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Histological Basis of Normal and Abnormal Embryonic Development: A Critical Analytical Review

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Abstract: Embryonic development is considered to be a highly intricate biological process that includes the differentiation of cells, morphogenesis of tissues, and formation of various organ systems at distinct temporal periods. Advances in stem cell-based embryo models, spatial transcriptomics, and three-dimensional organoids have significantly influenced the understanding of developmental processes in the context of histology. The present comprehensive review aims to provide an overview of the histology of normal embryonic development processes, including gametogenesis and organogenesis. In addition to that, it will provide a critical analysis of abnormal developmental processes, including teratogenesis, neural tube formation, and congenital anomalies in the context of histopathology. In accordance with recent advances in human embryo models, epigenetic reprogramming, and recent studies published during 2023–2025, this approach will contribute to the understanding of the structural basis of various physiological as well as abnormal embryonic development processes.

1. Introduction

The process of development from a single cell to a completely formed and differentiated organism is termed embryonic development. Embryology, which was once merely a descriptive and anatomical science, has evolved with the integration of molecular biology, genetics, and sophisticated imaging techniques. Today, global consortia and digitalized histology collections have emerged as important contributors to the documentation and conservation of developmental specimens, providing vital information on normal and abnormal developmental processes (Brand-Saberi, 2024). The science of embryonic development is on the cusp of a new chapter with the introduction of three-dimensional stem cell models and single-cell level temporo-spatial transcriptomics. These advances will significantly enhance our understanding of developmental processes and provide potent tools to study human abnormalities (Handford et al., 2024). In recent research in the field, models of mammalian embryos produced using stem cells have provided clues to developmental processes by enabling wider genetic and epigenetic variations compared to natural embryos (Dupont, 2024). Congenital abnormalities occur in 3% of all live births and are a major public health issue worldwide. Neural tube defects are the second most common congenital anomaly after heart defects and occur in about 1 in 1,000 births in different populations. Understanding the histology of normal and abnormal development processes is vital to unraveling their pathogenetic mechanisms and developing prevention strategies.

Literature Search Strategy

This review is prepared based on a narrative and critical analytical approach. To synthesize it, I undertook a general and non-systematic search of available literature through major databases like PubMed, Scopus, and Web of Science, starting from January 2000 and ending in December 2024. My search emphasized publications from 2020 to 2024, as they would contain more updated information. For this purpose, I employed various combinations of key words like embryonic developments, histology, gametogenesis, organogenesis, neural tube defects, teratogenesis, stem cell-based embryo models, spatial transcriptomics, and congenital malformations. However, my focus was on relevance to the histology of normal and abnormal embryogenesis, and preference was given to peer-reviewed research articles and review articles, especially those employing state-of-the-art techniques like single-cell transcriptomics and organoids. Relevant information was also obtained from the reference sections of key publications.

2. Histological Features of Gametogenesis

2.1 Primordial Germ Cell Development

Gametogenesis prepares for embryonic life by forming specialized gametes that fuse during fertilization. Gametogenesis commences with primordial germ cells (PGCs), which derive from the epiblast layer. PGCs then traverse the basement membrane and inhabit the endodermal layer of the embryonic hindgut. PGC migration is marked by significant genomic alterations, where silenced X chromosomes become reactivated, DNA methylation is decreased, and post-translational modifications of histone proteins change (Aizawa et al., 2025). PGCs reach the genital ridges by embryonic day 9.5. These structures derive from the coelomic epithelium of the intermediate mesoderm and appear at a mesenchymal location. PGCs transform into gametogenesis competent cells (GCCs), a process essential for gametogenesis and occurring between embryonic days 10.5 and 11.5. Dazl signaling is responsible for GCC formation and guides these cells towards either female or male gametogenesis based on gonadal environment.

2.2 Epigenetic Reprogramming in Gametogenesis

In 2024, a groundbreaking study succeeded in re-creating the process of epigenetic reprogramming within human primordial germ cells cultured in vitro. Murase et al. have demonstrated that the generation of human gametes from human pluripotent stem cells in vitro parallels the essential reprogramming event: the resetting or removal of the parental DNA methylation pattern. The resetting of the epigenetic profile is vital for the differentiation of the germ cells and entails a comprehensive reconfiguration of the epigenetic profile, which includes both DNA methylation and histone modifications. During gametogenesis, the gametes acquire specific epigenetic marks; these marks are usually erased at an early stage of development and replaced with the epigenetic marks of the embryo. At the tissue level, the elucidation of the epigenetic processes significantly improves our understanding of normal gametogenesis and the potential mechanisms for developmental abnormalities.

3. Histological Characteristics of Early Embryonic Development

3.1 Preimplantation Development

After fertilization occurs, the zygote starts to divide and form smaller and smaller cells known as blastomeres. The morula stage is made up of 16-32 cells and eventually develops into the blastocyst stage, which is the first sign of differentiation of tissues in the embryo. The blastocyst stage is divided into three layers of cells: trophectoderm, which will form the placenta; epiblast, which will form the embryo proper; and primitive endoderm, also known as hypoblast, which will form extraembryonic tissues. Recent developments in stem cell-based embryo models have helped researchers gain insight into the early stages of development. Blastoids, which are stem cell-based structures that resemble natural blastocysts, have been produced by combining embryonic stem cells that express an inducible GATA4 with trophoblast stem cells. These blastoids have shown potential in developing structures similar to natural blastocysts and have even shown 80% efficiency in developing blastocyst-like structures with a cavity in mouse systems. These structures are similar to natural blastocysts found in mature mouse embryos at the histological and transcript levels (Handford et al., 2024). It is crucial to note that this is only applicable to mouse blastoids and not human blastoids.

3.2 Implantation and Gastrulation

Implantation represents a critical step in the process in which the blastocyst attaches itself to the uterine walls. In the process, the trophoblast differentiates into cytotrophoblast and syncytiotrophoblast. Meanwhile, the inner cell mass reorganizes itself to form a bilaminar disc consisting of layers of epiblast and hypoblast. Gastrulation begins in the third week of human development. At this stage, the formation of the three primary layers of the embryo begins. The layers include ectoderm, mesoderm, and endoderm. In the process, there is considerable cell movement. The formation of the three primary layers of the human embryo results in the formation of the ectoderm, mesoderm, and endoderm. In recent times, new human embryo-like models have been proposed to mimic the process of peri-implantation development. In the process, there is the formation of a bilaminar-disc-like structure that resembles the natural human embryos. In essence, the formation of the bilaminar disc occurs in tandem with the formation of the amniotic cavity as well as the anterior hypoblast-like cells.

4. Histological Basis of Organogenesis

4.1 Neural Tube Formation

The development of the neural tube is a critical process in organogenesis, which establishes the primitive central nervous system. This process commences with the thickening of the dorsal ectoderm to form the neural plate, which folds and finally closes to form the neural tube. However, the process may not be the same in all species, with the human neural tube forming at least four zipper-like closure regions, though the process may be different in other mammals.

Recently, neural and non-neural ectoderm have been shown to be both necessary and sufficient to initiate neural tube folding morphogenesis, which is regulated by two major processes: apical contraction by the neural ectoderm and basal adhesion by the non-neural ectoderm, which is characterized by the production of the extracellular matrix (Karzbrun et al., 2021). Further, the process has been shown to occur using more advanced stem cell models, which have shown the folding of the neural tube using human stem cells in culture. For example, using a micropatterned human pluripotent stem cell culture system, the neural ectoderm has been shown to fold with 90% fidelity, forming neural tubes up to a millimeter in length, which are covered with non-neural ectoderm (Karzbrun et al., 2021). This refers to the neural tube forming with the stated percentage, but the process may not be the same in all other culture systems or developmental processes.

4.2 Skeletal Development

The development of bone and joints in the early developmental stage depends on the specialization of progenitor cells in the developing skeleton. The recent multi-omic atlas study on the development of human embryonic joints and skull development between 5 to 11 weeks after conception, using around 336,000 nucleus droplets and spatial transcriptomics, revealed the developmental paths of region-specific osteoprogenitors in the developing limbs and cranium, along with the regulatory networks that control intramembranous and endochondral ossification (Zhang et al., 2024). The process of suturogenesis has been observed to occur by the differentiation of cranial mesenchyme into suture mesenchyme, which develops along the predicted trajectory to the bone-forming lineage. HHIP is the osteogenic coronal suture mesenchyme that is enriched in diverse progeny populations within the developing ossifying cranial bone in the human fetus, thus depicting the importance of precise histological organization in the development of the skeleton.

5. Histopathology of Abnormal Embryonic Development

5.1 Teratogenesis and Environmental Factors

Teratogenesis is the abnormal development of an embryo, which occurs as a result of interruptions in the regular development process. Environmental teratogens can cause teratogenesis, which leads to abnormal development in fetuses, even when they have regular chromosomes and genes. However, these fetuses have abnormal structures and functions during development. The fundamental mechanism of teratogenesis is the abnormal regulation of genes, and the role of epigenetics has been very instrumental in understanding teratogenic processes (Walker and Burggren, 2020). The susceptibility of the fetus to teratogens is not constant but varies at different times. During development, teratogens can have the most severe effects on the formation of organs during the embryonic period, which occurs after implantation, approximately on day 14, and ends 60 days after conception. However, teratogens can cause loss during gametogenesis, fertilization, cleavage, and blastulation. Teratogens can have severe effects on the development of fetuses during the fetal period, affecting the differentiation, growth, and functioning of the organs. Oxygen concentration and the production of reactive oxygen species in developing organs are significant factors in teratogenic processes, which can be controlled pharmacologically. Past teratogenic effects of thalidomide and misoprostol have emphasized the importance of timing and dosage of teratogens. During diabetic pregnancy, hyperglycemia causes myoinositol uptake, which is essential during gastrulation and neurulation, affecting embryonic development. This leads to growth retardation and neural tube defects through interference with the phosphoinositide signaling pathway and the arachidonic acid–prostaglandin signaling pathways.

5.2 Neural Tube Defects

NTDs are the second most common birth defect worldwide. Incidence varies greatly from 0.7 per 10,000 births in central France to 11.7 per 10,000 births in South America. These serious congenital anomalies are the result of the neural tube not closing during early development. Neural tube defects appear in several forms, depending on where along the head-to-tail axis of the

embryo the neural tube closes improperly. These include anencephaly, craniorachischisis, and spina bifida. Anencephaly occurs when the rostral end of the neural tube does not close, resulting in the absence of the brain. This is fatal. Myelomeningocele, the most common open neural tube defect, occurs when there is an open spine with dysplastic spinal cord tissue, resulting in neurological deficits below the defect. Affected individuals have reduced movement, bowel/bladder difficulties, and require surgery to alleviate hydrocephalus. Recent research on neural tube organoids has provided new avenues of research into the timing of development and neural tube defects. Organoids mimic the neural tube defect process. These studies have shown that developmental timing, or allochrony, is preserved in these organoid systems (Rabeling et al., 2024). Understanding developmental timing in a species-specific way allows us to translate animal studies into human development.

5.3 Genetic and Multifactorial Etiologies

The occurrence of neural tube defects among people demonstrates the occurrence of disorders as a combination of genes and the environment. Even though more than 200 genes' mutations contribute to NTDs among mice, the occurrence of NTDs among people happens as a combination of genes and the environment. The combination of the mother and the fetus's genes makes a person more susceptible to teratogenic influences. The major cellular processes involved in the closure of the neural tube include the organization of the cytoskeleton, the cell cycle, and the control of cell death. The occurrence of mutations in these areas happens commonly among mice with NTDs. The occurrence of developmental disturbances causes abnormal differentiation, as evident from the fact that different NTDs have similar malformation patterns and from the fact that more than one embryonic structure can be considered an integrated developmental unit.

Table 1: Histological Comparison of Normal and Abnormal Embryonic Development

Developmental Stage	Normal Histological Features	Abnormal Histological Features	Clinical Correlation
Gametogenesis	Proper PGC migration, complete epigenetic reprogramming, normal gamete formation	Failed PGC migration, incomplete epigenetic reprogramming, abnormal gamete structure	Infertility, increased risk of chromosomal abnormalities
Fertilization & Cleavage	Regular cleavage divisions, normal blastomere morphology, timely morula formation	Asymmetric division, fragmentation, developmental arrest	Early pregnancy loss, failed implantation
Blastocyst Formation	Distinct trophectoderm, epiblast, and hypoblast lineages; normal cavitation	Poor lineage segregation, abnormal cavitation, reduced cell number	Implantation failure, placental insufficiency
Gastrulation	Proper primitive streak formation, coordinated cell ingression, three germ layer organization	Defective streak formation, aberrant cell migration, incomplete germ layer specification	Embryonic lethality, major structural anomalies
Neurulation	Neural plate thickening, coordinated folding, complete tube closure with patent lumen	Failed closure at various levels, persistent neuropore, dysplastic neural tissue	Neural tube defects (anencephaly, spina bifida)
Organogenesis	Appropriate cell differentiation, correct tissue architecture, proper organ patterning	Disrupted tissue organization, failed differentiation, structural hypoplasia or hyperplasia	Congenital heart defects, skeletal dysplasias, organ malformations
Fetal Period	Continued growth and	Growth restriction,	Variable clinical

	differentiation, functional maturation	delayed maturation, functional impairment	outcomes based on affected systems

6. Contemporary Approaches to Studying Embryonic Histology

6.1 Stem Cell-Based Embryo Models

The development of stem cell-based embryo models has signaled a dramatic shift in the study of embryology, enabling the study of development processes by introducing various tests, especially on genetics and epigenetics, which can be done more easily than in natural embryos. Recently, various models, such as blastoids, gastruloids, and extended embryo models, have been created to move through different phases of development. The ETiX-embryos model combines embryonic stem cells with other cells that are not part of the embryo. These exhibit a natural ability to self-organize and establish the anterior-posterior axis, reaching the stage of early organogenesis by the end of the 8.5th day in the development process of the mouse embryo (Amadei et al., 2022). These artificial embryos simulate the process of development by mixing different types of cells within the embryo, providing instructive cues, and using various artificial means such as transgenes and morphogens to drive development. This has allowed scientists to study the rules that allow the embryo to self-organize its development process.

6.2 Spatial Transcriptomics and Single-Cell Analysis

The single-cell tempo-spatial transcriptomics approach has gained traction in the study of embryonic development processes. Using programs like the Human Cell Atlas Project and other initiatives, researchers use spatial transcriptomics to study the different aspects of cells, epigenetic activities, and the factors that control them in the process of development. The latest imaging technologies and computer analysis have enabled researchers to achieve a complete picture of developmental processes. For instance, researchers have used a combination of transcription and epigenetic information to understand the different aspects of region-specific osteoprogenitor cells in the process of early skeleton development and the factors that control them. These integrative studies have helped researchers understand the molecular basis of how tissues are histologically arranged in the process of development.

6.3 Digitized Histological Collections

The increasing recognition of the importance of historical histological collections has led to worldwide initiatives to digitize these valuable collections. Human embryology collections, which have been running over the years, are now connected online, providing open access to important human development specimens. The most notable example is the Hinrichsen Embryology collection, which provides online access to historical human embryonic histological slides and MRI images from whole fetuses (Maricic et al., 2019). This has allowed the digitization of the material, which can be used for comparative study and education, preserving the original specimens.

7. Clinical Implications and Prevention Strategies

7.1 Diagnostic Approaches

In prenatal screening for congenital abnormalities, there are different approaches that are used, including blood tests and detailed ultrasound imaging of the fetus. In blood tests, alpha-fetoprotein levels are checked in the pregnant woman's blood to detect abnormalities in the development of the central nervous system in the fetus. Today, with the use of ultrasound imaging, abnormalities in the development of the fetus can be detected and the necessary steps can be taken to manage them. In the first and second trimesters, a systematic approach to ultrasound imaging is used to detect abnormalities in the development of the fetus. Once abnormalities in the development of the fetus are detected, the pregnant woman is given information on what to expect and what options are available to her in case of abnormalities in the development of the fetus, as in the case of

anencephaly. Understanding the histology of abnormalities in the development of the fetus helps in prognosis and counseling.

7.2 Preventive Strategies

Supplementation with folate before and during early pregnancy can also reduce the risk of neural tube defects, as confirmed in various studies, such as the study by Greene et al. (2017). Even though more research is needed to establish the mechanism by which folic acid protects against NTDs, it is undeniable that folic acid does not protect against all defects. This has led to more research and interest in other preventive strategies. The prevention of micronutrient deficiencies, such as folate, iodine, and vitamin A, is a major preventive measure against birth defects. Avoiding teratogens during critical periods of development is another preventive measure against birth defects. Educating pregnant women about the safe use of medications, avoidance of teratogens, and maintaining good metabolic control in conditions such as diabetes mellitus is also a preventive measure. Maintaining blood glucose at optimal levels in diabetic patients before and during pregnancy can help in the prevention of diabetic embryopathy. Awareness about the surroundings at work and at home, which may contain teratogens, is also a preventive measure.

8. Future Directions and Emerging Technologies

The field of embryology stands at the threshold of significant breakthroughs driven by converging technologies. In vitro gametogenesis holds promise for transforming infertility treatment through generation of gametes from patient-derived pluripotent stem cells. Recent advances in reconstituting epigenetic reprogramming in human germline cells in vitro represent important steps toward this goal (Murase et al., 2024).

Organoid innovations continue to advance, with neural tube organoids, cardiac organoids, and other systems providing increasingly accurate models of development and disease. These platforms facilitate study of human-specific developmental mechanisms that cannot readily be investigated in animal models. Integration of advanced organoid technologies with sophisticated imaging, genetic manipulation, and computational modeling holds potential for expanding understanding of morphogenetic pathways.

Several specific research priorities emerge from current knowledge:

- **Standardization of organoid models**: Establishing validated protocols to ensure reproducibility of findings such as the reported 80-90% efficiency and fidelity rates in different model systems
- **Interspecies comparative studies**: Systematically comparing human and animal developmental timing to improve translational relevance
- **Integration of multi-omics data**: Combining transcriptomic, epigenetic, and proteomic information with histological analysis to create comprehensive developmental atlases
- **Mechanistic studies of gene-environment interactions**: Elucidating how specific genetic variants modulate susceptibility to environmental teratogens

Ethical, legal, and social considerations in embryological research require continued attention. Balancing the potential benefits of embryonic research for disease treatment against moral considerations requires inclusive dialogue that respects diverse perspectives while maintaining human dignity. The varying legal frameworks across different countries create a fragmented regulatory landscape for embryonic development research; some jurisdictions permit comprehensive investigation while others impose substantial restrictions. International collaboration and continued dialogue are necessary to advance knowledge while maintaining appropriate ethical guidance.

The transition from inanimate matter to life represents one of biology's fundamental questions, exemplifying the profound connections between scientific inquiry into developmental origins and

deep philosophical questions about life itself (Gómez-Márquez, 2023). Future progress in embryonic sciences should continue to promote healthy human development while maintaining ethical boundaries as technologies evolve.

9. Conclusion

The histological perspective on the development process focuses on the role that cells and tissues play in the transition from a single cell to a fully formed organism. The normal process of development requires that the process proceed undisturbed through the gametogenesis, early patterning, and organogenesis phases, each with its own unique tissue characteristics that must be carefully regulated. Understanding the normal process is the key to understanding the development process that leads to disease. Abnormalities in the development process can be the result of a combination of genetic mutations, environmental teratogens, and their interactions. The neural tube defects, which occur because of disturbances in the basic shape change process, are a good example of how the development process can be disrupted, leading to serious congenital deformities with clinical consequences. A comparison between the normal histology and the abnormal histology, as represented in Table 1, reveals that the developmental process disruptions manifest themselves in unique tissue abnormalities that are associated with unique clinical outcomes. The advances in stem cells, spatial transcriptomics, and organoids have dramatically altered the way we approach the study of the development process with unprecedented accuracy. The recent advances in the study of the development process, which integrate the molecular, cellular, and tissue-wide approaches, are providing new insights into the basic structure that underlies the development process. When we read that the blastoid formation efficiency is 80% or that the neural tube folding process has a 90% fidelity, we must keep in mind that this is the result of the optimized process in the laboratory, which must be verified using different approaches before we consider this to be the truth. Such a histological lens has immediate clinical relevance. For instance, it can be used to interpret tissue-level signs of developmental disruption. In this regard, prenatal imaging will be enhanced. In addition, it will be instrumental in knowing when to make certain interventions. For example, nutrition will be optimized, as will the prevention of teratogens. Even with the use of the organoid platforms that have begun to emerge as a means to assess therapies as well as model genetic risks that are patient-specific, there is the integration of genetic and epigenetic markers to create a foundation for personalized prevention and management of congenital anomalies.

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