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Spatiotemporal Immunohistochemical Profiling and Comparative Analysis of HGF, IGF-I, FGF2, and TGF-α Expression in Goose (Anser anser) Kidney and Liver During Embryonic Hatching and Early Post-Hatch Development

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Abstract

Embryonic organogenesis in avian species is orchestrated through a tightly regulated network of growth factors that govern cellular proliferation, differentiation, migration, extracellular matrix remodeling, and tissue maturation. Among these regulatory molecules, hepatocyte growth factor (HGF), insulin-like growth factor-I (IGF-I), fibroblast growth factor-2 (FGF2), and transforming growth factor-α (TGF-α) represent fundamental signaling mediators involved in renal and hepatic morphogenesis. Although extensive investigations have characterized these factors in mammalian developmental biology, comparatively limited information is available regarding their spatiotemporal immunohistochemical distribution in geese (Anser anser), particularly during the transition from embryonic hatching to early post-hatch development. This review synthesizes current knowledge regarding the developmental anatomy of avian kidney and liver tissues and critically evaluates the reported localization patterns and biological functions of HGF, IGF-I, FGF2, and TGF-α within embryonic and neonatal stages. Comparative evidence from chickens, ducks, quails, rodents, and humans is integrated to establish mechanistic similarities and species-specific differences in organ maturation. Particular emphasis is placed on the coordinated interactions among these growth factors during nephrogenesis, hepatogenesis, epithelial differentiation, vascularization, and metabolic adaptation immediately following hatching. The review further identifies significant gaps in goose-specific immunohistochemical research and proposes future directions involving quantitative immunohistochemistry, molecular validation, and integrative developmental analyses. Collectively, the available evidence demonstrates that coordinated expression of HGF, IGF-I, FGF2, and TGF-α constitutes an essential regulatory network underlying functional maturation of avian renal and hepatic tissues, thereby providing valuable insights for developmental biology, veterinary histology, comparative anatomy, and poultry science.

Keywords: Goose (Anser anser), immunohistochemistry, HGF, IGF-I, FGF2, TGF-α, embryonic development, kidney development, liver development, avian histology.

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1. Introduction

Embryonic development in birds represents one of the most precisely coordinated biological processes in vertebrate organogenesis. During incubation, multiple signaling pathways regulate the sequential differentiation of tissues, enabling the transformation of a fertilized ovum into a physiologically competent hatchling. Among developing organs, the kidney and liver undergo extensive structural and functional remodeling because both organs become indispensable immediately after hatching for osmoregulation, metabolism, detoxification, hematopoiesis, nutrient storage, and endocrine regulation. Their successful maturation depends not only on genetically programmed developmental events but also on temporally controlled expression of numerous peptide growth factors that coordinate cellular communication throughout embryogenesis.

The avian kidney possesses distinctive anatomical and physiological characteristics that distinguish it from mammalian kidneys. It consists of reptilian- and mammalian-type nephrons distributed throughout three renal divisions, providing adaptations necessary for efficient water conservation and nitrogen metabolism. Comparative histological studies have demonstrated remarkable structural differences among avian species, including chickens, ducks, harriers, and other birds, emphasizing the evolutionary diversity of renal organization (Abood et al., 2014; Aslan, 2018). These observations indicate that species-specific developmental mechanisms influence nephron differentiation and maturation, highlighting the importance of investigating goose kidney development independently rather than extrapolating from other avian models.

The liver similarly undergoes rapid morphological transformation during embryonic development. Initially functioning primarily as a hematopoietic organ, the embryonic liver gradually acquires metabolic, synthetic, detoxification, and endocrine functions before hatching. Histogenetic studies in chickens have shown progressive differentiation of hepatocytes, hepatic cords, sinusoidal architecture, and vascular organization throughout embryogenesis (Doaa et al., 2013; Çöllü and Gürcü, 2017). These developmental changes establish the physiological competence required for post-hatch adaptation when nutrient metabolism shifts from yolk dependence to exogenous feeding.

Growth factors function as central regulators of these developmental transitions. Hepatocyte growth factor (HGF) is widely recognized for its mitogenic, morphogenic, and anti-apoptotic activities. Initially identified because of its regenerative effects on hepatocytes, HGF is now known to influence branching morphogenesis, epithelial differentiation, angiogenesis, and tissue repair in numerous organs. Developmental investigations have demonstrated HGF expression in fetal tissues during organ formation, suggesting that its biological functions extend well beyond hepatic regeneration into embryonic morphogenesis (Defrances et al., 1992). Experimental immunohistochemical studies in diabetic murine kidneys further demonstrate persistent HGF localization within renal tissues, indicating its continued physiological importance during tissue remodeling (Deprem et al., 2020).

Insulin-like growth factor-I (IGF-I) represents another essential developmental mediator. Through activation of IGF receptors, this peptide regulates cellular proliferation, differentiation, metabolism, and survival. IGF signaling contributes significantly to embryonic growth and organ maturation across vertebrate species. Studies examining human embryogenesis have demonstrated widespread expression of IGF receptors in developing tissues (Coppola et al., 2009), while more recent investigations emphasize the indispensable role of growth hormone–IGF-I interactions in kidney maturation and maintenance of renal function (Gurevich et al., 2021). Furthermore, supplementation of embryonic culture systems with IGF-I has been associated with improved developmental competence, highlighting its importance in embryogenesis (Choi et al., 2024).

Fibroblast growth factor-2 (FGF2) belongs to a large family of signaling molecules involved in embryonic induction, angiogenesis, mesenchymal-epithelial interactions, and tissue regeneration. Comprehensive reviews of FGF biology describe the family's broad involvement in developmental regulation and disease pathophysiology (Beenken and Mohammadi, 2009). Within the developing kidney, FGF2 contributes to

nephron induction, ureteric bud branching, stromal differentiation, and extracellular matrix remodeling (Cancilla et al., 1999; Drummond et al., 1998). Localization studies in fetal tissues further indicate extensive distribution of basic fibroblast growth factor within basement membranes and developing epithelial structures (Gonzalez et al., 1990), supporting its multifunctional role during organogenesis.

Transforming growth factor-α (TGF-α), acting primarily through epidermal growth factor receptor signaling, regulates epithelial proliferation, differentiation, and tissue remodeling. Found in numerous embryonic epithelial tissues (Alison et al., 1993), TGF-α contributes substantially to kidney morphogenesis and epithelial maturation. Investigations in avian kidneys have localized TGF-α during mesonephric and metanephric development, suggesting conserved developmental mechanisms across vertebrates (Diaz Ruiz et al., 1993; Diaz Ruiz et al., 1996). Similar observations in human embryonic kidneys further support its participation in nephrogenesis (Carev et al., 2008).

The coordinated interaction among HGF, IGF-I, FGF2, and TGF-α forms an integrated signaling network rather than independent molecular pathways. HGF promotes epithelial branching and morphogenesis; IGF-I enhances proliferative capacity and cellular survival; FGF2 stimulates angiogenesis and mesenchymal induction; whereas TGF-α regulates epithelial expansion and differentiation. Their overlapping biological activities collectively establish the microenvironment necessary for successful renal and hepatic maturation. Understanding these coordinated interactions is therefore essential for interpreting immunohistochemical localization patterns observed throughout embryonic and early post-hatch development.

Despite extensive research in mammalian developmental biology, significant knowledge gaps remain regarding these growth factors in geese. Most available studies focus on chickens, rodents, or humans, with relatively few investigations addressing goose embryology specifically. Comparative anatomical analyses of avian kidneys have underscored the importance of species-specific evaluation because structural variation may influence functional protein distribution and developmental timing (Abood et al., 2014). This limitation restricts comprehensive understanding of goose developmental physiology and highlights the need for systematic immunohistochemical characterization.

Accordingly, this review critically synthesizes available literature concerning HGF, IGF-I, FGF2, and TGF-α expression within developing renal and hepatic tissues, emphasizing embryonic hatching and early post-hatch periods in geese while incorporating evidence from related vertebrate models. By integrating comparative anatomy, developmental histology, growth factor biology, and immunohistochemical evidence, the review establishes a comprehensive framework for understanding molecular regulation of avian organogenesis and identifies promising directions for future investigation.

2. Literature Review

2.1 Developmental Anatomy of the Avian Kidney During Embryogenesis

The avian kidney is a highly specialized excretory organ whose developmental pattern differs considerably from that of mammals. During embryogenesis, renal differentiation progresses through successive developmental stages that culminate in the formation of the permanent metanephric kidney before hatching. Unlike mammalian kidneys, avian kidneys contain both reptilian-type and mammalian-type nephrons, reflecting an intermediate evolutionary adaptation that supports efficient osmoregulation while minimizing water loss. This anatomical specialization enables birds to maintain electrolyte balance under diverse environmental conditions and contributes significantly to post-hatch physiological adaptation.

Comparative anatomical investigations have demonstrated considerable variation in renal morphology among avian species. Abood et al. (2014) compared kidneys from harrier (Circus aueroginosus), domestic chicken (Gallus domesticus), and mallard duck (Anas platyrhynchos), reporting differences in nephron organization, cortical-medullary distribution, and vascular architecture while maintaining the fundamental structural organization common to birds. Their findings indicate that although general developmental mechanisms remain conserved, species-specific anatomical modifications may influence cellular localization of regulatory proteins and growth factors during organogenesis. Consequently, extrapolation of immunohistochemical observations from chickens or ducks directly to geese should be approached cautiously because subtle anatomical differences may alter spatial protein expression. The comparative observations presented by Abood et al. (2014) therefore provide an

important anatomical foundation for interpreting growth factor localization in goose kidneys.

Aslan (2018) further described the histological organization of the avian urinary system, emphasizing the coordinated differentiation of renal corpuscles, proximal and distal tubules, collecting ducts, and vascular components. During embryonic maturation, these structures develop simultaneously through reciprocal interactions between epithelial and mesenchymal tissues. Such reciprocal signaling is fundamental for nephron induction and branching morphogenesis, processes regulated by multiple growth factors including HGF, FGF2, IGF-I, and TGF-α. The structural maturation of renal tissues therefore provides an essential histological framework for understanding developmental immunohistochemical patterns.

Experimental investigations in chicken embryos reinforce these anatomical observations. Bolin and Burggren (2013) demonstrated progressive increases in glomerular number, vascular perfusion, and nephron maturation throughout embryonic development, indicating that renal functionality develops gradually before hatching. Their work highlights that glomerular differentiation is closely associated with vascular remodeling, suggesting that angiogenic mediators such as FGF2 participate alongside epithelial growth factors in coordinating nephrogenesis.

Davies (2001) emphasized that ureteric bud morphogenesis represents one of the most critical events in kidney development. Intracellular signaling pathways interact continuously with extracellular matrix components to regulate branching architecture, nephron induction, and epithelial differentiation. The study proposed that disruption of these signaling networks may impair normal renal morphogenesis, thereby illustrating the biological importance of growth factor-mediated cellular communication throughout embryogenesis.

Collectively, these investigations establish that avian kidney development depends upon coordinated structural differentiation and molecular regulation. Anatomical maturation provides the cellular substrate upon which growth factor signaling exerts spatially and temporally specific effects during embryogenesis.

2.2 Liver Histogenesis During Embryonic and Early Post-Hatch Development

Compared with the kidney, embryonic liver development is characterized by rapid cellular proliferation, vascular organization, and metabolic specialization. Initially functioning as a hematopoietic organ, the embryonic liver progressively acquires synthetic, detoxification, endocrine, and metabolic capacities required for independent life after hatching.

Doaa et al. (2013) investigated liver histogenesis in Dandarawi chicken embryos and demonstrated sequential differentiation of hepatic cords, hepatocytes, sinusoidal networks, portal structures, and connective tissue compartments throughout incubation. Their observations indicated that hepatocyte maturation occurs gradually, with increasing cytoplasmic differentiation and tissue organization approaching hatching. These structural modifications coincide with increasing metabolic activity, suggesting close coordination between morphological maturation and functional protein expression.

Similarly, Çöllü and Gürcü (2017) evaluated embryonic chick liver development through immunohistochemical localization of endothelial nitric oxide synthase (eNOS), inducible nitric oxide synthase (iNOS), and laminin α1. Their findings demonstrated dynamic changes in vascular and extracellular matrix-associated proteins during hepatic maturation. Although these markers differ from HGF, IGF-I, FGF2, and TGF-α, the study illustrates that developmental immunohistochemistry effectively characterizes temporal changes in regulatory molecules responsible for tissue organization.

Carlson (2018) described liver organogenesis as a complex interaction between endoderm-derived epithelial cells and surrounding mesenchyme. Reciprocal signaling pathways regulate hepatoblast proliferation, biliary differentiation, vascularization, and extracellular matrix remodeling throughout embryogenesis. This developmental framework explains why multiple growth factors operate simultaneously rather than independently during hepatic maturation.

Erhan and Ergün (2018) further emphasized functional differences between avian and mammalian livers, particularly regarding carbohydrate and lipid metabolism. Birds possess distinctive metabolic adaptations that become increasingly important immediately after hatching when nutritional dependence shifts from yolk reserves to external feeding. Consequently, growth factor expression within embryonic liver tissues likely reflects not only structural differentiation but also preparation for postnatal metabolic demands.

Taken together, available literature suggests that embryonic liver maturation is governed by coordinated morphological, metabolic, and molecular events, creating an ideal context for evaluating immunohistochemical localization of developmental growth factors.

2.3 Biological Functions of Hepatocyte Growth Factor (HGF)

Hepatocyte growth factor represents one of the most multifunctional cytokines involved in vertebrate organogenesis. Initially characterized because of its potent mitogenic effects on hepatocytes, subsequent investigations demonstrated broader biological activities encompassing epithelial proliferation, morphogenesis, angiogenesis, tissue regeneration, and cellular migration.

Defrances et al. (1992) identified HGF expression within developing rat embryos, demonstrating widespread localization during fetal organogenesis rather than exclusive hepatic expression. Their observations established that HGF functions as a developmental regulator influencing multiple organs simultaneously. The broad distribution of HGF throughout embryonic tissues suggests that its biological significance extends beyond regenerative physiology into fundamental mechanisms governing tissue differentiation.

Experimental immunohistochemical investigations by Deprem et al. (2020) further demonstrated HGF localization within renal tissues of diabetic and non-diabetic mice. Although conducted under pathological conditions, the study confirmed persistent HGF expression in glomerular and tubular compartments, supporting its contribution to epithelial maintenance and cellular proliferation. These findings provide indirect evidence that similar localization may occur during embryonic renal maturation when proliferative activity is substantially greater than in adult tissues.

Mechanistically, HGF promotes epithelial branching, stimulates cell motility, inhibits apoptosis, and enhances angiogenesis through activation of the c-Met receptor. During kidney development, these functions contribute to nephron formation, tubular elongation, and vascular integration. Within developing liver tissue, HGF facilitates hepatoblast expansion and hepatic cord organization while supporting vascular remodeling necessary for functional maturation.

The complementary roles of HGF in both kidney and liver development make it an important candidate for immunohistochemical evaluation during embryonic and post-hatch stages.

2.4 Developmental Significance of IGF-I

Insulin-like growth factor-I constitutes one of the principal endocrine and paracrine regulators of embryonic growth. Unlike many tissue-specific cytokines, IGF-I influences nearly every developing organ through stimulation of DNA synthesis, cellular proliferation, differentiation, metabolism, and survival.

Coppola et al. (2009) demonstrated extensive expression of IGF receptor-1 during human embryogenesis, indicating that responsiveness to IGF signaling develops early during organ formation. The widespread receptor distribution suggests that IGF-mediated regulation coordinates multiple developmental pathways rather than isolated cellular processes.

Gurevich et al. (2021) reviewed the physiological actions of growth hormone and IGF-I within kidney development and renal function. Their synthesis emphasized that IGF-I regulates nephron maturation, glomerular development, tubular differentiation, and renal growth while contributing to long-term maintenance of renal physiology. The review also proposed interactions between IGF-I and additional developmental growth factors, reinforcing the concept of integrated signaling networks.

Recent embryological research by Choi et al. (2024) demonstrated that supplementation of embryonic culture media with IGF-I significantly enhanced developmental competence under experimental conditions. Although performed in reproductive biology, these findings underscore the importance of IGF-mediated signaling during early embryogenesis and suggest that adequate IGF-I availability supports successful tissue differentiation.

Collectively, available evidence positions IGF-I as a central developmental regulator whose biological activities complement those of HGF and FGF2 during organ maturation.

2.5 Fibroblast Growth Factor-2 (FGF2) in Renal and Hepatic Organogenesis

Fibroblast growth factor-2 belongs to a highly conserved family of signaling proteins regulating embryonic induction, angiogenesis, wound repair, and stem cell maintenance. Beenken and Mohammadi (2009) comprehensively reviewed FGF biology and

demonstrated that members of the FGF family participate throughout embryogenesis by coordinating proliferation, migration, differentiation, and extracellular matrix interactions.

Within kidney development, Cancilla et al. (1999) localized FGF ligands and receptors throughout the developing rat kidney, demonstrating strong expression within nephrogenic regions. Their observations indicate that FGF signaling contributes directly to nephron induction and epithelial differentiation.

Similarly, Drummond et al. (1998) identified FGF2 expression in fetal kidney-derived cells and proposed its critical role during nephrogenesis. Experimental evidence suggested that FGF2 promotes proliferation of immature renal cells while supporting differentiation into functional nephron structures.

Gonzalez et al. (1990) further demonstrated widespread localization of basic fibroblast growth factor throughout fetal basement membranes. Since basement membranes regulate epithelial organization and cellular adhesion, FGF2 appears to influence both structural integrity and developmental signaling simultaneously.

Floege et al. (1992) reported endogenous synthesis of FGF2 by renal mesangial cells, indicating that kidney tissues themselves produce developmental growth factors capable of autocrine and paracrine regulation. Such endogenous production may contribute to localized immunohistochemical staining patterns frequently observed during embryonic organogenesis.

These investigations collectively indicate that FGF2 functions as a major regulator of cellular proliferation, vascularization, and epithelial differentiation during renal and hepatic development, complementing the biological actions of HGF and IGF-I.

2.6 Transforming Growth Factor-α (TGF-α) as a Regulator of Epithelial Differentiation

Transforming growth factor-α (TGF-α) is a polypeptide growth factor belonging to the epidermal growth factor (EGF) family and functions primarily through activation of the epidermal growth factor receptor (EGFR). During embryogenesis, TGF-α regulates epithelial proliferation, differentiation, migration, and tissue remodeling, making it an essential mediator of organ formation. Unlike growth factors that exhibit tissue-specific activity, TGF-α demonstrates broad expression throughout developing epithelial organs, indicating its role in coordinating multiple developmental processes simultaneously.

Burgess (1989) described TGF-α as a critical regulator of epithelial growth with biological activities overlapping those of EGF. The review highlighted that activation of EGFR stimulates intracellular signaling pathways responsible for DNA synthesis, cell-cycle progression, and differentiation. These molecular mechanisms are particularly important during embryonic development when rapid expansion of epithelial cell populations is required for organ formation.

Alison et al. (1993) extended these observations by demonstrating widespread immunoreactivity of TGF-α across diverse epithelial tissues. Their immunohistochemical findings confirmed that TGF-α expression is not confined to a single organ but is distributed throughout multiple embryonic epithelial structures. Such broad localization suggests that TGF-α contributes to coordinated maturation of various organ systems rather than acting independently within isolated tissues.

Specific evidence regarding avian renal development was provided by Diaz Ruiz et al. (1993), who localized TGF-α and epidermal growth factor receptors within the mesonephros and metanephros of developing chicken embryos. Strong immunoreactivity was observed during critical phases of nephron differentiation, indicating active participation of TGF-α signaling in avian kidney morphogenesis. Because the embryonic chicken shares many developmental characteristics with other domestic birds, these findings provide a valuable comparative framework for interpreting potential localization patterns in goose kidneys.

Further support was provided by Diaz Ruiz et al. (1996), who identified a TGF-α-related protein within chicken kidneys using immunochemical techniques. Their investigation demonstrated that expression persisted throughout developmental stages associated with epithelial maturation, suggesting that TGF-α contributes not only to initial nephron formation but also to subsequent functional differentiation.

Human developmental studies reached similar conclusions. Carev et al. (2008) demonstrated expression of EGF and TGF-α in early human kidney development, supporting the evolutionary conservation of EGFR-mediated signaling during vertebrate nephrogenesis. Although species-specific developmental timing differs,

the underlying molecular mechanisms appear remarkably consistent across birds and mammals.

Collectively, available evidence suggests that TGF-α functions primarily as an epithelial regulatory factor whose expression coincides with periods of intensive cellular proliferation and structural remodeling. Within embryonic kidneys and livers, TGF-α likely interacts with HGF, IGF-I, and FGF2 to coordinate tissue maturation through complementary signaling pathways.

2.7 Integrated Molecular Interactions Among HGF, IGF-I, FGF2, and TGF-α

Although HGF, IGF-I, FGF2, and TGF-α possess distinct biological properties, developmental evidence indicates that these molecules rarely function independently. Instead, embryonic organogenesis depends upon coordinated signaling networks in which multiple growth factors regulate overlapping cellular processes. Such integration enables precise spatial and temporal control of proliferation, differentiation, apoptosis, extracellular matrix remodeling, and vascular development.

HGF primarily promotes epithelial branching morphogenesis and cellular migration through activation of c-Met signaling. During kidney development, HGF stimulates tubular elongation and nephron maturation while simultaneously enhancing angiogenesis. In the liver, HGF supports hepatoblast proliferation and hepatic cord organization, thereby contributing to establishment of normal tissue architecture.

IGF-I complements HGF by promoting sustained cellular proliferation and protecting differentiating cells from apoptosis. Rather than initiating morphogenesis directly, IGF-I maintains proliferative capacity within developing tissues and facilitates metabolic maturation required for functional organ development. This complementary relationship explains why both growth factors are frequently expressed during overlapping developmental periods.

FGF2 functions predominantly within mesenchymal compartments, regulating angiogenesis, extracellular matrix organization, and epithelial–mesenchymal communication. Since nephrogenesis depends upon reciprocal interactions between epithelial and stromal tissues, FGF2 provides essential signaling that coordinates structural organization while supporting vascular expansion necessary for increasing metabolic demand.

TGF-α primarily influences epithelial proliferation through EGFR activation. Unlike FGF2, which regulates epithelial–mesenchymal interactions, TGF-α acts directly upon epithelial populations undergoing rapid expansion and differentiation. Consequently, TGF-α expression frequently overlaps with HGF during periods of epithelial remodeling but operates through distinct intracellular signaling mechanisms.

Rather than functioning sequentially, these molecules establish interconnected regulatory networks characterized by signaling redundancy and functional cooperation. Such integration enhances developmental robustness, ensuring successful organogenesis even when local fluctuations occur in individual signaling pathways. This systems-level perspective provides a more comprehensive explanation of developmental immunohistochemical patterns than interpretation based on isolated molecular expression.

2.8 Comparative Perspective: Goose Development in Relation to Other Avian and Mammalian Models

Because direct immunohistochemical investigations in goose embryos remain limited, comparative developmental biology provides an important framework for interpreting expected patterns of growth factor localization. Chickens have traditionally served as the principal avian developmental model because of their accessibility and well-characterized embryogenesis. Ducks, quails, and other domestic birds provide additional comparative systems that illustrate both conserved developmental mechanisms and species-specific adaptations.

The anatomical comparisons performed by Abood et al. (2014) demonstrated that although avian kidneys exhibit common organizational features, measurable interspecies differences exist in nephron distribution, cortical architecture, and vascular arrangement. These structural variations may influence regional localization of developmental proteins, emphasizing the necessity for species-specific immunohistochemical evaluation. Accordingly, observations derived from chickens should inform—but not replace—direct investigations in geese.

Similarly, studies involving Japanese quail have demonstrated physiological variation in renal function associated with biological characteristics such as sex (Ahmad Alabdallah et al., 2021). Although this investigation focused on adult physiology rather than embryogenesis, it illustrates the biological variability

that exists even among closely related avian species. Such variation reinforces the importance of conducting dedicated developmental investigations within individual species.

Mammalian developmental studies likewise provide valuable mechanistic insights. Investigations involving rats and humans consistently demonstrate conserved functions of HGF, IGF-I, FGF2, and TGF-α during nephrogenesis and hepatogenesis. Nevertheless, developmental timing, incubation strategy, metabolic adaptation, and renal architecture differ substantially between birds and mammals. Consequently, molecular functions may be evolutionarily conserved while immunohistochemical localization patterns exhibit species-specific variation.

The integration of avian and mammalian evidence therefore supports the hypothesis that goose embryonic development is regulated by conserved growth factor networks operating within species-specific anatomical contexts.

2.9 Knowledge Gaps and Theoretical Positioning

Despite substantial advances in developmental biology, several important gaps remain regarding the immunohistochemical characterization of growth factors in goose embryogenesis.

The first limitation is the scarcity of goose-specific investigations. Most available evidence originates from chickens, rodents, or human fetal tissues. Although comparative studies provide valuable biological context, they cannot fully account for anatomical and physiological characteristics unique to geese.

A second limitation concerns the predominance of single-marker investigations. Many published studies evaluate only one growth factor or signaling pathway, thereby overlooking coordinated molecular interactions that likely regulate organogenesis. Simultaneous immunohistochemical assessment of HGF, IGF-I, FGF2, and TGF-α would provide a more comprehensive understanding of developmental regulation.

Another important gap involves temporal analysis. Existing investigations often examine isolated developmental stages instead of continuous embryonic progression through hatching and early post-hatch adaptation. Because expression of developmental proteins changes dynamically, comprehensive spatiotemporal evaluation is essential for understanding functional maturation.

Finally, relatively few studies integrate anatomical observations with molecular localization. Combining detailed histological characterization with immunohistochemical profiling would improve interpretation of developmental mechanisms and facilitate comparisons among avian species.

Based on these limitations, the present review adopts an integrative theoretical framework in which kidney and liver organogenesis is viewed as the product of coordinated interactions among multiple growth factor systems operating within anatomically specialized tissues. Rather than considering HGF, IGF-I, FGF2, and TGF-α as isolated biomarkers, they are interpreted as components of a dynamic developmental signaling network regulating proliferation, differentiation, vascularization, epithelial organization, and functional maturation across embryonic hatching and early post-hatch development.

3. Methodology

3.1 Study Design

As this article is a Research & Review Journal manuscript synthesized from published evidence, the methodological framework is based on a structured narrative review integrating comparative developmental anatomy, embryology, immunohistochemistry, and growth factor biology. Only the references supplied for this manuscript were considered during evidence synthesis. No external literature, unpublished data, or additional databases were incorporated, thereby ensuring consistency with the predefined reference set.

The review employed a comparative analytical approach to evaluate the developmental significance of HGF, IGF-I, FGF2, and TGF-α in embryonic kidney and liver tissues. Evidence derived from avian models, including goose, chicken, duck, quail, and related species, was examined alongside mammalian developmental investigations to identify conserved molecular mechanisms and species-specific differences relevant to embryonic organogenesis.

3.2 Literature Selection Strategy

The evidence base consisted exclusively of the twenty-six references provided for this manuscript. These publications encompass comparative anatomy, embryology, developmental histology,

immunohistochemistry, molecular biology, renal physiology, hepatic development, and growth factor signaling.

The references were grouped into five analytical categories:

- Comparative anatomy and histology of avian kidney and liver.
- Embryonic development of renal and hepatic tissues.
- Immunohistochemical localization studies.
- Molecular biology of HGF, IGF-I, FGF2, and TGF-α.
- Functional mechanisms governing organogenesis and post-hatch adaptation.

This thematic classification facilitated systematic comparison of developmental findings across different experimental models.

3.1 Study Design

This study was conducted as a structured narrative review designed to synthesize published evidence concerning the spatiotemporal immunohistochemical distribution and biological functions of hepatocyte growth factor (HGF), insulin-like growth factor-I (IGF-I), fibroblast growth factor-2 (FGF2), and transforming growth factor-α (TGF-α) during embryonic kidney and liver development in avian species, with particular emphasis on geese (Anser anser). The review integrates findings from developmental anatomy, histology, immunohistochemistry, embryology, and molecular biology to provide a comprehensive understanding of growth factor-mediated organogenesis.

3.2 Data Sources

Only the twenty-six references supplied for this manuscript were included in the review. No additional literature, databases, unpublished reports, conference proceedings, or external sources were incorporated. Restricting the evidence base to the provided references ensured consistency in comparative analysis and prevented the introduction of unsupported information.

3.3 Evidence Organization

The selected literature was organized into thematic categories according to its primary research focus:

- Comparative anatomy and histology of avian kidneys and liver.
- Embryonic development and organogenesis.
- Immunohistochemical localization of developmental growth factors.
- Molecular biology and physiological functions of HGF, IGF-I, FGF2, and TGF-α.
- Comparative developmental studies involving avian and mammalian models.

This classification enabled systematic comparison of developmental mechanisms reported across different experimental systems.

3.4 Analytical Framework

A comparative qualitative synthesis approach was adopted to evaluate similarities and differences among published investigations. Particular attention was given to the temporal sequence of organ development, tissue-specific localization of growth factors, cellular targets identified by immunohistochemistry, and the proposed biological functions of each signaling molecule.

The review also examined the relationships among HGF, IGF-I, FGF2, and TGF-α rather than considering each factor independently. This integrated analytical framework facilitated interpretation of coordinated signaling events involved in nephrogenesis and hepatogenesis.

3.5 Comparative Evaluation

Comparisons were performed across multiple dimensions, including:

- Species investigated (goose, chicken, duck, quail, rodents, and humans).
- Developmental stage.
- Target organ (kidney or liver).
- Immunohistochemical localization.
- Functional role during embryogenesis.
- Developmental significance.

The comparative approach allowed identification of conserved developmental mechanisms while recognizing species-specific anatomical and physiological differences.

3.6 Data Synthesis

Information extracted from individual studies was synthesized into thematic narratives describing the developmental roles of HGF, IGF-I, FGF2, and TGF-α. Rather than summarizing each publication independently, evidence was integrated to identify common biological mechanisms, complementary signaling pathways, areas of agreement, and existing knowledge gaps. This approach emphasized interpretation of the collective body of evidence instead of isolated study outcomes.

3.7 Quality and Consistency Assessment

The consistency of published findings was evaluated by comparing reported immunohistochemical localization patterns, developmental timing, anatomical observations, and proposed physiological functions across the included studies. Greater interpretive weight was assigned to conclusions supported by multiple independent investigations and by evidence from both avian and mammalian developmental models.

3.8 Study Limitations

The principal limitation of this review arises from the limited number of goose-specific immunohistochemical investigations. Much of the available evidence originates from chickens, rodents, and human developmental studies, necessitating cautious interpretation when extrapolating findings to geese. In addition, methodological heterogeneity among the included studies—including differences in species, developmental stages, antibodies, staining protocols, and analytical techniques—may influence direct comparisons of reported localization patterns. Despite these limitations, integrating evidence from comparative developmental biology provides a valuable framework for understanding the coordinated roles of HGF, IGF-I, FGF2, and TGF-α during avian kidney and liver development.

4. Results

4.1 Overview of Synthesized Evidence

The synthesis of available literature indicates that kidney and liver development in avian species is governed by a tightly regulated network of growth factors, with HGF, IGF-I, FGF2, and TGF-α functioning as central molecular mediators. Across the reviewed studies, a consistent pattern emerges in which these signaling molecules exhibit temporally coordinated expression during embryogenesis, particularly during periods of rapid cellular proliferation, tissue differentiation, and vascular remodeling.

Comparative anatomical evidence demonstrates that avian renal architecture varies among species but retains a conserved nephron organization that supports functional maturation before hatching (Abood et al., 2014). These structural similarities suggest that molecular regulatory mechanisms, including growth factor signaling, are also likely conserved, although their spatial distribution may differ depending on species-specific developmental patterns.

4.2 Spatiotemporal Trends in Growth Factor Expression

Across avian and mammalian models, HGF, IGF-I, FGF2, and TGF-α exhibit distinct but overlapping temporal expression patterns during organogenesis. Early embryonic stages are characterized by high proliferative activity, during which FGF2 and IGF-I are consistently reported as dominant regulators of cellular expansion and tissue induction (Beenken and Mohammadi, 2009; Gurevich et al., 2021).

HGF expression is strongly associated with epithelial morphogenesis and branching events in both renal and hepatic tissues. Developmental studies indicate its presence during key phases of organ formation, suggesting a role in structural organization rather than terminal differentiation (Defrances et al., 1992). Similarly, TGF-α is frequently detected in epithelial compartments undergoing active proliferation and differentiation, particularly within renal tubular and hepatic epithelial structures (Alison et al., 1993; Diaz Ruiz et al., 1993).

In later embryonic stages approaching hatching, expression patterns tend to shift from proliferation-dominant signaling (FGF2, IGF-I) toward differentiation-associated pathways (HGF, TGF-α), reflecting the transition from organ formation to functional maturation.

4.3 Kidney Development: Integrated Growth Factor Activity

Evidence from avian kidney development suggests that nephrogenesis is regulated by coordinated activity among all four growth factors. FGF2 is primarily associated with early nephron induction and mesenchymal-epithelial interactions, where it supports

cellular proliferation and structural expansion (Cancilla et al., 1999; Drummond et al., 1998).

HGF contributes significantly to tubular elongation and epithelial branching, particularly during mid to late embryogenesis. Its role in promoting cellular migration and morphogenesis supports the formation of functional nephron architecture prior to hatching.

IGF-I acts as a sustaining factor for proliferating renal cells, ensuring continued growth and survival during periods of rapid nephron formation (Gurevich et al., 2021). In contrast, TGF-α is primarily associated with epithelial maturation and differentiation of renal tubular structures, reinforcing epithelial integrity and functional readiness.

Collectively, these factors demonstrate complementary roles in renal development, where no single growth factor operates independently, but rather within a coordinated signaling network.

4.4 Liver Development and Growth Factor Distribution

Liver development exhibits similar regulatory patterns, with early embryonic stages dominated by proliferative signals such as IGF-I and FGF2. These factors support hepatoblast expansion and vascular organization, which are essential for establishing the hepatic architecture.

HGF is strongly implicated in hepatocyte differentiation and hepatic cord formation, aligning with its known role in epithelial morphogenesis. Its expression is particularly important during the transition from hematopoietic function to metabolic specialization.

TGF-α contributes to epithelial maturation within hepatic tissue, promoting cellular organization and maintaining proliferative capacity during late developmental stages. This is consistent with its broader role in epithelial organ systems.

Histogenetic studies in avian liver development further support these findings, demonstrating progressive structural maturation of hepatic cords, sinusoids, and connective tissue frameworks during embryogenesis (Doaa et al., 2013; Çöllü and Gürcü, 2017).

4.5 Comparative Interpretation Across Species

Comparative evidence highlights both conserved and divergent aspects of growth factor expression. In mammalian systems, similar roles of HGF, IGF-I, FGF2, and TGF-α have been documented during kidney and liver development, suggesting evolutionary conservation of these signaling pathways (Carev et al., 2008; Coppola et al., 2009).

However, avian species demonstrate unique structural and functional adaptations, particularly in renal architecture and metabolic liver function, which may influence the spatial distribution and intensity of growth factor expression. These differences emphasize the importance of species-specific interpretation rather than direct extrapolation from mammalian models.

The comparative anatomical study by Abood et al. (2014) reinforces this interpretation by demonstrating variability in renal microarchitecture among bird species, which may correspond to differences in developmental signaling microenvironments.

4.6 Key Synthesized Outcomes

The integrated literature analysis suggests the following major findings:

- Growth factor expression during embryogenesis follows a coordinated temporal sequence linked to organ maturation stages.
- HGF primarily regulates morphogenesis and structural organization in both kidney and liver.
- IGF-I functions as a proliferative and survival factor during early development.
- FGF2 is central to early tissue induction, mesenchymal interactions, and angiogenesis.
- TGF-α regulates epithelial proliferation and differentiation during late developmental stages.
- All four growth factors operate as an integrated regulatory network rather than independent signaling systems.

These synthesized findings provide a conceptual framework for understanding avian organogenesis and highlight the need for goose-specific immunohistochemical studies to validate predicted expression patterns.

5. Discussion

5.1 Integrated Interpretation of Growth Factor Networks in Avian Organogenesis

The synthesized evidence indicates that avian kidney and liver development is not governed by isolated molecular pathways but rather by a highly coordinated network involving HGF, IGF-I, FGF2, and TGF-α. This integrated signaling architecture ensures precise regulation of cellular proliferation, differentiation, morphogenesis, and vascularization during embryogenesis. The overlapping yet functionally distinct roles of these growth factors suggest a hierarchical but flexible regulatory system in which multiple pathways converge to achieve structural and functional organ maturation.

FGF2 and IGF-I appear to dominate early developmental stages, where rapid cellular expansion and mesenchymal induction are essential for establishing organ primordia. This is consistent with the known biological properties of FGF signaling in promoting cell proliferation and tissue induction, as well as IGF-I's role in enhancing survival and metabolic priming of embryonic cells (Beenken and Mohammadi, 2009; Gurevich et al., 2021). As development progresses, HGF and TGF-α become more prominent, aligning with increased demands for epithelial organization, branching morphogenesis, and functional differentiation.

This transition reflects a fundamental biological principle of organogenesis: early proliferative expansion followed by structural refinement and functional specialization.

5.2 Kidney Development: Functional Integration of Signaling Pathways

The kidney represents a highly dynamic developmental system where epithelial–mesenchymal interactions are essential for nephron formation. The reviewed literature demonstrates that FGF2 acts as an early inducer of mesenchymal activation and nephron primordia formation (Cancilla et al., 1999; Drummond et al., 1998). This role is critical for initiating structural development and ensuring proper spatial organization of renal compartments.

HGF contributes primarily to branching morphogenesis and epithelial remodeling, facilitating the formation of tubular architecture. Its involvement in epithelial migration and morphogenetic patterning suggests that it acts downstream or in parallel with FGF-mediated induction signals. IGF-I provides proliferative support throughout nephrogenesis, ensuring sufficient cellular mass for nephron expansion and differentiation.

TGF-α, in contrast, appears to regulate epithelial maturation and stabilization of renal tubular structures. Its localization in developing kidney epithelia indicates a role in final-stage differentiation rather than early induction (Diaz Ruiz et al., 1993; Carev et al., 2008).

The convergence of these pathways highlights a tightly regulated developmental sequence in which structural complexity is achieved through sequential but overlapping molecular signals.

5.3 Hepatic Development and Functional Maturation

Liver development follows a similarly coordinated pattern, although the functional requirements differ due to its central role in metabolism. Early hepatic development is characterized by rapid proliferation of hepatoblasts, supported primarily by IGF-I and FGF2 signaling. These factors facilitate expansion of hepatic progenitor populations and establishment of vascular networks necessary for metabolic function.

HGF plays a central role in hepatic differentiation and structural organization, particularly in the formation of hepatic cords and sinusoidal architecture. Its morphogenetic properties align with its well-established role in epithelial organ development (Defrances et al., 1992). TGF-α contributes to epithelial stabilization and continued proliferation during late developmental stages, ensuring that hepatic tissue achieves functional maturity before hatching.

Histological evidence from avian models confirms progressive liver maturation, including increased organization of hepatocyte cords and vascular compartments (Doaa et al., 2013; Çöllü and Gürcü, 2017). These structural changes correspond closely with the expected temporal activity of the studied growth factors.

5.4 Species-Specific Variability and Evolutionary Conservation

Although the general roles of HGF, IGF-I, FGF2, and TGF-α appear conserved across vertebrate species, significant variability exists in their spatial distribution and developmental timing. The comparative anatomical evidence presented by Abood et al. (2014) demonstrates that avian kidney morphology differs across species, which may influence local microenvironments where growth factor signaling occurs.

Such variability suggests that while molecular pathways are evolutionarily conserved, their anatomical expression

patterns are adapted to species-specific physiological demands. This is particularly relevant for geese, which possess unique metabolic and ecological adaptations compared to chickens or ducks.

Mammalian studies further support the evolutionary conservation of these signaling systems, although differences in organ structure and developmental timing limit direct extrapolation. The presence of similar growth factor networks across vertebrates highlights their fundamental role in organogenesis but also underscores the necessity for species-specific investigations.

5.5 Functional Interdependence and Signaling Cross-Talk

One of the most significant insights from the literature is the degree of functional interdependence among the four growth factors. Rather than operating in parallel, these molecules exhibit extensive signaling cross-talk that enhances developmental robustness.

For example, FGF2-mediated mesenchymal activation may create permissive conditions for HGF-driven morphogenesis. Similarly, IGF-I may enhance cellular responsiveness to both FGF2 and HGF by promoting metabolic activity and survival signaling. TGF-α, acting through EGFR pathways, may integrate signals from multiple upstream regulators to fine-tune epithelial proliferation.

This multi-layered signaling architecture ensures redundancy and adaptability, reducing the likelihood of developmental failure due to perturbation of a single pathway. Such robustness is particularly important in avian embryogenesis, where development occurs within a constrained temporal window.

5.6 Limitations of Current Knowledge

Despite substantial insights, several limitations remain evident. The most critical gap is the absence of direct immunohistochemical studies specifically focusing on goose embryonic kidney and liver development. Most conclusions must therefore be inferred from chicken, rodent, and human models, which may not fully capture goose-specific developmental characteristics.

Additionally, many studies examine individual growth factors in isolation, limiting understanding of integrated signaling dynamics. Quantitative comparisons of expression levels across developmental stages are also limited, restricting precise temporal mapping of growth factor activity.

Methodological heterogeneity among studies—including differences in antibodies, staining protocols, and developmental staging—further complicates cross-study comparisons.

5.7 Theoretical and Practical Implications

The findings of this review support a systems-level model of avian organogenesis in which multiple growth factors interact to regulate kidney and liver development. This framework has several implications:

- It enhances understanding of embryonic developmental biology in birds.
- It provides a comparative foundation for veterinary histology and poultry science.
- It may inform future regenerative medicine strategies by highlighting conserved morphogenetic pathways.
- It establishes a conceptual basis for designing goose-specific experimental studies.

Understanding these molecular networks is particularly relevant for improving poultry health, developmental efficiency, and embryonic survival rates in agricultural contexts.

6. Conclusion

The present review integrates comparative developmental, histological, and molecular evidence to elucidate the coordinated roles of HGF, IGF-I, FGF2, and TGF-α in avian kidney and liver organogenesis, with specific relevance to Anser anser embryonic and early post-hatch development. The synthesized literature demonstrates that these growth factors collectively form a highly integrated regulatory network governing epithelial proliferation, mesenchymal induction, morphogenesis, vascular development, and functional maturation.

FGF2 and IGF-I predominantly regulate early developmental phases characterized by rapid cellular proliferation and tissue priming, while HGF and TGF-α assume greater roles during mid-to-late embryogenesis, facilitating structural organization and epithelial differentiation. Their overlapping temporal expression patterns indicate a coordinated transition from growth-driven expansion to functionally specialized organ maturation.

Comparative evidence further confirms that although the fundamental biological roles of these growth factors are conserved across vertebrates, their spatial distribution and developmental timing exhibit species-specific variations influenced by anatomical and physiological differences among avian species. The comparative anatomical framework provided by avian studies reinforces the necessity of interpreting molecular data within species-specific developmental contexts rather than relying solely on extrapolation from mammalian models.

A major outcome of this review is the identification of a significant knowledge gap in goose-specific immunohistochemical research. Most current understanding is derived from chickens and mammalian models, limiting precise characterization of growth factor localization in Anser anser. This gap underscores the need for targeted experimental studies using quantitative immunohistochemistry, molecular profiling, and stage-specific embryological sampling.

Future research should prioritize integrated multi-marker analyses to map the spatial and temporal distribution of HGF, IGF-I, FGF2, and TGF-α within developing renal and hepatic tissues. Such studies would significantly advance understanding of avian developmental biology and may also contribute to applied fields such as poultry science, developmental pathology, and regenerative medicine.

In conclusion, avian kidney and liver development is orchestrated through a complex and interdependent network of growth factors that ensures precise regulation of organogenesis. The coordinated action of HGF, IGF-I, FGF2, and TGF-α represents a fundamental biological framework essential for successful embryonic development and post-hatch functional adaptation.

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