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Exploring Common and Unique Developmental Mechanisms in Vertebrate Organogenesis

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ABSTRACT: Vertebrate embryogenesis is guided by a conserved molecular toolkit, including Wnt, BMP, Shh, and FGF signaling, which regulates gastrulation, neurulation, and organogenesis. While these processes are deeply conserved, species-specific adaptations reveal evolutionary flexibility and biomedical relevance. This review aimed to compare developmental trajectories in zebrafish (*Danio rerio*), frog (*Xenopus laevis*), chick (*Gallus gallus*), mouse (*Mus musculus*), and human (*Homo sapiens*) to identify common mechanisms and unique innovations. A systematic comparative literature review was conducted using PubMed, Scopus, and Web of Science covering the years 2000 to 2025. Studies were included if they reported molecular or morphological evidence of vertebrate embryonic development, whereas invertebrate studies and non–peer-reviewed sources were excluded. Extracted data focused on transcription factors (Hox, Pax, Sox), signaling pathways (Shh, BMP, FGF, Wnt), and key processes such as heart, limb, neural, and gut development. Findings show that all species undergo a conserved sequence of germ layer formation, neural tube closure, somitogenesis, and organogenesis, although their timing and morphogenetic strategies differ. Zebrafish complete gastrulation within five to ten hours after fertilization, whereas humans begin the process around fourteen to sixteen, underscoring divergent developmental tempos. Conserved regulators such as Nodal and Brachyury (germ layers), Pax6 and Shh (neural tube), and Nkx2.5 and GATA4 (heart) function consistently across taxa. Unique adaptations include limb regeneration in *Xenopus* tadpoles, extraembryonic yolk sac structures in chicks, placental development in mice, and prolonged neocortical expansion in humans. In conclusion, vertebrate development reflects a balance of conserved frameworks and evolutionary innovations. Comparative insights from model organisms not only illuminate developmental evolution but also advance biomedical understanding of congenital disorders and human-specific traits.

KEYWORDS: Vertebrate organogenesis; gastrulation; neurulation; developmental biology; model organisms; gene regulation; comparative embryology.

1. Introduction

Vertebrate organogenesis represents one of the most remarkable achievements of developmental biology, as it transforms a seemingly uniform group of embryonic cells into the

highly specialized organs required for survival and adaptation. Since the pioneering embryological observations of Karl Ernst von Baer in the nineteenth century, through Hans Spemann's organizer experiments in amphibians, to contemporary advances in molecular genetics, organogenesis has been recognized as a central process for understanding both evolution and human health [1–3]. This field remains significant because it not only explains how vertebrate form and function arise but also provides a framework for interpreting congenital malformations, guiding regenerative medicine, and informing evolutionary theory. Although numerous studies have established that vertebrate organs arise through broadly conserved genetic programs, including the Wnt, Hedgehog, FGF, and Notch signaling pathways [4–6], there is increasing recognition that species-specific modifications shape organ form and physiology. For instance, variations in heart chamber patterning, limb morphogenesis, and neural crest derivatives highlight how conserved developmental toolkits can be co-opted and modified to generate diversity [7–9]. Previous reviews have primarily emphasized either the conserved molecular mechanisms of organogenesis across model organisms such as zebrafish, mouse, and chick, or the evolutionary divergence of organ forms in specialized taxa. However, few have systematically integrated these two perspectives, linking conserved molecular pathways with species-specific innovations to provide a more comprehensive understanding of vertebrate organogenesis.

Bridging this gap is critical because it allows developmental biology to be appreciated not only as a catalog of shared genetic programs but also as a dynamic evolutionary process that generates functional diversity. Moreover, such integrative perspectives carry biomedical implications. Many congenital disorders arise from disruptions in conserved pathways, while species-specific insights can inspire translational advances in organ repair, bioengineering, and regenerative therapies [10–12]. In this review, the researcher critically synthesizes classical and contemporary findings on vertebrate organogenesis, with particular emphasis on identifying both shared developmental mechanisms and unique species-specific innovations. By tracing the interplay between evolutionary conservation and divergence, this work aims to provide a framework that links basic developmental biology with evolutionary perspectives and biomedical applications.

2. Materials and Methods

This study employed a systematic comparative literature review to examine conserved and species-specific developmental mechanisms in vertebrate organogenesis. The methodology was designed to identify, screen, and synthesize published findings rather than generate new experimental data.

2.1. Literature search strategy.

A structured search was conducted across three major scientific databases: PubMed, Scopus, and Web of Science. The search covered articles published between 2000 and 2025 to capture both foundational and recent research. Keywords and Boolean operators included "vertebrate organogenesis," "comparative embryology," "developmental pathways," "Hox genes," "Pax genes," "Sonic Hedgehog," "BMP signaling," "FGF signaling," and "Wnt signaling." Search results were screened in three stages: (1) title review, (2) abstract review, and (3) full-text assessment.

2.2. Inclusion and exclusion criteria.

The review included studies that reported either primary data or comprehensive reviews on vertebrate embryonic development. Eligible works were those that analyzed gene expression, signaling pathways, or organ-level morphogenesis, and specifically examined at least one of the selected model organisms. In addition, only studies that provided clear developmental staging together with molecular or morphological evidence were considered. Studies were excluded if they focused exclusively on invertebrate models, lacked sufficient detail on developmental mechanisms, or were published in formats such as commentaries, editorials, or other non–peer-reviewed sources.

2.3. Species selection.

The review focused on five widely recognized vertebrate models: zebrafish (*Danio rerio*), frog (*Xenopus laevis*), chick (*Gallus gallus*), mouse (*Mus musculus*), and human (*Homo sapiens*). These species were selected according to three criteria: (1) the availability of comprehensive genetic and embryological datasets, (2) their established use as standard models in developmental biology, and (3) their translational relevance for understanding both evolutionary processes and human health.

2.4. Data extraction and synthesis.

Relevant information was extracted on gene families (Hox, Pax, Sox), signaling pathways (Shh, BMP, FGF, Wnt), and developmental processes such as heart morphogenesis, neural crest formation, and limb development. Data were synthesized using narrative comparison and thematic grouping to highlight both conserved mechanisms and species-specific adaptations. Developmental staging timelines reported in the literature were used for side-by-side evaluation across species, enabling both visual and temporal comparisons.

2.5. Data Presentation.

To enhance clarity, a summary table (Table 1) was created to present the main sources, the species compared, and the developmental processes analyzed. Figures were also designed to illustrate developmental timelines of organogenesis, emphasizing areas of conservation and divergence.

2.6. Limitations.

This review acknowledges several limitations. First, potential bias arises from the unequal availability of literature, since species such as humans and mice are more extensively studied than others. Second, differences in experimental methods, staging criteria, and molecular tools across studies may complicate direct comparisons of developmental processes. Third, the synthesis may not fully reflect emerging insights, as unpublished data and very recent discoveries are not yet represented in the available literature.

Table 1. Summary of vertebrate species reviewed, their strengths as model organisms, and key developmental processes analyzed.

Species	Strengths as Model Organism	Key Developmental Processes Analyzed
Zebrafish (*Danio rerio*)	Transparent embryos, rapid development, high genetic tractability, suitability for live imaging	Heart chamber morphogenesis, craniofacial development, neural crest migration, vascular patterning
Frog (*Xenopus laevis*)	Large, manipulable embryos; classical embryology model; conserved vertebrate body plan	Germ layer induction, neural tube formation, organ rudiment specification, left–right asymmetry
Chick (*Gallus gallus*)	Accessible in ovo development, ease of microsurgery, long history in embryological studies	Limb development, somite segmentation, cardiovascular development, neural crest differentiation
Mouse (*Mus musculus*)	Mammalian model with extensive genetic tools, knockout/knock-in technology, disease modeling	Organ primordia specification, gene regulatory networks, placental development, congenital malformation studies
Human (*Homo sapiens*)	Direct clinical relevance, availability of organoid and stem cell models, genetic/clinical data	Comparative organogenesis, congenital disorder etiology, stem-cell-derived organoid development, regenerative potential

3. Results and Discussion

3.1.Developmental stages of vertebrates.

In zebrafish (*Danio rerio*), as illustrated in Table 2 and Figure 1, embryogenesis proceeds with remarkable speed due to external fertilization and the optical transparency of embryos, making them particularly well suited for live in vivo imaging and molecular dissection of early developmental events [13]. Because fertilization and subsequent stages occur externally, researchers can readily observe, manipulate, and track developmental progression from the single-cell zygote through complex organ formation [14].

Table 2. Development of zebrafish.

Item	Stage Description	Process Details
A	Gastrulation	Occurs around 5 to 10 hours post-fertilization (hpf); characterized by epiboly, involution, and convergence-extension movements, leading to the formation of the three germ layers: ectoderm, mesoderm, and endoderm [15].
B	Neurulation	Begins shortly after gastrulation (~10–12 hpf); the neural plate thickens and folds to form the neural keel, which later hollows out into the neural tube; somites begin to form alongside the notochord [18]
C	Organogenesis	Initiates around 24 hpf; major organs such as the heart, brain, eyes, and somites become morphologically distinct and functional systems start to develop rapidly due to the transparent nature of the embryo [24]

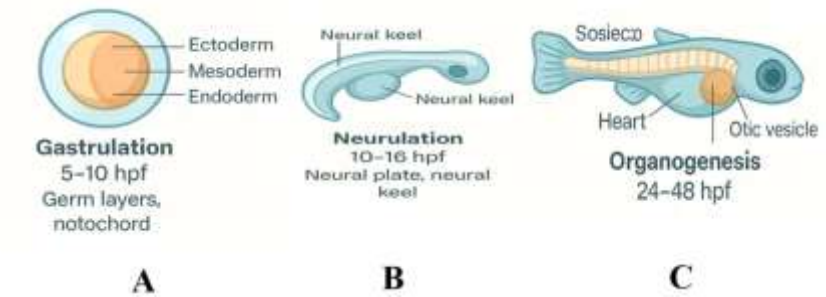

Figure 1. Development of Zebrafish showing gastrulation (a); neurulation (b); organogenesis (c).

Gastrulation in zebrafish begins between five- and ten-hours post-fertilization (hpf) and is characterized by epiboly, involution, and convergent extension, which collectively establish

the ectoderm, mesoderm, and endoderm [15]. This process also generates the notochord, an essential axial structure that regulates neuronal patterning and organ positioning through morphogen release, particularly Sonic Hedgehog (Shh) [16]. By 10 to 16 hpf, neurulation begins as the neural plate folds into the neural keel and subsequently into the neural tube, the precursor of the central nervous system. At the same time, somitogenesis commences along the embryonic midline, producing somites that prefigure the axial skeleton, skeletal muscles, and dermis, under the regulation of Wnt, FGF, and Notch gradients [17]. By 24 to 48 hpf, zebrafish embryos enter organogenesis: brain vesicles, a beating heart, optic cup and lens, otic vesicles, and somite-derived musculature are all discernible and functional. By 48 hpf, circulation, spontaneous motility, and basic sensory functions are established, underscoring the accelerated pace of zebrafish development [18]. With approximately 70% genetic homology to humans and compatibility with modern tools such as CRISPR-Cas9, morpholino knockdowns, and high-resolution live-cell imaging, zebrafish have become indispensable for studying gene regulation, embryonic patterning, congenital disorders, and regeneration [19].

Other vertebrate models contribute complementary insights. Frogs (*Xenopus laevis*) provide large, externally developing embryos that have historically been central for uncovering principles of germ layer induction and gastrulation [20]. Importantly, frogs exhibit robust regenerative capabilities in tail and limb tissues, making them uniquely valuable for investigating regenerative biology and its biomedical implications for tissue repair and wound healing [21]. Chicks (*Gallus gallus*) serve as classic in ovo models, valued for their accessibility to microsurgical manipulations and direct visualization of developmental processes such as limb bud outgrowth and neural crest migration [22]. In contrast, mice (*Mus musculus*), as mammalian models, offer unparalleled insights into placental development, maternal and fetal interactions, and mammalian-specific congenital disease modeling [23]. Finally, humans (*Homo sapiens*), although ethically and technically constrained for direct embryological studies, are increasingly represented through pluripotent stem cell–derived organoids, which replicate key aspects of organogenesis and allow modeling of congenital malformations and pharmacological responses in vitro with strong translational relevance [24].

The comparative richness of these models highlights the value of visual syntheses. We propose (1) a comparative developmental timeline depicting embryonic milestones across species; (2) gene expression pattern charts summarizing spatial and temporal activity of major regulatory genes such as Hox, Pax, Sox, and Shh; and (3) schematic diagrams illustrating organogenesis, emphasizing both conserved frameworks and divergent traits. These visual elements would enable clearer side-by-side comparisons and enhance accessibility of complex developmental data.

It is also important to emphasize that the major signaling pathways, Wnt, BMP, Shh, and FGF, rarely act independently. Instead, organogenesis is orchestrated through extensive pathway crosstalk. For example, Wnt and BMP gradients jointly regulate dorsal and ventral axis formation [25], while Shh and FGF interact to coordinate limb bud morphogenesis and neural tube specification [26]. Similarly, Notch integrates with Wnt and FGF during somitogenesis to ensure proper segmentation timing and boundary formation [27]. This dynamic interplay demonstrates that vertebrate development is not a simple sequence of linear signaling cascades but rather a highly interconnected network in which species-specific modulations of shared pathways generate evolutionary diversity while maintaining conserved developmental logic.

Similarly, in frogs (*Xenopus laevis*), as shown in Figure 2 and Table 3, the core developmental stages—gastrulation, neurulation, and organogenesis—occur in a conserved sequence comparable to that of zebrafish, yet they differ substantially in timing, morphological events, and embryonic organization. Whereas zebrafish undergo rapid external development with transparent embryos that complete gastrulation within five to six hours post-fertilization (hpf), *Xenopus* embryos develop at a slower pace, with gastrulation beginning around five to ten hpf and progressing through distinct morphological features such as the formation of the dorsal lip of the blastopore. These interspecies differences highlight a central theme of vertebrate development: while the mechanistic framework of germ layer specification and axis formation is conserved, the embryological strategies and temporal dynamics are species-specific, reflecting evolutionary divergence [28, 29].

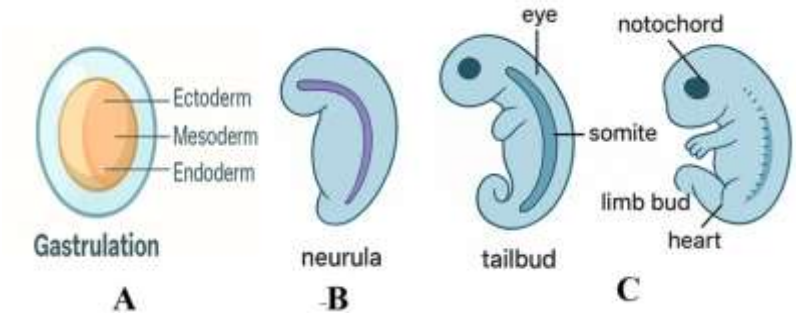

Figure 2. Development of frog organs showing gastrulation (a); neurulation (b); organogenesis (c).

Table 3. Development of frog organs.

Item	Stage Description	Process Details
A	Gastrulation	Begins shortly after fertilization (typically within 5–7 hours depending on temperature); marked by the formation of the blastopore and movement of cells to establish the three germ layers: ectoderm, mesoderm, and endoderm [28].
B	Neurulation	Starts after gastrulation (~12–20 hours post-fertilization); involves the thickening of the ectoderm to form the neural plate, which folds into the neural tube; somite formation begins alongside the notochord [31].
C	Organogenesis	Occurs over the next 1–3 days; the brain subdivides, the heart tube forms and begins beating, eyes and limb buds appear, and key systems begin rudimentary function in preparation for larval (tadpole) life [36].

In *Xenopus*, gastrulation is orchestrated by the dorsal lip of the blastopore, also known as Spemann's organizer, which directs axis formation through the secretion of signaling molecules including Chordin, Noggin, and BMP antagonists [30]. Although zebrafish employ a functionally analogous structure, the embryonic shield, the cellular architecture and morphogenetic movements differ. *Xenopus* gastrulation relies heavily on involution and convergent extension, whereas zebrafish emphasize epiboly and deep cell intercalation [31]. These comparisons indicate that organizer-based control of body axes is a common mechanism, but the morphological processes by which tissues are rearranged are unique to each species, an insight crucial for evaluating whether developmental mechanisms are universally shared or context dependent.

During neurulation, *Xenopus* embryos (13–20 hpf) form the neural plate and subsequently the neural tube, guided by conserved morphogens such as Shh, FGF, and Wnt [32]. Zebrafish follow a similar molecular trajectory in neural induction; however, their neural

keel transforms into the neural rod before cavitating into a tube, in contrast to the folding mechanism observed in *Xenopus*. This divergence underscores a shared molecular toolkit implemented through distinct morphogenetic strategies, which is directly relevant to the research question of whether developmental outcomes stem from universal or lineage-specific mechanisms. Both species also form somites alongside the notochord, yet the timing and segmental organization differ, reinforcing the interplay between conserved genetic regulation and species-specific embryonic architecture [33].

By two to three days post-fertilization (dpf), *Xenopus* embryos enter organogenesis, initiating heart contractions, pronephric development, and sensory organ differentiation [34]. These processes parallel zebrafish organogenesis, in which the heart also begins beating around 24 to 30 hpf and the pronephros develops functional nephrons. Despite this temporal offset, the transition from tissue patterning to functional organ systems illustrates a conserved developmental trajectory, whereas distinct embryonic morphologies such as yolk utilization in zebrafish versus tadpole feeding in *Xenopus,*exemplify evolutionary adaptations [35].

The enduring significance of *Xenopus laevis* in developmental biology lies in its experimental accessibility. Its large eggs, transparent tissues, and suitability for approaches such as in situ hybridization, mRNA microinjection, and CRISPR-Cas9 editing make it a powerful complement to zebrafish research [36]. Together, comparative studies in these species reinforce that vertebrate development is governed by a shared molecular and cellular blueprint, but the morphogenetic routes are tailored to each species' evolutionary and ecological context. This comparative framework provides critical leverage in addressing the overarching research question of whether embryonic development is driven primarily by conserved universal principles or by species-specific innovations [28, 29, 36].

As illustrated in Figure 3 and Table 4, the embryonic development of chicks (*Gallus gallus*), a bird species developing externally within a hard-shelled egg, follows the conserved vertebrate stages—gastrulation, neurulation, and organogenesis—while exhibiting avian-specific adaptations. The chick embryo, with its disc-shaped, flat blastodisc structure, is uniquely suited for microscopic observation and microsurgical manipulation, making it a classic model in developmental biology for more than a century [37, 38]. Its utility has expanded with the advent of genome editing, electroporation, and single-cell imaging, reinforcing its role as a key organism for understanding vertebrate patterning and morphogenesis [39].

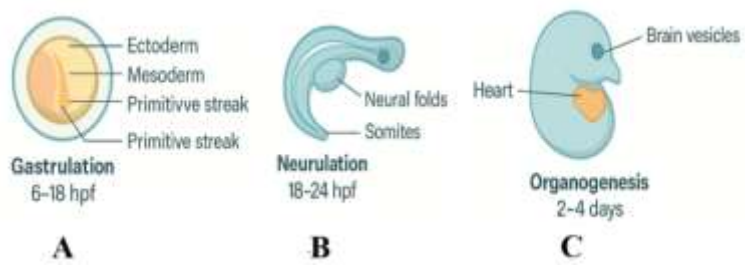

Figure 3. Development of chicks organs showing gastrulation (a); neurulation (b); organogenesis (c).

Table 4. Development of chicks organs.

Item	Stage Description	Process Details
A	Gastrulation	Occurs between 6–18 hours post-fertilization (hpf); marked by the formation of the primitive streak, which facilitates the differentiation of the three germ layers: ectoderm, mesoderm, and endoderm [41-42].
B	Neurulation	Begins around 18–24 hpf; involves the elevation and fusion of neural folds to form the neural tube; somite segmentation also initiates during this phase [40]
C	Organogenesis	Takes place between the 2nd and 4th day of incubation; major organs such as brain vesicles, heart, and limb buds begin to form, establishing the foundation of the chick's organ systems [45].

Gastrulation in chicks begins approximately 6 to 18 hours post-fertilization (hpf) with the formation of the primitive streak, a midline structure that directs the ingression and migration of epiblast cells to establish the three germ layers: ectoderm, mesoderm, and endoderm. At its anterior end, Hensen's node functions as an organizer, analogous to Spemann's organizer in amphibians and the embryonic shield in zebrafish. It secretes morphogens such as Nodal, BMP antagonists, and FGFs that regulate notochord formation and axial patterning [40]. Morphogenetic movements including epiboly and convergent extension extend the body axis and position germ layer progenitors [41]. Compared to *Xenopus laevis*, where gastrulation begins at 5 to 10 hpf with invagination at the dorsal lip of the blastopore, or zebrafish, where it begins at 5 to 6 hpf through epiboly over the yolk cell, the chick employs a streak-based mechanism. Thus, while axis specification by organizer-derived morphogens represents a conserved principle, the morphological strategies, blastopore lip, embryonic shield, or primitive streak, are divergent outcomes shaped by evolutionary history.

Following gastrulation, chick embryos undergo neurulation between 18 and 24 hpf. During this stage, neural folds rise, converge, and fuse at the dorsal midline to generate the neural tube, which later develops into the brain and spinal cord. Somite segmentation occurs simultaneously along the paraxial mesoderm, laying the foundation for the vertebral column, skeletal muscles, and dermis [42]. Neural crest cells delaminate from the neural tube and migrate extensively to form craniofacial elements, peripheral neurons, pigment cells, and adrenal tissues [43]. Cross-species comparisons reveal shared molecular regulation—Shh, Wnt, and FGF are central to neurulation in all vertebrates—but differing morphogenetic strategies: *Xenopus* embryos close the neural tube by folding of the neural plate, while zebrafish first form a solid neural keel that cavitates into a tube. This pattern demonstrates that the genetic toolkit for neurulation is conserved, while the geometric mechanisms of neural tube closure are lineage specific.

By day 2 to 4 of incubation, chick embryos enter organogenesis. The forebrain, midbrain, and hindbrain vesicles become distinct; the heart tube loops and begins to beat by day 2, initiating circulation; and sensory organs such as optic vesicles and otic placodes begin to differentiate under the regulation of Hox genes, Shh, and retinoic acid gradients [44]. Limb buds also emerge; a feature not observed in zebrafish or *Xenopus* at comparable stages. In zebrafish, organogenesis begins around 24 to 30 hpf with heart contractions and pronephric development, while in *Xenopus* it begins 2 to 3 days post-fertilization with the onset of heartbeat and kidney primordia. The conservation lies in the sequential transition from tissue patterning to functional organ systems, while divergence is evident in timing and life history

adaptations, chicks develop limbs before hatching, whereas aquatic vertebrates delay appendage development until larval or metamorphic stages.

Chick embryos remain indispensable for the study of gastrulation, neurulation, and organogenesis, particularly due to their tractability for in ovo imaging, CRISPR-mediated gene editing, and transcriptomic profiling [45]. Taken together, comparisons across chick, zebrafish, and *Xenopus* reveal a unifying theme: vertebrates share a conserved molecular and cellular framework for embryogenesis, yet each lineage has evolved distinct morphogenetic strategies and temporal dynamics. This duality, conserved genetic control alongside divergent developmental pathways, directly addresses the research question of whether embryonic development is governed primarily by universal mechanisms or by species-specific innovations [37, 39, 45].

As illustrated in Figure 4 and Table 5, the embryonic development of mammals, particularly the mouse (*Mus musculus*), demonstrates both deep conservation of vertebrate developmental stages, gastrulation, neurulation, and organogenesis, and lineage-specific strategies adapted to internal gestation. Unlike externally developing vertebrates such as zebrafish, *Xenopus*, and chick, the mouse embryo develops within the uterus, requiring specialized extraembryonic structures, including the placenta and yolk sac. The mouse has become a premier model for vertebrate genetics and developmental biology due to the availability of transgenic systems, lineage tracing, and CRISPR-Cas9–based gene editing [35].

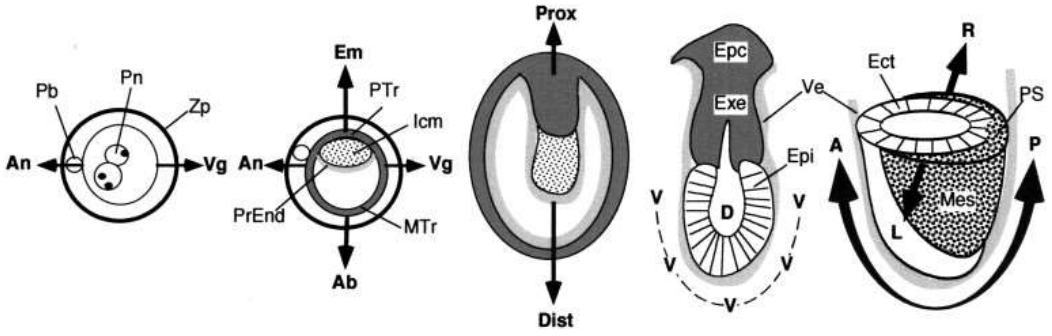

Figure 4. Development of Chicks Organs showing zygote (a); blastocyst (b); early egg cylinder (c); pre-gastrula (d); gastrula (e) [30].

Table 5. Development of mice organs.

Item	Stage Description	Process Details
A	Zygote	A single-cell formed after fertilization. Contains male (Pn) and female pronuclei, surrounded by zona pellucida (Zp). This stage marks the beginning of embryonic development [36]
B	Blastocyst	A fluid-filled structure composed of an inner cell mass (Icm) that will form the embryo, and a surrounding layer of trophoblast cells (MTr). Also includes primitive endoderm (PrEnd) and polar/trophectoderm regions (PTr) [37–39].
C	Early Egg Cylinder	The blastocyst reorganizes into a cylindrical structure with clearly defined proximal-distal polarity. The embryonic (Em) and abembryonic (Ab) regions begin to specialize [40].
D	Pre-Gastrula	Prior to gastrulation, the embryo displays distinct embryonic (Epi), extraembryonic ectoderm (ExE), and ectoplacental cone (Epc) regions. Visceral endoderm (Ve) surrounds the epiblast [41].
E	Gastrula	Characterized by the formation of the primitive streak (PS) and beginning of germ layer formation (ectoderm, mesoderm, and endoderm). Mesodermal cells (Mes) ingress through the streak, and the embryo begins anterior-posterior patterning (A-P) [42].

In the mouse, gastrulation begins around embryonic day (E) 6.5 with the formation of the primitive streak on the posterior epiblast. This structure is analogous to the chick primitive streak and functionally comparable to Spemann's organizer in amphibians and the embryonic shield in zebrafish. Epiblast cells ingress through the streak to form mesoderm and definitive endoderm, while cells that remain on the surface differentiate as ectoderm. At its anterior end, the mouse node secretes morphogens such as Nodal, Lefty, and BMP antagonists, which pattern the axial mesoderm [36]. Compared to gastrulation in zebrafish (5–6 hpf) and *Xenopus* (5–10 hpf), mouse gastrulation is delayed, reflecting slower developmental pacing under internal gestation. Despite these temporal differences, the reliance on organizer-derived morphogens highlights a conserved genetic program across vertebrates, while the distinct morphogenetic architectures, blastopore lip, shield, or primitive streak, represent divergent solutions to the same developmental challenge.

Between E8.0 and E9.5, the neural plate elevates, folds, and fuses to form the neural tube, regulated by Shh, Wnt, and FGF signaling, as in other vertebrates. Neural tube closure in the mouse initiates at multiple sites along the anterior–posterior axis and progresses bidirectionally until the cranial and caudal neuropores close [37]. This contrasts with *Xenopus*, where closure begins at a single midline site, zebrafish, where a neural keel cavitates into a tube, and chick, where neurulation occurs around 18–24 hpf through dorsal neural fold fusion. The mouse completes neural tube closure by E9.5 (~4–5 somite stage), compared to ~20 hpf in zebrafish or day 2 in chick. These comparisons reveal conservation in molecular signaling but divergence in closure mechanics and timing, emphasizing that the genetic toolkit for neurulation is shared, yet its morphogenetic execution is lineage specific.

From E9.5 to E14.5, the mouse undergoes extensive organogenesis. The heart tube begins beating by E8.0, slightly earlier than in other vertebrates (zebrafish ~24 hpf; *Xenopus* ~2–3 days post-fertilization; chick ~day 2 of incubation). By E9.5, the liver, pancreas, and lung buds are evident, limb buds emerge around E9.25–E9.5, and brain vesicles expand into forebrain, midbrain, and hindbrain regions [38]. Neural crest cells contribute to craniofacial structures and peripheral ganglia; paralleling patterns observed in chick and amphibians [39]. Unlike external developers, whose organogenesis progresses rapidly toward hatching or metamorphosis, mouse organogenesis is protracted due to placental support. This underscores a conserved sequence of organ primordia formation but divergent temporal scaling, shaped by reproductive mode and gestational environment.

Mouse embryogenesis illustrates how vertebrates share a conserved molecular and cellular framework (organizer signaling, morphogen gradients, germ layer specification) but diverge in morphogenetic strategies, developmental timing, and dependence on extraembryonic tissues. These comparisons reinforce the view that vertebrate embryonic development is governed by both common genetic programs and species-specific innovations, directly addressing the question of conserved versus unique developmental mechanisms [40–41].

In humans (*Homo sapiens*), the sequence of gastrulation, neurulation, and organogenesis follows the conserved vertebrate framework but unfolds over a longer and more intricate timeframe, reflecting the complexity of human physiology (Figure 5; Table 6). Gastrulation begins around day 14–16 post-fertilization, establishing the three definitive germ layers, ectoderm, mesoderm, and endoderm, each committed to specialized tissue and organ fates [39–40]. The primitive streak orchestrates axial patterning and cell migration, analogous to the

organizer structures in chick, frog, and zebrafish embryos. However, while zebrafish complete gastrulation in under 10 hours and mice at embryonic day (E) 6.5–7.5, the human process progresses more slowly within the uterine environment. This extended pace likely reflects evolutionary adaptations to larger body size and longer gestation, even as the core signaling pathways (Wnt, BMP, Nodal) remain deeply conserved [41].

(a) **(b)** **(c)** **(d)**

Figure 5. Development of human organs showing fertilization (a); ectoderm (b); mesoderm (c); endoderm (d) [31].

Table 6. Development of human organs

Item	Stage Description	Process Details
A	Fertilization	Fusion of a sperm and an oocyte typically occurs in the ampulla of the fallopian tube, resulting in a zygote. This marks the beginning of embryonic development, where the diploid genome is restored [34-35]
B	Ectoderm	The outermost germ layer formed during gastrulation. It differentiates into the nervous system (brain and spinal cord), epidermis (skin), hair, nails, and sensory organs. It also forms the lens of the eye and enamel of the teeth [41]
C	Mesoderm	The middle germ layer that forms during gastrulation. It develops into muscles, bones, the circulatory system, kidneys, gonads, and connective tissues. The mesoderm also contributes to the formation of the dermis and body cavities [38]
E	Endoderm	The innermost germ layer formed during gastrulation. It gives rise to the epithelial lining of the gastrointestinal tract, liver, pancreas, lungs, thyroid, bladder, and other internal organs [39] [43].

Recent advances in human gastruloid models, stem-cell derived 3D systems mimicking post-implantation stages, have confirmed that Wnt, BMP, and Nodal signaling regulate mesoderm and endoderm induction, consistent with findings from amphibians, chicks, and mice [42]. Unlike amphibians, where organizer activity can be probed by physical grafting, human models rely on in vitro self-organization. This methodological difference highlights challenges unique to studying human embryos directly, while quantitative analyses of gastruloids (~40–50% mesoderm, ~10–15% endoderm) provide comparative benchmarks aligned with in vivo vertebrate proportions.

Neurulation occurs between days 19–27, when the neural plate folds and fuses into the neural tube, the precursor of the brain and spinal cord. As in mice and chicks, closure proceeds from multiple initiation points along the anterior–posterior axis, and defects in this process (spina bifida, anencephaly) parallel experimental outcomes in frog and mouse models [28, 33]. Nonetheless, the timeline differs: neural tube closure in humans spans 8–10 days, compared to E8.5–E9.5 in mice. Single-cell transcriptomic studies have shown conserved lineage trajectories across vertebrates, while also revealing uniquely human features, such as delayed neural crest emergence and expanded forebrain development [34]. These differences

underscore how shared cellular mechanisms are adapted to support human-specific innovations in brain structure and function.

Between weeks 4–8, organogenesis drives the formation of most major organ systems. The heart begins beating around day 22—later than in zebrafish (24 hpf) or chick (day 2), but comparable to the mouse (E8.0) when adjusted for developmental scale [36]. Limb buds emerge by week 4, governed by SHH, FGF, and HOX gene networks, echoing conserved appendage programs observed across vertebrates [37]. However, in humans organogenesis proceeds over several weeks rather than days, highlighting a divergence in tempo shaped by reproductive strategy and body plan. Emerging spatial transcriptomics further demonstrates conservation of transcriptional regulators (HOX, Pax, Sox, GATA) across species, while uncovering uniquely human regulatory delays that extend developmental plasticity [38]. Importantly, ethical and technical constraints on studying human embryos beyond 14 days necessitate reliance on comparative models, underscoring the interplay between conserved vertebrate principles and human-specific adaptations.

Taken together, human embryogenesis illustrates a central theme of vertebrate development: a deeply conserved molecular toolkit (Wnt, BMP, Nodal, SHH, FGF) orchestrates gastrulation, neurulation, and organogenesis across species, but humans deploy these pathways within a uniquely prolonged temporal and spatial framework. This balance between shared genetic mechanisms and species-specific elaborations highlights evolutionary continuity while explaining how humans achieve greater structural and functional complexity.

The developmental timelines summarized in Table 7 highlight both conserved processes and species-specific variations in vertebrate embryogenesis across zebrafish, frogs, chicks, mice, and humans. All species progress through the universal stages of gastrulation, neurulation, and organogenesis, yet the rate and morphology of these events differ markedly. In zebrafish (*Danio rerio*), external fertilization and transparent embryos enable rapid development, with organogenesis largely completed by 48 hours post fertilization (hpf) [45]. Frogs (*Xenopus laevis*) undergo gastrulation and neural tube formation within the first 20 hpf, and major organs such as the eyes, heart, and kidneys appear by day 3 [44].

Table 7. Summary of key developmental stages in model vertebrates.

Vertebrate Species	Organ Development Stage	Primary Organs Formed	Timeframe (Post-Fertilization)	Sources
Zebrafish (*Danio rerio*)	Gastrulation (5–10 hpf)	Germ layers, notochord	5–10 hours	[46]
	Neurulation (10–16 hpf)	Neural plate, neural keel	10–16 hours	
	Organogenesis (24–48 hpf)	Brain, somites, heart, eye, otic vesicle	1–2 days	
Frog (*Xenopus laevis*)	Gastrulation (5–10 hpf)	Germ layers, dorsal lip formation	5–10 hours	[45]
	Neurulation (13–20 hpf)	Neural tube, somites	13–20 hours	
	Organogenesis (2–3 dpf)	Eyes, heart, kidney, gut	2–3 days	
Chick (*Gallus gallus*)	Gastrulation (6–18 hpf)	Primitive streak, germ layers	6–18 hours	[25]
	Neurulation (18–24 hpf)	Neural folds, somites	18–24 hours	
	Organogenesis (2–4 dpf)	Brain vesicles, limb buds, heart	2–4 days	
Mouse (*Mus musculus*)	Gastrulation (6.5–7.5 dpf)	Germ layers, primitive streak	6.5–7.5 days	[38]
	Neurulation (8.0–8.5 dpf)	Neural tube, somite formation	8.0–8.5 days	
	Organogenesis (9.5–13.5 dpf)	Brain, heart chambers, limb buds, liver	9.5–13.5 days	
Human (*Homo sapiens*)	Gastrulation (Day 14–16)	Ectoderm, mesoderm, endoderm	Day 14–16	[43-44]
	Neurulation (Day 19–27)	Neural tube, early brain structures	Day 19–27	
	Organogenesis (Weeks 4–8)	Heart, brain, limbs, liver, kidney, gastrointestinal tract	Week 4–8	

In chicks (*Gallus gallus*), which also develop externally in eggs, the primitive streak emerges by 18 hpf and key organs including the brain and heart form by day 4 [25]. By contrast, mice (*Mus musculus*) develop internally, with gastrulation initiating at 6.5–7.5 days post fertilization (dpf) and organogenesis continuing through day 13.5 [38]. Humans (*Homo sapiens*) display the most extended timeline: gastrulation begins around day 14, neurulation occurs between days 19 and 27, and organogenesis spans weeks 4 to 8 of gestation, establishing systems such as the heart, brain, limbs, liver, kidneys, and gastrointestinal tract [43, 44].

3.2. Common developmental mechanisms across vertebrates.

Development across vertebrate species is remarkably orchestrated by a core set of genetic and molecular processes that have been conserved through millions of years of evolution (Table 8). Despite differences in morphology, environment, and reproductive strategies, fundamental processes such as germ layer formation, neural tube development, somite segmentation, and organogenesis rely on similar gene networks and signaling pathways. This conservation underscores both a shared ancestry and the evolutionary robustness of these developmental mechanisms, while species-specific variations provide opportunities to study how conserved pathways adapt to unique physiological needs [5–6]. Importantly, these similarities make vertebrate model organisms indispensable not only for understanding evolution but also for advancing biomedical research.

Table 8. Conserved developmental mechanisms across vertebrates.

Developmental Process	Shared Genes Involved	Common Signaling Pathways	Vertebrates Showing Conservation	Sources
Germ Layer Formation	*Nodal*, *FoxA2*, *Brachyury (T)*	Nodal, Wnt	Zebrafish, Frog, Chick, Mouse, Human	[13]
Neural Tube Development	*Pax6*, *Sox2*, *Olig2*	BMP, Shh, FGF	Zebrafish, Chick, Mouse, Human	[1]
Somite Segmentation	*Mesp2*, *Hairy1*, *Notch1*	Notch, FGF, Wnt	Frog, Chick, Mouse, Human	[25]
Heart Development	*Nkx2.5*, *Gata4*, *Tbx5*	BMP, FGF, Wnt	Zebrafish, Mouse, Human	[36]
Eye Development	*Pax6*, *Rx*, *Six3*	Shh, FGF, BMP	Frog, Chick, Mouse, Human	[34]
Limb Development	*HoxA/D*, *Tbx5*, *Shh*	Shh, FGF, Wnt	Chick, Mouse, Human	[18]
Gut Tube Formation	*Hnf1β*, *Sox17*, *Cdx2*	Wnt, BMP, Hedgehog	Zebrafish, Mouse, Human	[29]
Axis Patterning (A-P & D-V)	*Hox*, *Otx2*, *Gbx2*	Wnt, BMP, Shh	Frog, Chick, Mouse, Human	[40]

Germ layer formation is one of the earliest and most critical events in vertebrate development, establishing the foundation for all tissues and organs. Key regulators such as Nodal, FoxA2, and Brachyury (T) drive mesoderm and endoderm specification, while Wnt and Nodal pathways orchestrate body axis establishment. From zebrafish, where gastrulation occurs within the first 10 hours post fertilization, to humans, where it extends across several days, the genetic framework remains deeply conserved [7,8]. Studies in chick embryos have been particularly informative, showing how disruptions in primitive streak formation and morphogen gradients can lead to axial defects—findings directly applicable to congenital conditions such as caudal dysgenesis in humans [9,10]. These models demonstrate how conserved signaling systems, when perturbed, can yield divergent outcomes with clinical relevance.

Neural tube development, which generates the brain and spinal cord, provides another prime example of conservation. Genes such as Pax6, Sox2, and Olig2 define neural progenitor domains, while BMP, Shh, and FGF signaling regulate neural plate folding and tube closure [11,12]. Comparative studies in zebrafish, chicks, mice, and humans reveal that although the molecular players are conserved, the timing and morphology of closure differ. Zebrafish form a neural keel that later cavitates, whereas in chicks and mammals the neural plate folds dorsally. Experimental manipulations in chicks have been

critical for modeling neural tube defects such as spina bifida, yielding insights into human congenital anomalies and supporting preventative strategies such as folate supplementation [13–15].

Somite segmentation, essential for vertebral column and skeletal muscle formation, is governed by the clock-and-wavefront mechanism, driven by Notch, Wnt, and FGF oscillations together with genes such as Mesp2 and Hairy1 [16, 17]. The periodicity of somite formation is species-specific approximately 30 minutes in zebrafish, 90 minutes in chicks, and 120 minutes in humans, yet the underlying regulatory mechanism is universally conserved [18, 19]. These differences illustrate evolutionary divergence in tempo without altering core genetic circuitry. Studies of segmentation defects in mice have provided critical insights into human congenital scoliosis, underscoring the translational value of conserved developmental systems.

Organogenesis—including the heart, eye, limb, gut, and body axis further demonstrates conservation with species-specific refinements. Early heart development is directed by Nkx2.5, Gata4, and Tbx5 in all vertebrates, while the optical transparency of zebrafish embryos has accelerated gene-function studies on cardiac looping and chamber formation, directly informing congenital heart defect research [20,21]. Similarly, eye development is patterned by Pax6, Rx, and Six3; Pax6 knockout studies in mice and misexpression experiments in flies have established its evolutionary role as a “master regulator” of eye formation [22]. Limb development illustrates conserved roles for HoxA/D, Shh, and Tbx5, with the chick embryo serving as a pivotal model for elucidating signaling centers such as the apical ectodermal ridge (AER), findings later applied to human limb malformation syndromes [23, 24]. Gut tube formation, controlled by Sox17, Cdx2, and Hnf1β, also shows deep conservation, with zebrafish models providing insights into congenital disorders such as Hirschsprung’s disease [25, 26]. Finally, embryonic body axis patterning, directed by Hox clusters, Otx2, and Gbx2, exemplifies the conserved genetic toolkit underlying vertebrate body plans. Comparative studies reveal that expansions in HOX gene clusters in mammals contribute to the greater axial complexity of humans [27, 28].

In summary, conserved developmental mechanisms across vertebrates carry dual significance. Evolutionarily, they highlight shared ancestry and the robustness of genetic pathways; biomedically, they demonstrate how model organisms such as zebrafish, chicks, and mice serve as indispensable proxies for uncovering the molecular basis of human congenital disorders. Understanding gastrulation in chicks has illuminated axial malformations, zebrafish have accelerated gene-function discovery in heart and gut formation, and mouse models have revealed mechanisms of neural tube and skeletal defects. These cross-species comparisons show that while the molecular toolkit is deeply conserved, its tempo and morphological execution vary, offering a powerful framework that bridges evolutionary biology with human health.

3.3 Unique developmental mechanisms across vertebrates.

While vertebrates share a conserved genetic toolkit, each species also exhibits unique developmental adaptations shaped by ecological niche, reproductive strategy, and evolutionary history (Table 9). These species-specific features are not merely curiosities; they provide powerful insights into how developmental pathways can be modified for specialized functions and how such modifications can inform human biology and medicine. From regeneration in amphibians to placental evolution in mammals and cortical expansion in humans, unique mechanisms illustrate the plasticity of embryogenesis across vertebrates [5–6].

In the frog (*Xenopus laevis*), one of the most remarkable traits is the ability of tadpoles to regenerate lost limbs during early larval stages. This regenerative capacity is orchestrated by regulators such as msx1, fgf8, and wnt5a, which coordinate the formation of a proliferative blastema capable of rebuilding skeletal, muscular, and neural tissues [7–8]. Evolutionarily, this trait provides a survival advantage in predator-rich aquatic environments by enabling recovery from otherwise lethal injuries. Biomedically, *Xenopus* regeneration studies inform human

regenerative medicine by identifying conserved pathways that could potentially be reactivated in adult tissues, offering models for limb regeneration, spinal cord repair, and wound healing [9]. Importantly, the decline of regenerative ability as frogs mature underscores stage-specific regulation of developmental plasticity, a finding directly relevant to understanding why humans exhibit limited regenerative potential.

Table 9. Species-specific organogenesis features.

Vertebrate Species	Unique Developmental Trait	Divergent Genes or Pathways	Functional/Evolutionary Significance	Sources
Frog (*Xenopus laevis*)	Limb regeneration capacity (tadpole stage)	*msx1*, *fgf8*, *wnt5a*	Enables regrowth of lost appendages during early stages; advantageous for survival and predator escape	[21]
Chick (*Gallus gallus*)	Enlarged yolk sac and early extraembryonic membrane development	*VEGF*, *BMP4*, *GATA6*	Supports nutrient uptake in shelled eggs; adaptation to terrestrial reproduction	[12]
Mouse (*Mus musculus*)	Placental development and decidualization	*Hand1*, *Esx1*, *Csh1*	Enables internal gestation and nutrient transfer; supports embryonic development within the uterus	[33]
Zebrafish (*Danio rerio*)	Rapid external development and transparency of embryos	*ntl*, *pou5f3*, *nanog*	Facilitates optical observation of embryogenesis; adaptation for fast reproduction in aquatic environments	[34-35]
Human (*Homo sapiens*)	Expanded neocortex and prolonged brain development	*ARHGAP11B*, *NOTCH2NL*, *SRGAP2*	Supports advanced cognitive functions and complex behavior; hallmark of human brain evolution	[41-42]

In contrast, the chick (*Gallus gallus*) demonstrates adaptations to terrestrial reproduction within a shelled egg. Because nutrient transfer from the mother is absent, chick embryos depend on specialized extraembryonic structures, particularly the yolk sac and chorioallantoic membrane. Genes such as VEGF, BMP4, and GATA6 regulate vasculature and membrane development, ensuring efficient nutrient absorption and gas exchange [10–12]. This innovation represents an evolutionary response to life on land, allowing avian embryos to thrive in enclosed environments. For biomedicine, chick embryos have been invaluable in studies of gastrulation and neural tube closure—processes highly relevant to human congenital defects such as spina bifida. Experimental manipulations in the primitive streak have clarified how perturbations in BMP and Wnt signaling disrupt axis formation, providing direct parallels to human axial malformations [13–14].

Mice (*Mus musculus*), as mammals, evolved a distinct strategy of internal gestation supported by placental development. Key processes such as trophoblast differentiation and uterine decidualization are regulated by genes including Hand1, Esx1, and Csh1, ensuring nutrient and hormonal exchange between mother and embryo [15–16]. Evolutionarily, this adaptation permits extended gestation periods and greater offspring viability by providing a stable, protected environment. Biomedically, the mouse placenta serves as a critical model for pregnancy-related disorders such as preeclampsia and intrauterine growth restriction, with direct implications for maternal-fetal health in humans.

The zebrafish (*Danio rerio*) exemplifies a developmental strategy optimized for rapid, external embryogenesis. Embryos develop outside the mother, are optically transparent, and complete early patterning within hours. Genes such as ntl (Brachyury ortholog), pou5f3, and nanog coordinate pluripotency and germ layer specification [17–18]. Evolutionarily, this rapid development maximizes survival in unpredictable aquatic habitats by enabling high reproductive output. For biomedical research, zebrafish embryos are uniquely powerful because every stage of organogenesis can be imaged live. This feature has accelerated gene-

function discovery through CRISPR-Cas9 screens and forward genetics, especially in cardiac, hematopoietic, and neural development, yielding insights directly translatable to human congenital disorders [19–20].

Finally, humans (*Homo sapiens*) exhibit one of the most profound evolutionary specializations: the dramatic expansion of the neocortex and prolonged brain development. Genes such as ARHGAP11B, NOTCH2NL, and SRGAP2, which are either human-specific or modified from ancestral versions, promote neural progenitor proliferation and delay differentiation [21–22]. Evolutionary, these modifications underpin advanced cognitive traits such as language, symbolic reasoning, and cultural transmission. Biomedically, studies of human cortical development—through organoids and comparative primate models—have deepened understanding of neurodevelopmental disorders including autism spectrum disorders and microcephaly, conditions often linked to disruptions in cortical progenitor proliferation [23–24].

In sum, vertebrates share a conserved developmental toolkit but display species-specific innovations reflecting ecological and evolutionary pressures. Frog regeneration informs strategies for human tissue repair, chick gastrulation provides insight into the origins of neural tube and axial defects, zebrafish accelerate discovery due to rapid and transparent development, mice offer critical models of placental biology and maternal-fetal interactions, and humans exemplify the evolutionary pinnacle of cortical expansion driving higher cognition. Together, these findings demonstrate how integrating conserved and unique mechanisms across vertebrates bridges evolutionary biology with translational medicine.

Conclusions

Across zebrafish, Xenopus, chick, mouse, and human, vertebrate embryogenesis relies on a conserved molecular toolkit including Wnt, BMP, Nodal, FGF, and Shh signaling; transcriptional regulators such as Brachyury/T, FoxA2, and Pax/Sox families; and shared cellular behaviors including epiboly, involution, convergent extension, neurulation, somitogenesis, and organ primordia formation. This conservation explains why developmental events unfold in a predictable sequence, gastrulation, neurulation, organogenesis, despite differences in anatomy and life history. It also underpins the utility of comparative models, since the same pathways that specify germ layers or pattern the neural tube in fish and frogs govern analogous processes in birds, mice, and humans. Each lineage, however, deploys these tools differently. Zebrafish complete early patterning within hours and form a neural tube by cavitation, Xenopus shapes the body axis via a blastopore lip organizer and convergent extension, chick employs a primitive streak with Hensen’s node suited to a yolky blastodisc, mouse integrates development with the placenta and uses multiple neural tube closure sites, while humans extend the same sequence across weeks with enlarged anterior brain regions. These differences in timing, geometry, environment, and life history fine-tune a conserved blueprint to meet species-specific challenges. Evolutionarily, constraint arises from indispensable gene networks that stabilize early development, while innovation emerges through shifts in tempo, morphology, and context for example, avian extraembryonic membranes enabling terrestrial reproduction, mammalian placentation supporting prolonged gestation, zebrafish rapidity favoring fecundity, amphibian regeneration sustaining larvae, and human neocortical expansion through extended progenitor proliferation. Biomedically, this interplay forms a translation pipeline: zebrafish enable rapid genetics and imaging, Xenopus

illuminates organizer function and regenerative capacity, chick allows direct access to gastrulation and neurulation, mouse provides mammalian models of congenital disease, and human organoids or gastruloids validate human-specific timing and regulatory logic. Together, these systems reveal both a conserved vertebrate core and meaningful mechanistic differences, providing evolutionary insight while advancing clinical understanding of developmental disorders.

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Competing Interest

The author declares no competing interests related to the publication of this research.

Author Contribution

The author took the lead in drafting the introduction and methodology sections, carefully summarized relevant literature and related studies to establish a strong foundation for the research, and thoughtfully guided the process of presenting the gathered data in clear and meaningful figure formats to enhance understanding and interpretation.

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