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MOLECULAR REGULATION OF GERM CELL SPECIFICATION AND ITS IMPLICATIONS FOR HUMAN FERTILITY

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ABSTRACT: *Germ cell specification represents a fundamental biological process that underpins heredity, reproductive function, and species continuity. This review provides a comprehensive synthesis of the molecular and developmental mechanisms governing germ cell formation, from early specification to sex-specific differentiation and functional maturation. Germ cell fate is established through tightly regulated transcriptional networks, prominently involving PRDM1, PRDM14, and TFAP2C, which integrate extracellular signaling inputs from key pathways such as bone morphogenetic protein (BMP), WNT, and NODAL/Activin. These regulatory systems coordinate the transition of pluripotent embryonic cells into primordial germ cells (PGCs), while suppressing somatic differentiation programs. A defining feature of germ cell development is extensive epigenetic reprogramming, including genome-wide DNA demethylation, imprint erasure, histone modification remodeling, and X-chromosome reactivation, which collectively reset the epigenetic landscape to ensure genomic integrity and developmental potency. Beyond transcriptional and epigenetic control, post-transcriptional regulatory mechanisms, including non-coding RNAs and RNA-binding proteins, play essential roles in maintaining germline identity and regulating gene expression during stages of limited transcriptional activity. Following specification, PGCs undergo migration, proliferation, and colonization of the gonadal ridges, processes that are tightly controlled by chemokine signaling, cytoskeletal dynamics, and interactions with the somatic niche. Subsequent sex-specific differentiation into spermatogonial stem cells or oocytes is orchestrated by local signaling environments, particularly retinoic acid dynamics and somatic–germ cell interactions. Disruptions in these processes are closely linked to a spectrum of reproductive disorders, including infertility, disorders of sex development, epigenetic syndromes, and germ cell tumors. Environmental factors such as endocrine-disrupting chemicals, oxidative stress, and nutritional imbalances further modulate germ cell development, with potential transgenerational consequences mediated through epigenetic mechanisms. Concurrently, advances in experimental models, including human pluripotent stem cell-derived germ cell systems, organoids, and multi-omics technologies, have significantly expanded the capacity to investigate human germline biology with high resolution. These innovations are driving translational applications in fertility preservation, artificial gametogenesis, biomarker discovery, and targeted therapeutics. This review highlights the intricate interplay between genetic, epigenetic, and environmental factors in germ cell development and underscores their critical implications for reproductive health and disease. Continued integration of developmental biology with emerging technologies will be essential for advancing precision reproductive medicine and addressing unresolved challenges in germline biology.*

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INTRODUCTION

Germ cell specification is a fundamental developmental process through which a distinct lineage of cells is established to ensure the transmission of genetic information across generations (Hansel & Pelegri, 2021). Unlike somatic cells, which contribute to the structure and function of the organism, germ cells are uniquely responsible for preserving genomic integrity and enabling reproduction. This biological distinction places germ cells at the center of heredity, evolution, and species continuity. Consequently, understanding how germ cells are specified, maintained, and differentiated into functional gametes is essential for both developmental biology and reproductive medicine (Hancock et al., 2021). A key event in early embryogenesis is the segregation of germline and somatic cell fates. While somatic cells undergo progressive differentiation to form specialized tissues and organs, germ cells follow a distinct developmental trajectory characterized by the preservation of developmental potential and extensive epigenetic reprogramming. This divergence is tightly regulated by coordinated genetic and signaling mechanisms that suppress somatic differentiation pathways while promoting germline identity (Saitou et al., 2025). Disruption of this balance can result in developmental abnormalities, infertility, or germ cell tumorigenesis (Oosterhuis & Looijenga, 2019; Müller et al., 2020).

Primordial germ cells (PGCs) represent the earliest identifiable germline precursors and serve as the foundation for gametogenesis. In mammals, PGCs arise from pluripotent epiblast cells and undergo a series of coordinated processes, including specification, migration, proliferation, and differentiation (Hancock et al., 2021). During these stages, PGCs exhibit a unique molecular profile that combines features of pluripotency with germline-specific gene expression. They also undergo extensive epigenetic reprogramming, including genome-wide DNA demethylation and imprint erasure, which resets the epigenetic landscape and prepares the genome for transmission to the next generation. This dynamic developmental program reflects their dual role as carriers of genetic information and as participants in developmental regulation (Saitou et al., 2025).

From an evolutionary perspective, germ cell specification occurs through two principal mechanisms: preformation and epigenesis. Preformation involves the inheritance of maternally deposited determinants that specify germ cell fate early in embryogenesis (Hansen & Pelegri, 2021). In contrast, epigenesis relies on inductive signaling processes that direct pluripotent cells toward a germline fate through intercellular communication and environmental cues (Colonnetta et al., 2022). These distinct strategies highlight the evolutionary diversity of germ cell development while revealing conserved molecular principles underlying germline establishment.

The relevance of germ cell biology extends beyond development to human fertility and clinical applications. Defects in germ cell specification and development are a major cause of infertility, a condition affecting a significant proportion of the global population (Czukiewska & De Sousa Lopes, 2022). In addition, advances in assisted reproductive technologies (ART), such as in vitro fertilization, have intensified interest in the molecular and epigenetic integrity of germ cells and early embryos. These concerns are particularly relevant given the potential for epigenetic perturbations during in vitro manipulation (Sciorio & Hajj, 2022). A deeper understanding of germ cell biology is therefore critical for improving reproductive outcomes and minimizing associated risks (Cheung et al., 2024; Zhang et al., 2023). This review aims to provide a comprehensive synthesis of the molecular regulation of germ cell specification and

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its implications for human fertility. It will examine the signaling pathways and transcriptional networks that govern germ cell induction, the epigenetic and post-transcriptional mechanisms that stabilize germline identity, and the developmental processes leading to gametogenesis.

Developmental Origins and Molecular Basis of Germ Cell Specification

Germ Cell Specification across Species

Germ cell specification exhibits remarkable diversity across the animal kingdom, yet converges on a conserved developmental objective: the establishment of a lineage dedicated to transmitting genetic information across generations (Hansen & Pelegri, 2021). Two principal modes of germ cell specification, which are preformation and epigenesis, have been identified, reflecting distinct evolutionary strategies for segregating the germ line from somatic tissues. Preformation, observed in organisms such as Drosophila melanogaster and Caenorhabditis elegans, relies on the asymmetric inheritance of maternally deposited cytoplasmic determinants, collectively termed germ plasm (Colonnetta et al., 2022). These determinants, which include RNA-binding proteins and translational regulators, are localized within the oocyte before fertilization and are partitioned into specific blastomeres during early cleavage stages. Cells inheriting this specialized cytoplasm are thereby committed to germ cell fate, often prior to the onset of zygotic transcription. This mechanism enables rapid and deterministic germline segregation, effectively insulating germ cells from inductive somatic signals and establishing lineage identity at the earliest stages of development (Perillo et al., 2021; Hansen and Pelegri, 2021).

In contrast, epigenesis represents an inductive mechanism of germ cell specification that predominates in mammals, including humans (Hancock et al., 2021). In this paradigm, germ cells arise from a population of pluripotent embryonic cells that acquire germline identity in response to extrinsic signaling cues. In the mouse, primordial germ cells (PGCs) are specified from the proximal epiblast around embryonic day 6.25, following the integration of WNT and bone morphogenetic protein (BMP) signaling pathways originating from adjacent extraembryonic tissues (Morgani & Hadjantonakis, 2021). This inductive process is spatially and temporally restricted, requiring both cellular competence and positional information within the embryo. Cells that are initially equivalent in developmental potential can be redirected toward germ cell fate when exposed to appropriate signaling environments, highlighting the plasticity inherent in early embryogenesis (Castillo-Venzor et al., 2022). Importantly, comparative analyses suggest that epigenesis is likely the ancestral mode of germ cell specification, with preformation representing a derived adaptation that evolved independently in multiple lineages (Hansen & Pelegri, 2021; Roelen & De Sousa Lopes, 2022).

Although both mouse and human germ cell specifications follow an epigenetic framework, important species-specific differences have emerged. In the mouse, germ cell specification is driven by a transcriptional network centered on PRDM1 (BLIMP1) and PRDM14, which are induced downstream of BMP signaling (Kojima et al., 2021). These factors initiate germline fate by repressing somatic gene expression programs and promoting epigenetic reprogramming. In humans, however, recent evidence indicates a distinct regulatory hierarchy in which SOX17 functions as a primary determinant of germ cell fate, acting upstream of BLIMP1 (Tang et al., 2022). This divergence reflects broader differences in early embryonic architecture and lineage specification between rodents and primates (Castillo-Venzor et al., 2022). Furthermore, the timing of germ cell specification differs substantially: whereas mouse

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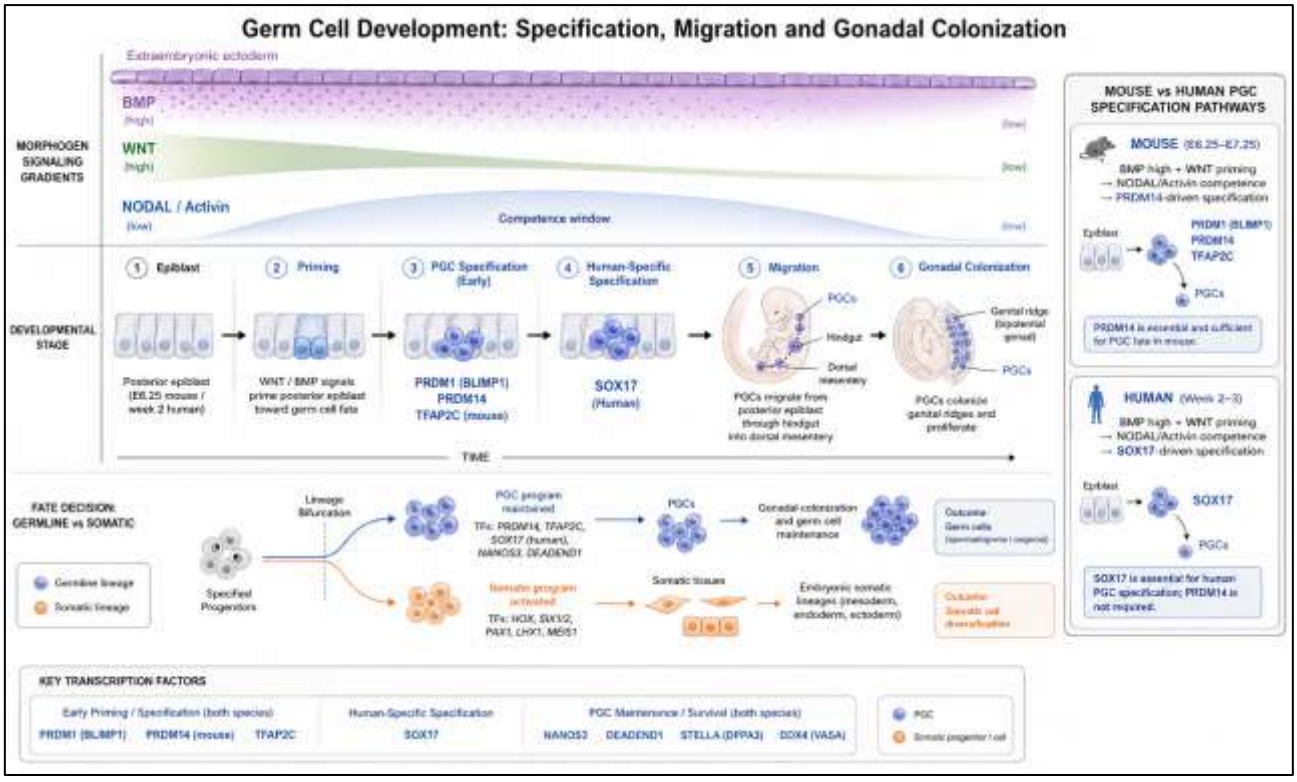
PGCs are specified during early gastrulation, human PGC-like cells are thought to arise slightly later, potentially within the developing amniotic membrane or posterior epiblast during weeks 2–3 of embryogenesis (Saitou et al., 2025; Yu et al., 2025). These differences underscore the limitations of extrapolating murine models directly to human development and highlight the necessity of species-specific investigations in reproductive biology.

The concept of embryonic niches provides an additional layer of regulation in germ cell specification. In epigenetic systems, germ cell fate is not solely determined by intrinsic factors but is critically dependent on the microenvironment in which precursor cells reside (Roelen & De Sousa Lopes, 2022). In the mouse embryo, the proximal-posterior epiblast adjacent to the extraembryonic ectoderm constitutes a permissive niche enriched in BMP signals that promote germ cell induction (Morgani & Hadjantonakis, 2021). Conversely, inhibitory signals from regions such as the anterior visceral endoderm restrict germ cell formation to specific embryonic domains, thereby establishing spatial patterning. This interplay between inductive and repressive cues ensures that only a small subset of competent cells adopts a germline fate (Hancock et al., 2021; Saitou et al., 2025). Moreover, the temporal window during which cells remain responsive to germline-inducing signals is tightly regulated, emphasizing the importance of developmental timing in germ cell specification. Together, these observations illustrate that germ cell fate emerges from a finely tuned balance between intrinsic competence and extrinsic signaling within defined embryonic niches.

Figure 1. Spatiotemporal regulation of primordial germ cell (PGC) development from epiblast to gonadal colonization (Wear et al., 2016).



A schematic timeline illustrating germ cell specification, migration, and lineage segregation. Epiblast cells undergo inductive signaling driven by graded BMP, WNT, and NODAL/Activin pathways, establishing a competence window for PGC fate acquisition. Early germ cell

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specification is marked by the coordinated expression of PRDM1 (BLIMP1), PRDM14, and TFAP2C (predominantly in mouse), while SOX17 serves as the key determinant in human PGC specification. A lineage bifurcation highlights divergence between germline (blue/purple) and somatic (orange/gray) fates. Specified PGCs migrate from the posterior epiblast through the hindgut to the genital ridges, where they undergo proliferation and colonization. A comparative inset delineates species-specific regulatory differences, emphasizing PRDM14-dependent pathways in mouse versus SOX17-driven specification in human.

Core Transcriptional Regulatory Network

The induction of germ cell fate is orchestrated by a highly coordinated transcriptional network that integrates signaling inputs with epigenetic remodeling to establish and stabilize germline identity (Kojima et al., 2021). Central to this network are the transcriptional regulators PRDM1 (also known as BLIMP1), PRDM14, and TFAP2C, which function collectively to repress somatic differentiation programs while activating germ cell-specific gene expression. These factors operate within a hierarchical framework, acting downstream of inductive signaling pathways such as BMP and WNT to convert pluripotent epiblast cells into primordial germ cells (Hancock et al., 2021; Saitou et al., 2025).

PRDM1 is widely regarded as a master regulator of germ cell specification, primarily due to its role in repressing somatic gene expression (Kojima et al., 2021). Upon induction, PRDM1 initiates a transcriptional silencing program that suppresses genes associated with mesodermal and endodermal differentiation, thereby preventing the adoption of alternative cell fates. This repression is achieved through the recruitment of chromatin-modifying complexes, including histone methyltransferases, which establish repressive epigenetic marks such as histone H3 lysine 27 trimethylation (Ramakrishna et al., 2021). In the absence of PRDM1, cells that initially exhibit germ cell-like characteristics fail to maintain their identity and instead activate somatic developmental programs, ultimately leading to cell death or aberrant differentiation. Thus, PRDM1 functions as a gatekeeper of germline identity, ensuring that germ cell precursors are insulated from competing lineage signals (Müller et al., 2020; Liu et al., 2021).

Complementing the function of PRDM1, PRDM14 plays a critical role in re-establishing pluripotency and facilitating epigenetic reprogramming within germ cells (Kojima et al., 2021). Unlike PRDM1, which primarily represses somatic genes, PRDM14 promotes the activation of pluripotency-associated transcriptional networks and contributes to the global erasure of DNA methylation marks. This dual function is essential for resetting the epigenetic state of germ cells, thereby enabling the transmission of a totipotent genome to the next generation (Hill et al., 2018; Singh et al., 2023). PRDM14 also enhances the responsiveness of cells to germline-inducing signals, reinforcing commitment to germ cell fate. The coordinated activity of PRDM1 and PRDM14 thus ensures both the suppression of inappropriate gene expression and the restoration of developmental potential (Ramakrishna et al., 2021; Lee & Surani, 2024).

TFAP2C (transcription factor AP-2 gamma) acts in concert with PRDM1 and PRDM14 to stabilize germ cell identity and promote lineage-specific gene expression (Kojima et al., 2021). TFAP2C is required for the maintenance of germ cell transcriptional programs and contributes to the regulation of genes involved in cell survival, proliferation, and migration. Its role extends beyond initial specification, as it helps sustain germline identity during the migratory phase of PGC development (Barton et al., 2024). Loss of TFAP2C function results in defective germ

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cell development and increased susceptibility to apoptosis, highlighting its importance in maintaining the integrity of the germline lineage (Müller et al., 2020; Fichtner et al., 2024).

A defining feature of this transcriptional network is its capacity to enforce a robust suppression of somatic differentiation programs while simultaneously activating germline-specific pathways (Saitou et al., 2025). This is achieved through a combination of direct transcriptional repression, chromatin remodeling, and modulation of signaling responsiveness. Germ cell precursors must resist the pervasive influence of somatic inductive cues present during gastrulation, a process that is facilitated by global transcriptional repression mechanisms and selective gene activation (Ramakrishna et al., 2021; Gleason & Chen, 2022). The integration of these regulatory processes ensures that germ cell identity is both precisely specified and stably maintained.

Signaling Pathways in Primordial Germ Cell Induction

The specification of primordial germ cells (PGCs) within epigenetic systems is critically dependent on the integration of extracellular signaling pathways that confer germline competence and initiate lineage commitment (Hancock et al., 2021). Among these, the bone morphogenetic protein (BMP), WNT, and NODAL/Activin pathways constitute a highly coordinated signaling network that governs the emergence of germ cells from pluripotent embryonic precursors. These pathways do not operate in isolation; rather, their spatial distribution, temporal activation, and quantitative intensity collectively determine whether a subset of embryonic cells adopts a germ cell fate or diverges toward somatic lineages (Morgani & Hadjantonakis, 2021; Saitou et al., 2025).

BMP signaling plays a central and indispensable role in PGC induction, particularly in mammalian systems (Hancock et al., 2021). In the mouse embryo, BMP4 and BMP8b, secreted from the extraembryonic ectoderm, and BMP2 from the visceral endoderm, establish a signaling gradient across the proximal epiblast. This gradient provides the instructive cues necessary for germ cell specification by activating downstream SMAD1/5/8 transcription factors, which in turn induce germline-associated genes (Morgani & Hadjantonakis, 2021). Importantly, BMP signaling functions not merely as a permissive factor but as a decisive determinant of germ cell fate, as evidenced by the failure of PGC formation in embryos deficient in BMP pathway components. The spatial restriction of BMP activity ensures that only epiblast cells within a defined embryonic niche acquire germline potential, reinforcing the concept that positional information is a key determinant of cell fate (Roelen & De Sousa Lopes, 2022; Saitou et al., 2025).

Complementing BMP signaling, the WNT pathway serves as a priming mechanism that prepares epiblast cells to respond effectively to germline-inducing cues (Morgani & Hadjantonakis, 2021). WNT3 signaling has been shown to enhance the competence of epiblast cells by modulating chromatin accessibility and facilitating the activation of germ cell-specific transcriptional programs. This priming effect emphasizes the hierarchical nature of signaling interactions, whereby WNT activity establishes a permissive state that enables subsequent BMP-mediated induction (Hancock et al., 2021). Without this preparatory phase, BMP signaling alone is insufficient to drive robust germ cell specification, highlighting the necessity of coordinated pathway interactions (Castillo-Venzor et al., 2022; Saitou et al., 2025).

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The NODAL/Activin signaling axis further refines the process of PGC induction by regulating early embryonic patterning and maintaining pluripotency within the epiblast (Morgani &Hadjantonakis, 2021). Through SMAD2/3-mediated transcriptional regulation, NODAL signaling contributes to the establishment of mesendodermal competence, a developmental state from which germ cells can emerge. In human systems, this pathway appears to play a more prominent role than in the mouse, particularly in facilitating the expression of SOX17, a key determinant of human germ cell fate (Kojima et al., 2021). The interplay between NODAL/Activin and BMP signaling thus exemplifies the context-dependent nature of germ cell specification, with species-specific variations reflecting differences in embryonic architecture and lineage segregation (Saitou et al., 2025; Yu et al., 2025).

A defining characteristic of these signaling pathways is their integration into a dynamic and dose-dependent regulatory network. Germ cell specification is highly sensitive to the concentration and duration of signaling inputs, with threshold effects determining cell fate outcomes (Morgani and Hadjantonakis, 2021). Suboptimal levels of BMP signaling may fail to induce germ cell fate, whereas excessive signaling can lead to aberrant differentiation or apoptosis. Similarly, the balance between inductive signals (such as BMP and WNT) and inhibitory cues from regions like the anterior visceral endoderm establishes a finely tuned signaling landscape that restricts germ cell formation to a precise developmental window (Roelen and De Sousa Lopes, 2022). This dose-dependent modulation ensures that only a limited population of cells is specified as PGCs, preserving the integrity of embryonic patterning while enabling the emergence of the germ line (Hancock et al., 2021; Saitou et al., 2025).

Epigenetic Reprogramming

A hallmark of primordial germ cell development is the extensive epigenetic reprogramming that redefines the genomic landscape of these cells, effectively resetting epigenetic marks inherited from the parental genome (Ramakrishna et al., 2021). This process is essential for restoring developmental potency, erasing lineage-specific modifications, and establishing a germline-specific epigenetic state capable of supporting gametogenesis and subsequent embryonic development. Epigenetic reprogramming in PGCs encompasses genome-wide DNA demethylation, erasure of genomic imprinting, dynamic histone modifications, and X-chromosome reactivation, all of which occur in a tightly regulated and sequential manner (Lee and Surani, 2024; Saitou et al., 2025).

One of the most prominent features of this reprogramming process is the global reduction in DNA methylation levels. Following their specification, PGCs undergo extensive demethylation, reducing methylation marks across the genome, including repetitive elements, gene bodies, and regulatory regions (Hill et al., 2018). This demethylation occurs through both passive mechanisms, such as the dilution of methylation marks during cell division due to reduced maintenance methyltransferase activity, and active mechanisms involving enzymatic processes such as TET-mediated oxidation of 5-methylcytosine (Singh et al., 2023). The erasure of DNA methylation is critical for removing parental epigenetic memory, thereby preventing the inappropriate transmission of somatic or lineage-specific information to the next generation (Gruhn et al., 2023; Shirane, 2022).

Closely associated with DNA demethylation is the erasure and subsequent re-establishment of genomic imprinting. Imprinted genes, which are expressed in a parent-of-origin-specific

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manner, must undergo epigenetic resetting in germ cells to ensure that appropriate imprinting patterns are established according to the sex of the individual (Anvar et al., 2021). Failure to properly erase or re-establish these imprints can result in severe developmental disorders, including imprinting syndromes and infertility. The timing and precision of imprint erasure in PGCs thus represent a critical checkpoint in germline development, linking epigenetic regulation to reproductive health (Monk et al., 2019; Roidor et al., 2024).

In parallel with DNA methylation changes, PGCs undergo extensive remodeling of histone modifications, which play a crucial role in regulating chromatin structure and gene expression (Ramakrishna et al., 2021). Early in PGC development, there is a reduction in repressive histone marks associated with somatic differentiation, followed by the establishment of a chromatin landscape that balances transcriptional repression with the maintenance of developmental potential. Notably, increased levels of histone H3 lysine 27 trimethylation (H3K27me3) contribute to the silencing of somatic genes, while the modulation of activating marks such as H3K4 methylation reflects the dynamic regulation of gene expression during germ cell development (Mallol et al., 2019; Gruhn et al., 2023). These histone modifications work in concert with DNA methylation changes to establish a chromatin environment that supports germline identity while preserving genomic integrity.

Another critical aspect of epigenetic reprogramming in PGCs is the reactivation of the X chromosome in female germ cells. During early embryogenesis, one of the two X chromosomes in female cells undergoes inactivation to achieve dosage compensation. However, in PGCs, this inactivated X chromosome is reactivated, restoring biallelic expression of X-linked genes (Lee and Surani, 2024). This reactivation is essential for ensuring that both X chromosomes are epigenetically reset prior to gametogenesis, allowing for the appropriate establishment of sex-specific epigenetic patterns in oocytes. The process of X-chromosome reactivation is tightly coordinated with other epigenetic changes, reflecting the global nature of the reprogramming events occurring in germ cells (Ramakrishna et al., 2021; Singh et al., 2023).

The extensive epigenetic remodeling observed in PGCs underscores their unique developmental role as custodians of the genome. By erasing and re-establishing epigenetic marks, germ cells ensure that genetic information is transmitted without the confounding influence of acquired modifications (Saitou et al., 2025). However, this process also represents a period of heightened vulnerability, as disruptions in epigenetic reprogramming can lead to genomic instability, aberrant gene expression, and long-term reproductive consequences. Environmental factors, including endocrine-disrupting chemicals and metabolic stress, have been shown to influence epigenetic states in germ cells, raising important questions about the impact of early-life exposures on fertility and transgenerational health (Xavier et al., 2019; Wu et al., 2024).

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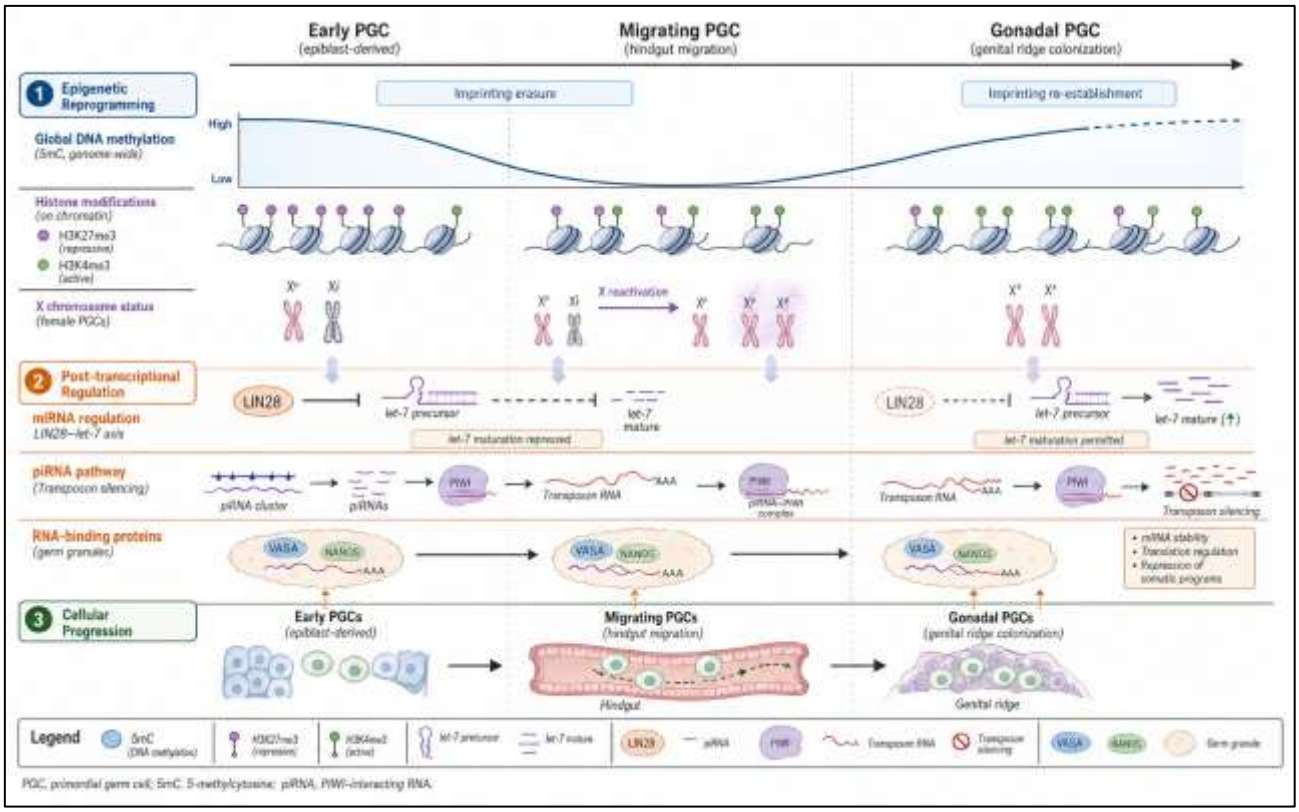
Figure 2: Integrated epigenetic and post-transcriptional regulation during primordial germ cell (PGC) development.



A multi-layered schematic illustrating the coordinated molecular and cellular dynamics of PGC development along a temporal axis from early specification to gonadal colonization. The top layer depicts epigenetic reprogramming, including genome-wide DNA methylation dynamics (global demethylation followed by remethylation), imprinting erasure and re-establishment, and key histone modifications (H3K27me3 and H3K4me3). X-chromosome reactivation in female PGCs is highlighted as a stage-specific event. The middle layer represents post-transcriptional regulatory mechanisms, including the LIN28–let-7 miRNA axis, piRNA-mediated transposon silencing, and RNA-binding proteins (e.g., VASA and NANOS) associated with germ granules. The bottom layer illustrates cellular progression from epiblast-derived early PGCs through migratory stages to gonadal colonization. Inter-layer connections emphasize the integration of epigenetic and RNA-based regulatory networks in maintaining germ cell identity and genomic integrity.

Post-Transcriptional Regulation

Beyond transcriptional and epigenetic control, germ cell specification and early development are critically shaped by post-transcriptional regulatory mechanisms that govern RNA stability, localization, and translation (Gleason and Chen, 2022). These processes are particularly important in the germline context, where transcriptional activity is often globally repressed during early stages, necessitating a reliance on pre-existing transcripts and tightly controlled translational programs. Post-transcriptional regulation thus serves as a pivotal layer of control

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that ensures temporal precision and fidelity in gene expression during primordial germ cell (PGC) specification, migration, and early differentiation (Ramakrishna et al., 2021; Saitou et al., 2025).

A central component of post-transcriptional regulation in germ cells is the activity of non-coding RNAs, particularly microRNAs (miRNAs) and PIWI-interacting RNAs (piRNAs) (Gleason and Chen, 2022). miRNAs are short, endogenous RNA molecules that modulate gene expression by promoting mRNA degradation or inhibiting translation through sequence-specific interactions with target transcripts. In the context of germ cell development, miRNAs contribute to the fine-tuning of gene expression networks, including the regulation of pluripotency factors and signaling pathway components. For instance, the LIN28–let-7 axis plays a critical role in maintaining germ cell identity by suppressing premature differentiation and sustaining a pluripotent-like state in early germ cells (Kojima et al., 2021). In parallel, the piRNA pathway represents a germ cell-specific RNA silencing system essential for maintaining genomic integrity. piRNAs associate with PIWI family proteins to form complexes that target transposable elements for silencing, particularly during periods of epigenetic reprogramming when transposon activation poses a significant threat to genome stability (Bloom et al., 2019; Anjum et al., 2025).

Complementing the role of non-coding RNAs, RNA-binding proteins (RBPs) constitute another major class of post-transcriptional regulators that orchestrate germ cell development (Perillo et al., 2021). These proteins interact with specific RNA sequences or structures to control mRNA localization, stability, and translational efficiency. Many RBPs are evolutionarily conserved and exhibit germ cell-specific expression patterns, reflecting their fundamental roles in germline biology. For example, members of the Vasa/DDX4 family function as RNA helicases that facilitate the assembly of ribonucleoprotein complexes and regulate the translation of germ cell-specific transcripts. Similarly, proteins such as NANOS and PUMILIO act as translational repressors, preventing the activation of somatic gene expression programs (Hansen and Pelegri, 2021; Perillo et al., 2021). The importance of RBPs is further highlighted by their involvement in the formation of specialized cytoplasmic structures, such as germ granules, which serve as hubs for RNA processing and storage and enable localized control of gene expression.

Translational control mediated by RBPs and associated complexes is particularly critical during stages when transcription is limited or absent (Ramakrishna et al., 2021). In early PGCs, global transcriptional repression necessitates reliance on post-transcriptional mechanisms to regulate protein synthesis. RBPs achieve this by selectively activating or repressing the translation of stored mRNAs in response to developmental cues, thereby ensuring that proteins required for germ cell survival, migration, and differentiation are produced at the appropriate time and location (Barton et al., 2024). Importantly, post-transcriptional regulation also intersects with other regulatory layers, forming an integrated network that governs germ cell fate. For instance, miRNAs can modulate the expression of transcription factors and epigenetic regulators, while RBPs can influence the stability of transcripts encoding signaling pathway components, thereby enhancing the robustness of germ cell specification (Gleason & Chen, 2022; Saitou et al., 2025).

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Germ Cell Migration, Survival, and Differentiation

Following specification, primordial germ cells (PGCs) embark on a highly coordinated developmental trajectory encompassing directed migration, controlled proliferation, and eventual differentiation into sex-specific gametes (Barton et al., 2024). This phase is critical for establishing a functional germline, as errors in migration or survival can result in infertility, ectopic germ cell localization, or tumorigenesis. Unlike many somatic cell populations, PGCs must navigate a dynamic embryonic environment while preserving their unique identity, resisting differentiation cues, and undergoing extensive epigenetic remodeling (Saitou et al., 2025). The successful integration of migratory guidance, cell cycle control, and differentiation signals reinforces the complexity of germline development and highlights the interplay between intrinsic genetic programs and extrinsic microenvironmental cues (Goodwin, 2025; Roelen and De Sousa Lopes, 2022).

Migration and Gonadal Colonization

The migration of PGCs from their site of specification to the developing gonadal ridges is a defining feature of germ cell development in most metazoans (Barton et al., 2024). This process is highly conserved and involves long-range, directional movement through embryonic tissues, including the hindgut endoderm and dorsal mesentery in mammals. Migration is not a passive event but rather a tightly regulated process that integrates chemotactic signaling, cytoskeletal remodeling, and interactions with the extracellular matrix (Goodwin, 2025). Successful colonization of the gonadal ridges is essential for subsequent germ cell survival and differentiation, as these structures provide the niche required for further development. Central to the guidance of PGC migration is chemokine signaling, particularly the stromal cell-derived factor 1 (SDF1, also known as CXCL12) and its receptor CXCR4. This signaling axis establishes a chemotactic gradient that directs PGCs toward the gonadal region. Cells expressing CXCR4 respond to SDF1 signals by undergoing directional migration, a process that is essential for proper germ cell localization (Jaszczak et al., 2025). Disruption of this pathway leads to impaired migration, resulting in the accumulation of PGCs in ectopic sites and reduced colonization of the gonads. Such defects are associated with infertility and an increased risk of germ cell tumor formation, emphasizing the functional importance of chemokine-mediated guidance (Oosterhuis and Looijenga, 2019; De Felici et al., 2021).

In addition to chemotactic cues, PGC migration requires dynamic regulation of the cytoskeleton to facilitate cell movement through diverse tissue environments (Goodwin, 2025). Actin polymerization, regulated by small GTPases such as RAC1 and CDC42, drives the formation of cellular protrusions that enable directional motility. Integrins and other adhesion molecules mediate interactions with the extracellular matrix, allowing PGCs to navigate complex anatomical structures. Furthermore, repulsive signals and guidance molecules ensure that PGCs follow appropriate migratory routes, preventing aberrant localization (Barton et al., 2024; Jaszczak et al., 2025). The integration of these molecular mechanisms enables PGCs to maintain directional persistence while adapting to changing environmental conditions during migration.

Proliferation and Quality Control

Concurrently with migration, PGCs undergo a phase of mitotic proliferation that expands the germ cell population prior to differentiation (Saitou et al., 2025). This proliferative phase is

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tightly regulated to ensure that enough germ cells reach the gonads while maintaining genomic integrity. Cell cycle progression in PGCs is influenced by both intrinsic regulators and extrinsic signals from the surrounding microenvironment, reflecting the importance of coordinated growth and developmental timing (Roelen and De Sousa Lopes, 2022). Regulation of the PGC cell cycle involves canonical cell cycle machinery, including cyclins, cyclin-dependent kinases (CDKs), and checkpoint proteins that monitor DNA integrity. These regulatory systems ensure that cell division proceeds in a controlled manner, preventing the accumulation of mutations during rapid proliferation (Anjum et al., 2025). Importantly, PGCs exhibit unique cell cycle dynamics compared to somatic cells, including periods of cell cycle arrest that coincide with key developmental transitions, such as entry into meiosis or differentiation into germline stem cells (Maroto et al., 2025; Guo et al., 2021).

Given the critical role of germ cells in transmitting genetic information, stringent quality control mechanisms are in place to eliminate defective cells. Apoptosis serves as a primary mechanism for removing PGCs that fail to migrate correctly, exhibit DNA damage, or lose germline identity (Liu et al., 2021). The tumor suppressor protein p53 plays a central role in this process by mediating DNA damage responses and triggering programmed cell death when genomic integrity is compromised. This selective elimination ensures that only healthy, functionally competent germ cells contribute to the germline, thereby safeguarding reproductive fitness (Bloom et al., 2019; Müller et al., 2020). In addition to apoptosis, other quality control mechanisms, including DNA repair pathways and oxidative stress responses, contribute to maintaining genomic stability in PGCs. These processes are particularly important during periods of epigenetic reprogramming, when chromatin is more accessible and potentially vulnerable to damage (Dutta et al., 2024; Wu et al., 2024). The balance between proliferation and quality control is therefore essential for maintaining a robust and functional germ cell population.

Sex-Specific Differentiation

Following successful colonization of the gonadal ridges, primordial germ cells (PGCs) undergo sex-specific differentiation, a process that is tightly coordinated with the development of the surrounding somatic gonadal environment (Czukiewska and De Sousa Lopes, 2022). This transition marks the point at which germ cells lose their pluripotent characteristics and commit to either the male or female developmental pathway (Webster et al., 2021). The timing and nature of this differentiation are influenced by both intrinsic genetic programs and extrinsic signals from the gonadal niche (Guo et al., 2021). In the male pathway, germ cells differentiate into spermatogonial stem cells (SSCs), which serve as the foundation for lifelong spermatogenesis. During fetal development, male germ cells typically enter a state of mitotic arrest, maintaining a quiescent state until after birth (Maroto et al., 2025). This arrest is essential for preventing premature entry into meiosis and is regulated by a combination of intrinsic factors and signals from Sertoli cells within the testis. Upon reaching puberty, SSCs resume proliferation and initiate spermatogenesis, a process characterized by continuous production of sperm throughout adult life. Key regulators of this pathway include RNA-binding proteins such as NANOS2, which suppress meiotic entry and maintain stem cell identity (Hofmann and McBeath, 2022; Maroto et al., 2025).

In contrast, female germ cells undergo a distinct developmental trajectory characterized by early entry into meiosis (Czukiewska and De Sousa Lopes, 2022). In the fetal ovary, PGCs initiate meiotic prophase I in response to retinoic acid (RA) signaling, which induces the

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expression of meiotic genes such as STRA8. This process leads to the formation of primary oocytes, which subsequently become arrested in prophase I until ovulation. Unlike the continuous production of sperm in males, the female germ cell pool is finite, with oocytes established during fetal development and gradually depleted over the reproductive lifespan (Sindik et al., 2024). The regulation of meiotic entry and oocyte maturation is therefore critical for female fertility. Retinoic acid signaling plays a central role in coordinating sex-specific differentiation by promoting meiosis in female germ cells while being actively degraded in the male gonadal environment (Maroto et al., 2025). In the fetal testis, enzymes such as CYP26B1 degrade RA, thereby preventing meiotic initiation and maintaining germ cells in an undifferentiated state. This differential regulation of RA availability illustrates how local somatic environments shape germ cell fate decisions (Hofmann and McBeath, 2022; Guo et al., 2021). Additionally, interactions between germ cells and somatic support cells (Sertoli cells in males and granulosa cells in females) provide essential signals that regulate proliferation, differentiation, and survival (Webster et al., 2021).

The establishment of sex-specific germ cell identity represents a critical developmental transition with profound implications for reproductive function. Disruptions in this process can lead to disorders of sex development, infertility, and germ cell tumors (Baroniet et al., 2019; Oosterhuis and Looijenga, 2019). Moreover, the dependence of germ cell differentiation on somatic niche interactions highlights the importance of coordinated development between germline and somatic compartments (Hofmann and McBeath, 2022). These insights underscore the clinical relevance of understanding sex-specific germ cell development in the context of reproductive health and disease (Fichtner et al., 2024; Kilic et al., 2024).

Implications for Human Fertility and Reproductive Disorders

The integrity of germ cell specification, migration, and differentiation is indispensable for human reproductive capacity (Saitou et al., 2025). Given the highly coordinated and multistep nature of germline development, perturbation at any stage from early specification to postnatal maturation can have profound consequences for fertility. Increasing evidence indicates that a significant proportion of reproductive disorders originate from defects in germ cell development, many of which remain clinically classified as idiopathic due to incomplete mechanistic understanding (Czukiewska and De Sousa Lopes, 2022). Elucidating the molecular and developmental basis of these defects is therefore essential for advancing diagnostic precision and therapeutic interventions in reproductive medicine (Cheung et al., 2024; Anton et al., 2025).

A key conceptual advance in this field is the recognition that germ cells undergo critical windows of vulnerability during embryogenesis, particularly during epigenetic reprogramming and migratory phases (Ramakrishna et al., 2021). Disruptions in these processes, whether genetic, epigenetic, or environmental, can lead to quantitative and qualitative abnormalities in the germ cell pool. These abnormalities may manifest as reduced germ cell numbers, impaired differentiation, or aberrant persistence of undifferentiated cells, each of which has direct implications for fertility outcomes (Barton et al., 2024). Furthermore, the dependence of germ cells on tightly regulated signaling pathways and somatic niche interactions brings into focus the systemic nature of reproductive disorders, linking germline defects to broader developmental dysregulation (Roelen and De Sousa Lopes, 2022; Saitou et al., and De 2025).

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Infertility and Germ Cell Defects

Infertility represents a major global health challenge, affecting a substantial proportion of reproductive-age individuals, with germ cell defects constituting a central underlying cause (Czukiewska and De Sousa Lopes, 2022). One of the most prominent manifestations of such defects is germ cell depletion, characterized by a reduced or absent population of functional germ cells within the gonads. In males, this may present as azoospermia or severe oligozoospermia, while in females, it is associated with diminished ovarian reserve or premature ovarian insufficiency (Cheung et al., 2024). These conditions often arise from disruptions in early germ cell development, including impaired specifications, defective migration, or failure of proliferation and survival during embryogenesis (Barton et al., 2024). The concept of idiopathic infertility, where no clear anatomical or endocrine cause is identified, has increasingly been linked to subtle molecular abnormalities in germ cell development. For example, defects in key regulatory pathways governing germ cell specification, such as BMP signaling or transcriptional regulators like PRDM1 and PRDM14, may result in insufficient germ cell formation (Hancock et al., 2021). Similarly, disruptions in post-specification processes, including epigenetic reprogramming and genome integrity maintenance, can compromise germ cell viability (Ramakrishna et al., 2021; Bloom et al., 2019). In such cases, germ cells may undergo apoptosis or fail to progress through critical developmental transitions, leading to a depleted germline pool.

In addition to quantitative defects, qualitative abnormalities in germ cells also contribute to infertility. Errors in epigenetic reprogramming, including incomplete DNA demethylation or improper imprint erasure, can lead to aberrant gene expression in gametes, affecting fertilization, embryonic development, and implantation (Anvar et al., 2021). These epigenetic defects are particularly relevant in the context of assisted reproductive technologies (ART), where external manipulation of gametes and embryos may influence epigenetic states (Sciorio and Hajj, 2022). Moreover, the activation of transposable elements due to impaired piRNA pathway function can result in genomic instability, further compromising germ cell function (Bloom et al., 2019; Anjum et al., 2025). Environmental and lifestyle factors have also emerged as significant modulators of germ cell integrity. Exposure to endocrine-disrupting chemicals, oxidative stress, and metabolic imbalances during critical developmental windows can adversely affect germ cell survival and differentiation (Dutta et al., 2024). These factors may exert their effects through alterations in signaling pathways, induction of DNA damage, or epigenetic modifications, thereby contributing to both male and female infertility. Importantly, the impact of such exposures may extend beyond the individual, influencing reproductive outcomes in subsequent generations through epigenetic inheritance (Xavier et al., 2019; Wu et al., 2024).

Developmental and Genetic Disorders

Beyond infertility, disruptions in germ cell development are closely associated with a spectrum of developmental and genetic disorders that affect gonadal formation and sexual differentiation (Oosterhuis and Looijenga, 2019). Among these, gonadal dysgenesis represents a major category characterized by incomplete or abnormal development of the gonads, often resulting in impaired germ cell survival and function. This condition can arise from mutations in genes involved in germ cell specification, migration, or interaction with the somatic gonadal environment (De Felici et al., 2021). In such cases, the failure of germ cells to properly colonize

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or integrate into the developing gonads leads to streak gonads or hypoplastic reproductive tissues, which are typically non-functional (Fichtner et al., 2024; Kilic et al., 2024).

Disorders of sex development (DSDs) further illustrate the intricate relationship between germ cell biology and the broader reproductive axis (Czukiewska and De Sousa Lopes, 2022). These conditions encompass a range of phenotypes resulting from discordance between chromosomal, gonadal, and phenotypic sex. Germ cells play a critical role in this process, as their presence and developmental state influence gonadal differentiation and endocrine function (Guo et al., 2021). For example, aberrant signaling between germ cells and somatic support cells, such as Sertoli or granulosa cells, can disrupt the establishment of sex-specific gonadal structures. Additionally, defects in pathways regulating meiotic entry, such as retinoic acid signaling, may lead to inappropriate timing of germ cell differentiation, contributing to DSD phenotypes (Hofmann and McBeath, 2022; Maroto et al., 2025).

Genetic mutations affecting key regulators of germ cell development have been implicated in both gonadal dysgenesis and DSDs (Müller et al., 2020). These include genes involved in transcriptional regulation, epigenetic remodeling, and RNA processing. Mutations in such genes can impair the ability of germ cells to maintain identity, respond to developmental cues, or undergo proper differentiation (Ramakrishna et al., 2021). In some cases, these defects also increase the risk of germ cell tumors, reflecting the persistence of undifferentiated, pluripotent-like cells within the gonads (Oosterhuis and Looijenga, 2019; Liu et al., 2021). The relationship between germ cells and their somatic environment is a critical determinant of normal gonadal development. Germ cells not only respond to signals from somatic cells but also actively influence the differentiation and function of the gonadal niche (Hofmann and McBeath, 2022). Disruption of this bidirectional communication can therefore have cascading effects on reproductive development, including structural and functional abnormalities in gonadal tissues (Guo et al., 2021; Fichtner et al., 2024).

Epigenetic Dysregulation and Transgenerational Effects

Extensive epigenetic reprogramming that characterizes germ cell development is essential for restoring developmental potency and ensuring faithful transmission of genetic information (Lee and Surani, 2024). However, this process also constitutes a critical window of vulnerability during which errors in epigenetic resetting can have profound consequences for fertility, embryonic development, and long-term health across generations. Epigenetic dysregulation in germ cells encompasses abnormalities in DNA methylation, imprinting control, chromatin organization, and non-coding RNA function (Ramakrishna et al., 2021; Roidor et al., 2024).

One of the most clinically significant consequences of epigenetic dysregulation is the occurrence of imprinting errors. Genomic imprinting involves parent-of-origin-specific gene expression mediated by differential DNA methylation at imprinting control regions (Monk et al., 2019). During germ cell development, these imprints are erased and subsequently re-established in a sex-specific manner, a process that is essential for normal embryogenesis. Failure to properly erase or re-establish imprinting marks can lead to aberrant monoallelic expression or biallelic activation of imprinted genes, resulting in developmental disorders such as Beckwith–Wiedemann syndrome, Prader–Willi syndrome, and Angelman syndrome (Anvar et al., 2021; Roidor et al., 2024). These conditions highlight the critical importance of precise

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epigenetic regulation in the germline and underscore the role of imprinting defects as a mechanistic link between germ cell biology and congenital disease.

In addition to intrinsic regulatory failures, assisted reproductive technologies (ART) have been associated with an increased risk of epigenetic abnormalities, particularly those involving imprinting (Sciorio and Hajj, 2022; Popoola et al., 2024). Procedures such as in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI), and embryo culture expose gametes and early embryos to non-physiological conditions that may interfere with epigenetic programming (Murase et al., 2024). Alterations in culture media composition, oxygen tension, and timing of developmental events can influence DNA methylation patterns and chromatin states, potentially leading to long-term consequences for offspring health (Zhang et al., 2023). Although the absolute risk of ART-associated imprinting disorders remains relatively low, accumulating evidence suggests subtle epigenetic differences in ART-conceived individuals, including changes in gene expression and metabolic profiles (Sciorio and Hajj, 2022; Zhang et al., 2023).

Beyond immediate developmental outcomes, epigenetic alterations in germ cells may have transgenerational effects, influencing phenotypes in subsequent generations. This phenomenon arises when epigenetic marks escape reprogramming and are transmitted through the germline, thereby affecting gene expression in descendants (Xavier et al., 2019). Environmental exposures, such as endocrine-disrupting chemicals, nutritional imbalances, and stress, have been shown to induce epigenetic changes in germ cells that persist across generations in animal models (Wu et al., 2024). These findings raise important questions about the long-term impact of environmental and lifestyle factors on reproductive health and disease susceptibility. The potential for transgenerational inheritance of epigenetic information draws attention to the need for a comprehensive understanding of germ cell epigenetics in both physiological and pathological contexts (Zheng et al., 2021; Moazamian et al., 2025).

Germ Cell Tumorigenesis

Germ cell tumorigenesis represents a significant pathological consequence of disrupted germ cell development, arising primarily from the failure of primordial germ cells to properly differentiate and commit to the germline lineage (Oosterhuis and Looijenga, 2019). Unlike most somatic tumors, germ cell tumors (GCTs) originate from cells that retain features of pluripotency, reflecting their developmental origin from PGCs or closely related progenitors. This unique origin underlies the distinctive biological and clinical characteristics of GCTs, including their ability to differentiate into multiple tissue types and their sensitivity to specific therapeutic interventions (Nicholls and Page, 2021). A central concept in germ cell tumor biology is that tumorigenesis often results from the aberrant persistence of undifferentiated germ cells. During normal development, PGCs undergo a transition from a pluripotent-like state to a committed germline identity, a process that involves the repression of pluripotency genes and activation of germ cell-specific pathways (Saitou et al., 2025). Failure of this transition due to genetic mutations, epigenetic dysregulation, or environmental influences can result in the retention of pluripotent characteristics, predisposing cells to neoplastic transformation. These aberrant cells may give rise to various types of GCTs, including seminomas, non-seminomatous tumors, and teratomas, depending on the extent and direction of differentiation (Müller et al., 2020; De Felici et al., 2021).

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Molecularly, GCTs are characterized by the expression of pluripotency-associated markers such as OCT4, NANOG, and SOX2, which are also expressed in early germ cells (Nicholls and Page, 2021). These markers serve not only as indicators of tumor origin but also as diagnostic and prognostic tools in clinical practice. Additionally, dysregulation of signaling pathways involved in germ cell development, including KIT/KITLG, BMP, and WNT pathways, has been implicated in the pathogenesis of GCTs (Fichtner et al., 2024). Mutations or altered expression of these pathways can disrupt normal germ cell survival and differentiation, contributing to tumor initiation and progression (Kilic et al., 2024; Müller et al., 2020). Epigenetic abnormalities also play a critical role in germ cell tumorigenesis. GCTs often exhibit global DNA hypomethylation, reflecting the epigenetic state of PGCs during early development (Müller et al., 2020). However, localized hypermethylation of tumor suppressor genes may also occur, contributing to oncogenesis. The epigenetic plasticity of germ cells, while essential for normal development, thus becomes a liability when regulatory mechanisms fail, enabling the activation of oncogenic programs (Liu et al., 2021; Lee and Surani, 2024). Furthermore, defects in the piRNA pathway and other genome defense mechanisms can lead to transposable element activation and genomic instability, further promoting tumor development (Bloom et al., 2019; Anjum et al., 2025).

From a clinical perspective, the developmental origin of GCTs provides valuable insights into their diagnosis and treatment (Oosterhuis and Looijenga, 2019). The presence of specific molecular markers enables early detection and classification of tumor subtypes, while the retained sensitivity of germ cell-derived tumors to DNA-damaging agents contributes to their generally favorable response to chemotherapy (Fichtner et al., 2024). However, challenges remain in understanding the precise mechanisms that trigger the transition from normal germ cell development to malignancy, particularly in relation to environmental and genetic risk factors (Kilic et al., 2024; Liu et al., 2021).

Environmental Influences and Emerging Technologies

The development of the germline occurs within a highly sensitive biological context in which intrinsic genetic programs are continuously modulated by extrinsic environmental factors (Saitou et al., 2025). Given the extensive epigenetic reprogramming and proliferative activity that characterize primordial germ cells (PGCs), these cells are particularly susceptible to environmental perturbations. Concurrently, advances in experimental technologies have transformed the study of germ cell biology, enabling mechanistic interrogation of human germline development with unprecedented resolution (Rodríguez-Polo and Moris, 2024; Yu et al., 2025).

Environmental and Lifestyle Modulators

Environmental and lifestyle factors exert profound effects on germ cell development, with implications that extend from individual fertility to transgenerational health outcomes (Xavier et al., 2019). Among these factors, endocrine-disrupting chemicals (EDCs) have emerged as major contributors to reproductive dysfunction. EDCs, including compounds such as bisphenol A (BPA), phthalates, and persistent organic pollutants, interfere with hormonal signaling pathways that are critical for germ cell specification, migration, and differentiation. By mimicking or antagonizing endogenous hormones, these chemicals disrupt key regulatory axes, including estrogen, androgen, and retinoic acid signaling, thereby altering germ cell fate decisions and developmental timing (Wu et al., 2024; Moazamian et al., 2025).

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At the molecular level, EDCs can perturb signaling pathways central to germ cell development, such as BMP, WNT, and NODAL/Activin pathways, leading to impaired germ cell induction or aberrant differentiation (Hancock et al., 2021). Additionally, these compounds are known to induce epigenetic modifications, including altered DNA methylation and histone modification patterns, which can compromise genomic imprinting and gene regulation in germ cells (Dutta et al., 2024). Given the critical role of epigenetic reprogramming during germline development, such disruptions may have lasting effects, including reduced fertility and increased susceptibility to reproductive disorders. Notably, the ability of certain EDC-induced epigenetic changes to persist across generations highlights their potential role in transgenerational inheritance of disease risk (Xavier et al., 2019; Wu et al., 2024).

Nutrition represents another key determinant of germ cell health, influencing both metabolic and epigenetic processes (Anvar et al., 2021). Adequate availability of nutrients involved in one-carbon metabolism, such as folate, methionine, and vitamin B12, is essential for maintaining proper DNA methylation patterns during germ cell development. Nutritional deficiencies or imbalances during critical developmental windows can lead to aberrant epigenetic programming, affecting germ cell survival and function (Monk et al., 2019). Conversely, excessive caloric intake and metabolic disorders, such as obesity and diabetes, have been associated with increased oxidative stress and inflammation, which can impair germ cell integrity and reduce reproductive capacity (Dutta et al., 2024; Cong et al., 2025).

Oxidative stress, arising from an imbalance between reactive oxygen species (ROS) production and antioxidant defenses, is a major mediator of environmental and metabolic effects on germ cells (Dutta et al., 2024). Elevated ROS levels can induce DNA damage, disrupt mitochondrial function, and trigger apoptosis in PGCs, particularly during periods of active proliferation and epigenetic remodeling. The germline is especially vulnerable to oxidative damage due to its role in preserving genomic integrity for future generations (Bloom et al., 2019). Mechanisms such as DNA repair pathways and antioxidant systems are therefore critical for mitigating oxidative stress, but their capacity may be overwhelmed under conditions of environmental or metabolic challenge (Wu et al., 2024; Moazamian et al., 2025).

The concept of early-life programming provides a unifying framework for understanding how environmental exposures during embryonic and fetal development influence long-term reproductive outcomes (Xavier et al., 2019). During these periods, germ cells undergo critical developmental transitions that are highly sensitive to external cues. Perturbation during this window can lead to permanent alterations in germ cell number, epigenetic state, and functional capacity, thereby affecting fertility in adulthood (Ramakrishna et al., 2021). Importantly, because germ cells contribute to the next generation, these effects may be transmitted to offspring, linking environmental exposures to multigenerational health outcomes (Zheng et al., 2021; Wu et al., 2024).

Experimental Models

Advances in experimental models have significantly enhanced our understanding of germ cell biology, providing platforms for dissecting the molecular mechanisms underlying germ cell specification and development (Hancock et al., 2021). Traditional in-vivo models, particularly the mouse, have been instrumental in elucidating the genetic and signaling pathways involved in germline formation. Mouse models have enabled detailed characterization of key regulatory factors, such as PRDM1, PRDM14, and BMP signaling components, through gene knockout

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and lineage-tracing studies (Morgani and Hadjantonakis, 2021). These models have also provided insights into the dynamics of germ cell migration, epigenetic reprogramming, and sex-specific differentiation (Barton et al., 2024; Saitou et al., 2025). Despite their contributions, in vivo models have inherent limitations, particularly with respect to their translational relevance to human biology. Species-specific differences in germ cell specification, such as the reliance on SOX17 in humans versus PRDM14 in mice, highlight the challenges of extrapolating findings across systems (Kojima et al., 2021; Tang et al., 2022). Additionally, ethical and technical constraints limit direct study of human embryonic germ cell development, necessitating the development of alternative experimental approaches.

In this context, in vitro models derived from human pluripotent stem cells (hPSCs) have emerged as powerful tools for studying human germline development (Yu et al., 2025). These systems enable the generation of PGC-like cells (PGCLCs) through the recapitulation of key signaling pathways, including BMP, WNT, and NODAL/Activin signaling, in a controlled environment. hPSC-derived PGCLCs exhibit molecular and epigenetic features similar to early human PGCs, including the expression of germline markers and initiation of epigenetic reprogramming (Tang et al., 2022). These models provide a valuable platform for investigating the mechanisms of germ cell specification, as well as for assessing the impact of genetic and environmental perturbations (Rodríguez-Polo and Moris, 2024; Saitou et al., 2025).

Beyond two-dimensional culture systems, the development of three-dimensional organoid models has further advanced the field by enabling the study of germ cell–somatic cell interactions within a more physiologically relevant context (Rodríguez-Polo and Moris, 2024). Gonadal organoids, which incorporate both germ cell-like and somatic cell components, allow for the investigation of niche-dependent processes such as germ cell differentiation and maturation. These models are particularly useful for studying sex-specific developmental pathways and the role of the microenvironment in regulating germ cell fate (Guo et al., 2021; Hofmann and McBeath, 2022).

Emerging technologies, including single-cell transcriptomics, epigenomics, and spatial profiling, are providing unprecedented insights into the heterogeneity and dynamic regulation of germ cell populations (Gu et al., 2024). These approaches enable the identification of transient cell states, regulatory networks, and lineage trajectories that were previously inaccessible. When combined with genome editing tools such as CRISPR/Cas9, these technologies facilitate functional interrogation of candidate genes and pathways, accelerating the discovery of mechanisms underlying germ cell development and disease (Garcia-Alonso et al., 2021; Yu et al., 2025).

Multi-Omics and Functional Genomics

The advent of multi-omics technologies has transformed germ cell biology from a predominantly descriptive discipline into a quantitatively driven, systems-level science (Gu et al., 2024). By integrating transcriptomic, epigenomic, proteomic, and spatial datasets, researchers can now reconstruct the dynamic regulatory landscapes that govern primordial germ cell (PGC) specification, migration, and differentiation with unprecedented resolution. These approaches are particularly powerful in the context of germ cell development, where transient cell states, rare populations, and rapid epigenetic transitions complicate traditional bulk analyses (Garcia-Alonso et al., 2021; Saitou et al., 2025).

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Single-cell transcriptomics have been instrumental in delineating the heterogeneity and developmental trajectories of germ cells (Guo et al., 2021). By profiling gene expression at the level of individual cells, this approach enables the identification of discrete cellular states along the continuum from pluripotent epiblast cells to specified PGCs and beyond. In both mouse and human systems, single-cell RNA sequencing (scRNA-seq) has revealed sequential activation of germline transcriptional programs, including the induction of key regulators such as PRDM1, TFAP2C, and species-specific determinants like SOX17 in humans (Kojima et al., 2021). Importantly, these datasets have uncovered intermediate states characterized by partial pluripotency and lineage priming, providing mechanistic insight into how germ cell fate is progressively established rather than abruptly determined (Tang et al., 2022; Yu et al., 2025).

Complementing transcriptomic analyses, single-cell epigenomic approaches such as ATAC-seq, DNA methylome profiling, and ChIP-seq have elucidated the regulatory architecture underlying germ cell development (Li et al., 2020). These techniques allow for the mapping of chromatin accessibility, transcription factor binding, and histone modification landscapes at high resolution. In PGCs, such analyses have revealed widespread chromatin remodeling events associated with epigenetic reprogramming, including the opening of germline-specific regulatory regions and the closure of somatic gene loci (Gruhn et al., 2023). The integration of transcriptomic and epigenomic data has thus provided a comprehensive view of how gene regulatory networks are orchestrated during germ cell specification (Lee and Surani, 2024; GU Et Al., 2024).

Functional genomics approaches have further enabled the direct interrogation of gene function within these regulatory networks (Yu et al., 2025). The CRISPR/Cas9 genome editing system has revolutionized the ability to manipulate specific genes and regulatory elements in both in vivo and in vitro models. By enabling targeted gene knockouts, knock-ins, and epigenetic modifications, CRISPR-based strategies have facilitated the identification of key regulators of germ cell development, including transcription factors, signaling pathway components, and non-coding RNAs (Garcia-Alonso et al., 2021). In human pluripotent stem cell-derived PGC-like cell (PGCLC) systems, CRISPR-mediated perturbations have been used to dissect the roles of species-specific factors such as SOX17, providing insights that are not readily accessible in traditional animal models (Kojima et al., 2021; Tang et al., 2022).

Lineage tracing technologies represent another critical component of functional genomics in germ cell research (Garcia-Alonso et al., 2021). These approaches, which often employ genetic barcoding or inducible reporter systems, enable the tracking of cell fate decisions over time, revealing the origins and developmental trajectories of germ cells within complex tissues. In combination with single-cell sequencing, lineage tracing allows for the reconstruction of developmental hierarchies and the identification of progenitor populations that give rise to the germline (Guo et al., 2021). This is particularly valuable in resolving questions related to germ cell competence, timing of specification, and the distinction between specification and determination (Saitou et al., 2025; Yu et al., 2025).

Translational Applications

The growing understanding of germ cell biology has opened new avenues for translational applications in reproductive medicine, particularly in the areas of fertility preservation, artificial gametogenesis, and the development of diagnostic and therapeutic tools (Saitou et al., 2025). These advances are especially relevant in the context of increasing infertility rates, the

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impact of environmental exposures on reproductive health, and the need for novel interventions to address germ cell-related disorders (Czukiewska and De Sousa Lopes, 2022; Cheung et al., 2024).

Fertility preservation strategies have become a critical component of clinical care for individuals at risk of losing reproductive function, such as cancer patients undergoing gonadotoxic therapies (Sciorio and Hajj, 2022). Current approaches include cryopreservation of sperm, oocytes, and ovarian or testicular tissue. However, these methods are limited by factors such as patient age, availability of mature gametes, and the risk of reintroducing malignant cells (Fichtner et al., 2024). Insights into germ cell development have facilitated the exploration of alternative strategies, including the in vitro derivation of germ cells from pluripotent stem cells. The generation of PGC-like cells (PGCLCs) from human pluripotent stem cells represents a significant step toward artificial gametogenesis, offering the potential to produce functional gametes for individuals lacking viable germ cells (Kojima et al., 2021; Yu et al., 2025).

Artificial gametogenesis, while still in its early stages, holds transformative potential for reproductive medicine (Saitou et al., 2025). By recapitulating the stages of germ cell development in vitro, this approach aims to generate fully functional sperm and oocytes capable of supporting fertilization and embryonic development. Experimental success in animal models has demonstrated the feasibility of this approach, with stem cell-derived gametes giving rise to viable offspring (Hancock et al., 2021). However, significant challenges remain in translating these findings to humans, including ensuring the fidelity of epigenetic reprogramming, preventing genetic abnormalities, and addressing ethical considerations associated with germline manipulation (Ramakrishna et al., 2021; Rodríguez-Polo and Moris, 2024).

The identification of biomarkers for germ cell competence and reproductive potential represents another important translational application (Garcia-Alonso et al., 2021). Molecular markers derived from transcriptomic and epigenomic studies, such as the expression of germline-specific genes or epigenetic signatures, have the potential to improve the diagnosis and prognosis of infertility. For example, biomarkers indicative of oocyte quality or spermatogonial stem cell function could guide clinical decision-making in assisted reproductive technologies (ART) (Cassuto et al., 2024). Additionally, the detection of aberrant epigenetic patterns in germ cells may provide early indicators of reproductive disorders or developmental risks in offspring (Cheung et al., 2024; Anton et al., 2025).

Therapeutic targeting of pathways involved in germ cell development also offers promising avenues for intervention (Hancock et al., 2021; Ofor et al., 2026). Modulation of signaling pathways such as BMP, WNT, and retinoic acid signaling could potentially enhance germ cell specification or differentiation in clinical settings. Similarly, targeting epigenetic regulators or RNA-based mechanisms may provide strategies for correcting defects in germ cell development (Ramakrishna et al., 2021; Lee and Surani, 2024). In the context of germ cell tumors, understanding the molecular pathways underlying tumorigenesis has already led to the development of targeted therapies and improved treatment outcomes (Fichtner et al., 2024; Kilic et al., 2024).

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CONCLUSION

Germ cell specification represents a foundational event in developmental biology, integrating signaling pathways, transcriptional regulation, epigenetic reprogramming, and post-transcriptional control into a coherent framework that establishes the germline. Across species, the convergence of diverse mechanisms ranging from preformation to epigenesis accentuates both the evolutionary adaptability and the conserved principles governing germ cell fate. Central to this process is the precise coordination of inductive signals such as BMP, WNT, and NODAL/Activin pathways with core transcriptional regulators, including PRDM1, PRDM14, and TFAP2C, which collectively repress somatic programs and initiate germline identity. This regulatory architecture is further reinforced by extensive epigenetic remodeling and post-transcriptional modulation, ensuring that primordial germ cells (PGCs) maintain genomic integrity while retaining developmental plasticity. The integration of these molecular mechanisms highlights the germline as a uniquely regulated system, poised at the intersection of pluripotency and lineage commitment.

Beyond its developmental significance, germ cell specification exerts a profound influence on lifelong reproductive health. The establishment of a functional germ cell pool during early embryogenesis determines the reproductive capacity of an individual, with implications that extend into adulthood and, potentially, across generations. Disruptions in germ cell development, whether arising from genetic mutations, epigenetic dysregulation, or environmental exposures, can lead to infertility, developmental abnormalities, and germ cell tumors. The sensitivity of germ cells to both intrinsic and extrinsic perturbations supports their role as critical mediators of reproductive health and disease. Moreover, the unique epigenetic reprogramming events that occur within germ cells position them as key conduits for transgenerational inheritance, linking early developmental processes to long-term phenotypic outcomes.

Despite significant advances, important knowledge gaps remain in our understanding of germ cell biology. One of the foremost challenges lies in elucidating the precise molecular determinants that govern the transition from germ cell specification to irreversible commitment, particularly in human systems where direct study is limited. While animal models have provided invaluable insights, species-specific differences in germ cell regulatory networks necessitate caution in extrapolating findings to human biology. Additionally, the mechanisms underlying germ cell competence, the integration of signaling gradients, and the temporal regulation of epigenetic reprogramming remain incompletely defined. The interplay between environmental exposures and germ cell epigenetics also represents a critical area of investigation, particularly in the context of increasing global infertility rates and emerging evidence of transgenerational effects.

Emerging technologies are poised to address many of these challenges, offering new avenues for both fundamental discovery and clinical translation. Advances in single-cell multi-omics, spatial transcriptomics, and genome editing are enabling high-resolution mapping of germ cell development and the functional interrogation of regulatory networks. In vitro systems, including human pluripotent stem cell-derived PGC-like cells and organoid models, provide scalable platforms for studying human germline development under controlled conditions. However, these systems must be further refined to accurately recapitulate in vivo processes, particularly with respect to epigenetic fidelity and long-term functionality.

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