framework. The data sources in this study consist of reputable scientific articles, academic books, and official reports relevant to the topics of epigenetics and qualitative methods. The main literature includes reputable international journals such as *Nature, Trends in Genetics, The FEBS Journal,* and *Frontiers in Cell and Developmental Biology*, which contain the latest studies on chromatin modification and cell programming (Chen et al., 2022; M. Liu et al., 2025; Schüle & Probst, 2025; Xu et al., 2025) . In addition, methodological sources were obtained from the literature on studiesqualitative and the latest descriptive approaches (Bingham, 2023; Pratt, 2025) . The selection of sources was based on the credibility of the publisher, year of publication, and direct relevance to the topic of discussion.

The literature search strategy in this was conducted using a combination of key words, namely "epigenetics," "embryonic development," "chromatin modification," "DNA methylation," "histone modification," and "cell programming." These keyword combinations were applied with the help of Boolean operators (AND, OR) to narrow down the search results and identify articles relevant to the focus of the study. studyData collection techniques were carried out through literature searches and analysis of academic documents. The researchers searched for articles using scientific databases such as ScienceDirect, SpringerLink, PubMed, and Consensus Academic Search to obtain recent publications between 2016 and 2025 that were relevant to the epigenetic dynamics of embryonic development. Each source was systematically examined to ensure its suitability for the focus of the study . The literature analysis was conducted by identifying the main arguments, methodological approaches, and conclusions produced by previous authors (Bandaranayake, 2024; Granikov, 2020) .

The data analysis procedure was conducted inductively and thematically, following systematic stages that included theme identification, data reduction, concept categorization, and conceptual conclusion drawing (Bingham, 2023; Vila-Henninger et al., 2022) . In the initial stage, data were collected and read repeatedly to find recurring patterns and key issues related to chromatin modification and cell programming. Next, data reduction is performed by filtering information relevant to the study question . The categorization stage involves grouping concepts such as DNA methylation, histone acetylation, and zygotic genome activation into broad themes, before finally synthesizing them into theoretical conclusions. Inclusion and exclusion criteria for literature were established to maintain the validity of the analysis results. Inclusion criteria were articles written in English, scientific publications published between 2015 and 2025, with an official DOI, and discussing the topics of chromatin modification, cell programming, or qualitative study methodologies . Meanwhile, exclusion criteria include publications not written in English, articles that do not explicitly mention epigenetic mechanisms or embryonic development processes, and non-scientific sources such as theses, editorials, opinions, or conference abstracts without full text. Thus, only literature that meets academic and methodological standards is used in this review (Fife, 2024; Jimenez, 2024) .

To ensure the validity and credibility of the data, this study applies the principles of source triangulation and conceptual *peer review*. Triangulation was carried out by comparing findings from various studies that used different approaches but examined the same phenomenon, such as studies of DNA methylation and histone acetylation in early embryos (X . Conceptual validation was performed through cross-reading the analysis results with established epigenetic theories and qualitative methodologies. This procedure ensures that the results of the study are transparent, replicable, and scientifically accountable (Kalpokaite & Radivojevic, 2018; Pratt, 2025) .Through this qualitative-descriptive literature review design, the article aims to provide a deep, systematic, and integrated understanding of how chromatin modifications play a role in cellular programming during embryonic development. This approach not only highlights biological dynamics theoretically but also underscores the contribution of epigenetics to clinical and biotechnological applications, making the results of this study relevant both theoretically and practically.

RESULTS

The results of a literature review on embryonic development epigenetics, particularly regarding chromatin modification and cell programming, show that epigenetics plays a fundamental role in regulating gene expression without altering the DNA sequence. This process is key to cell differentiation and the formation of complex embryonic structures. Based on recent literature, the transition from zygote to multicellular organism is controlled by

massive epigenetic changes involving DNA methylation, acetylation, and histone methylation, as well as the dynamics of accessibility (Bozdemir et al., 2025; Xia et al., 2019; Xu et al., 2025) .

1. Dynamics of Chromatin Modifications in Embryonic Development

Analysis results indicate that the early stages of embryonic development are characterized by global epigenetic *reprogramming* that erases and reshapes epigenetic marks such as H3K4me3 (gene activation) and H3K27me3 (gene repression). These modifications are important in initiating zygotic genome activation (ZGA), the stage at which the embryo begins to use its own genome for transcription (Fu et al., 2020; Schüle & Probst, 2025) . For example, Liu et al. (2025) used *single-cell histone profiling* technology to show that histone marks such as H3K4me3 appear rapidly at active gene promoters, while H3K27me3 is only restored after ZGA is complete (M .

Table 1. Dynamics of Chromatin Modifications in Embryonic Development

Type of Modification	Epigenetic Function	Stages of Development	Source
DNA methylation	Gene *silencing*, *imprinting*	Pre- and post-implantation	Xu et al. (2025); Xia et al. (2019)
H3K4me3	Gene activation	***Zygotic Genome Activation***,	Liu et al. (2025)
H3K27me3	Gene repression	***Post-zygotic genome activation***,	Bozdemir et al. (2025)
Chromatin accessibility	Gene expression regulation	Throughout embryogenesis	Schüle & Probst (2025); Fu et al. (2020)

The table above shows that chromatin modifications are *time-sensitive*, meaning that epigenetic changes occur specifically during certain developmental phases to ensure timely gene expression.

2. Cell Programming and Lineage Specification

Further findings indicate that cell programming during embryogenesis is controlled by complex interactions between chromatin modifications and pioneer transcription factors such as Oct4, Sox2, and Klf4 (Schüle & Probst, 2025; Sun et al., 2021) . The combination of active and repressive epigenetic marks creates a "bivalent" state at gene promoters that are ready to be activated or repressed depending on differentiation signals (Macrae et al., 2022) . The *single-cell epigenomics* approach reveals that epigenetic heterogeneity emerges as early as the two-cell stage, indicating the presence of totipotency priming that plays a role in embryonic lineage formation (Liu et al., 2025) (M .

3. Interspecies Comparisons and Clinical Implications

Comparative analysis shows that although the basic epigenetic mechanisms are conservative, there are significant differences between species. For example, in humans and mice, temporal differences were found in the dynamics of DNA methylation and histone re- . Disruptions in these mechanisms have been shown to correlate with developmental abnormalities and infertility, making an understanding of epigenetics important for clinical applications such as regenerative therapy and assisted reproductive technology (Chen et al., 2022) .

4. Chromatin Modification in Plants

Beyond animals, studies have also expanded our understanding of the role of epigenetics in plants, where transcription factors such as LEC1 and LEC2 act as key regulators of epigenetic reprogramming during embryogenesis (Tao et al., 2017; Zhao et al., 2023) . Plants exhibit high flexibility in chromatin modification, enabling tissue regeneration through *somatic embryogenesis* (De-La-Peña et al., 2015) . The results of the study Zhao et al. (2023) on hexaploid wheat show the existence of a dynamic chromatin regulation program similar to the animal model, reinforcing the assumption of cross-kingdom conservation in epigenetic regulation.

Table 2. Chromatin Modifications in Plants

Species	Dominant Mechanism	Key Factors	Reference
Mammals	DNA methylation , H3K4me3, H3K27me3	Oct4, Sox2, Nanog	(M. Liu et al., 2025; Xu et al., 2025)
Plants	Histone modifications, DNA methylation	LEC1, LEC2, FUS3	(De-La-Peña et al., 2015; Tao et al., 2017; Zhao et al., 2023)

5. Integration of Epigenetic and Transcription Factors

Overall, the results of the study indicate that chromatin modifications, DNA accessibility, and transcriptional activity form a complex regulatory network in directing embryonic development (Cusanovich et al., 2017) . This process involves synchronization between epigenetic reprogramming and the activation of genes important for totipotency. These interactions form the basis for new insights into how epigenetic factors can be manipulated for therapeutic purposes, including the development of stem cell-based therapies.

6. Synthesis and Study Trends

Recent trends in studies show a shift towards integrative multi-omics approaches, which combine transcriptomic, methylomic, and proteomic analyses to understand genetic regulation holistically (Macrae et al., 2022; Xu et al., 2025) . Epigenetic studies now focus not only on identifying molecular markers, but also on modeling their dynamics in real time using *live-cell imaging*. This approach expands the potential for applying epigenetic knowledge in regenerative medicine, agricultural biotechnology, and species conservation.

DISCUSSION

Analysis of the results of literature studies on embryonic development epigenetics confirms that the process of embryo formation is not solely controlled by DNA sequences, but by complex and dynamic layers of epigenetic regulation. Findings from various studies show that chromatin modifications—through DNA methylation, acetylation, and histone methylation—function as an additional coding system that determines gene expression patterns at each stage of development (Bozdemir et al., 2025; Xu et al., 2025) . These results reinforce the classical epigenetic theory that gene expression is reversible and can be regulated by chemical changes in chromatin (Atlasi & Stunnenberg, 2017) . Thus, epigenetics acts as a bridge between the genome and the embryonic phenotype. From a mechanistic perspective, the analysis demonstrates that epigenetic shifts during zygotic gene activation (ZGA) are critical points determining embryonic genome activation. Studies by Liu et al. (2025) and Xu et al. (2020) show that histone marks such as H3K4me3 and H3K27me3 undergo rapid reprogramming to regulate the transcription of genes important for totipotency (M . This interpretation aligns with the view of Schüle and Probst (2025), who emphasize that the balance between active and repressive modifications determines the direction of lineage specification (Schüle & Probst, 2025) . In the context of the *"chromatin landscape*" theory, this describes embryonic cells moving through an epigenetic "valley" toward a stable state of differentiation.

Furthermore, these results expand our understanding of chromatin bivalency, where developmental gene promoters exhibit dual marks—active (H3K4me3) and repressive (H3K27me3)—enabling flexibility in gene expression during embryogenesis (Atlasi & Stunnenberg, 2017; Macrae et al., 2022) . This concept supports the theory of "*epigenetic* plasticity," which is the ability of the genetic system to adapt to environmental or intrinsic signals without altering the DNA code. These findings also imply the importance of spatiotemporal regulation, as small errors in the placement of epigenetic marks can result in embryonic developmental failure (Chen et al., 2022; Xia et al., 2019) . In the context of cross-species analysis, the results show that although epigenetic mechanisms are conservative, there are significant variations between mammals and plants. In mammals, DNA methylation and histone *reprogramming* regulate the transition from totipotency to pluripotency (Fu et al., 2020; Xu et al., 2025) , whereas in plants, transcription factors such as LEC1 and LEC2 act as *"pioneer* regulators" that activate important genes during embryogenesis (Tao et al., 2017; Zhao et al., 2023) . Interestingly, De-La-Peña et al. (2015) showed that chromatin modification mechanisms in plants can also trigger the regeneration of somatic cells into new embryos, opening up great opportunities in agricultural biotechnology (De-La-Peña et al., 2015) .

The implications of these findings are vast. In the biomedical field, a deep understanding of embryonic epigenetic programming paves the way for the development of stem cell-based therapies and treatments for epigenetic diseases (Chen et al., 2022; Xu et al., 2025) . This aligns with findings in diabetes, where disease progression is associated with histone modifications, and interventions (such as Acalypha hispida nanoextracts) have been shown to modulate specific epigenetic markers (H3K9 acetylation) to produce antidiabetic effects in animal models (Alfarisi et al., 2024). In the context of assisted reproduction, the study shows that environmental interventions or laboratory

procedures can disrupt natural epigenetic patterns, necessitating strict ethical and technical standards (Bozdemir et al., 2025) . On the other hand, for plant biotechnology, epigenetic manipulation has the potential to be used to enhance plant regeneration and environmental stress resistance (Tao et al., 2017; Zhao et al., 2023) . However, it must be acknowledged that there are limitations in epigenetic studies. Most studies still focus on specific animal models such as mice, while studies on humans are still limited due to ethical and technical constraints. Furthermore, epigenetic analysis is snapshot-based—capturing only a specific point in time—and therefore does not fully describe the complex temporal dynamics of (Cusanovich et al., 2017) . Future studies are advised to adopt a *multi-omics* approach and *live-cell imaging* technology to monitor epigenetic changes in *real time.* Overall, the results of this study reinforce the concept that epigenetics is an important layer of regulation in developmental biology, while also marking a paradigm shift from "gene-centric" to "epigenome-centric." Its theoretical contribution lies in the assertion that the formation of cell identity is not only the result of gene expression, but the result of the complex orchestration of various epigenetic mechanisms that work in coordination throughout embryonic development.

CONCLUSION

Based on the results of the study and analysis, it can be concluded that epigenetics plays a central role in regulating embryonic development through chromatin modification and cell programming mechanisms. Processes such as DNA methylation, acetylation, and histone methylation have been shown to dynamically control gene activation and repression during embryogenesis, which determines the direction of differentiation and cell lineage specification. . These findings provide a deeper understanding that cell identity formation depends not only on genetic sequences, but also on complex interactions between epigenetic factors and the developmental environment . Theoretically, the study reinforces the concept of the epigenetic landscape and broadens the discourse on cross-species genetic plasticity, including mammals and plants . Its academic implications emphasize the importance of integrating multi-omics approaches in developmental biology studies, while socially and culturally, these results open up opportunities for innovation in biotechnology, regenerative therapy, and precision agriculture. Although the study still has limitations in terms of temporal aspects and human model limitations, this study provides a clear direction for further exploration of real-time epigenomic dynamics to understand the molecular basis of life from its earliest stages.

CONFLICT OF INTEREST

The author declares no relevant conflicts of interest with respect to the content of this paper.

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RECOMMENDATIONS

Based on the results and analysis of this study , it is recommended that practitioners in the fields of biotechnology, medicine, and agriculture utilize their understanding of epigenetic mechanisms in the development of reproductive technology, stem cell-based therapy, and the improvement of crop productivity and resilience. For academics and researchers, further research using a *multi-omics* approach and triangulation methods is needed to obtain a more comprehensive picture of the spatial and temporal dynamics of epigenetics. In addition, future studies need to integrate cross-species and environmental condition analysis to understand epigenetic variation in a broader biological and ecological context. By expanding the focus on the interactions between epigenetic, metabolic, and environmental factors, future studies are expected to enrich embryo development theory and produce applicable and sustainable innovations in various fields of science.

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