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Peculiarities of morphogenesis of the urinary system of the laboratory mouse

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Abstract. The process of initiation and formation of the urinary system is similar among mammals. Experimental models using the laboratory mouse serve as an effective tool for elucidating the mechanisms of urinary tract development, since analogous studies on human embryos are associated with serious methodological and bioethical limitations. An important region that ensures the functioning of the upper and lower parts of the urinary system is the ureterovesical junction. In the definitive state, it performs the function of a physiological valve that provides unobstructed unidirectional urine passage. The study of its formation is fundamental for understanding the etiology of anomalies in this region. The aim of the study was to determine the main regularities and chronological sequence of prenatal ontogenesis of the ureterovesical junction in the laboratory mouse. The study was performed on 15 series of histological sections of laboratory mouse embryos. The material was obtained from the collection of the Department of Histology, Cytology and Embryology of Bukovinian State Medical University. A complex of morphological research methods was applied (morphometry, microscopy, three-dimensional computer reconstruction, and statistical analysis). In the early stages of mammalian development, the mesonephric (Wolffian) ducts open into the cloaca, which separates into the caudal part of the hindgut and the urogenital sinus, the primordium of the urinary bladder and urethra. This period covers days 10–15 of gestation (stages E10.5–14.5) in the laboratory mouse, corresponding to weeks 4–8 of gestation in humans. The caudal part of the mesonephric duct is the anlage of the upper urinary tract. In the laboratory mouse, at stage E10.5–11.5, the cranial part of the ureteric bud connects with the renal mesenchyme and forms the renal collecting system, whereas the caudal part of the ureteric bud differentiates into the ureter. During E10.5, the ureters connect with the urinary bladder via the common nephric duct. By stage E14.5, the ureters have separated from the mesonephric ducts and fused with the structures of the urinary bladder, in particular with the anlage of Lieutaud's trigone. Thus, the normal architectonics of the intramural segment and ureteral orifice in the laboratory mouse directly depends on coordinated remodeling of the common nephric duct through local apoptosis at stage E11–E13. Differentiation of the ureter from the mesonephric duct and its connection with the urinary bladder in the laboratory mouse are ensured by a sequence of morphological transformations: apoptosis of the common nephric duct at stage E11–E12, fusion of the epithelial layers of the ureter and urinary bladder at stage E13, and accelerated growth of the urogenital sinus during E12–E14.

Keywords: anatomy; embryology; microanatomy; comparative anatomy; urinary system; sphincter muscles; laboratory mouse; human.

INTRODUCTION

The formation of a functionally complete urinary system is a complex and sequential process of histogenesis, differentiation of primordia, and organogenesis of its components, which determines critical periods already at the early stages of prenatal ontogenesis in mammals. Excretion of toxic metabolic products and maintenance of body homeostasis directly depend on

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coordinated regulation of temporal transformations of primordia and subsequent complication of the histological structure and syntopic changes of relatively independent organs of the upper (kidneys, ureters) and lower (urinary bladder, urethra) urinary tract. An important segment that ensures the connection and functioning of these two divisions is the ureterovesical junction. In the mature organism, it functions as a physiological contractile complex that ensures and controls unobstructed urine passage, preventing reflux during contraction of the detrusor muscle of the bladder [1]. Pathological disorders of morphogenesis of the ureterovesical junction cause urinary system anomalies that are included in CAKUT syndrome (Congenital Anomalies of the Kidney and Urinary Tract), which occurs in 1–2 % of newborns. This group of combined congenital malformations of the kidneys and urinary tract includes, in particular, such anomalies as vesicoureteral reflux, megaureter, ectopia of the ureteral orifice, ureteral duplication, and ureterocele [2–5].

The sources of the primordia and the process of urinary system formation are similar in mammals [6–8]. The use of the laboratory mouse as an experimental model serves as an effective tool for detailed study of urinary tract morphogenesis, since analogous studies on human embryos are associated with certain methodological and bioethical limitations [9–11].

The upper and lower urinary tracts have different embryological origins. Fusion of the ureteric bud, which branches from the caudal part of the mesonephric (Wolffian) duct, with the urogenital sinus occurs through cellular remodeling and spatial transformations of this region. For a long time, the theory of Mackie and Stephens (1975) [12] remained the generally accepted paradigm of embryogenesis of the lower urinary tract; it stated that formation of the ureterovesical junction and Lieutaud's trigone occurs through morphological expansion of the ureteric bud and its subsequent integration into the wall of the urogenital sinus. Modern studies on laboratory mouse embryos using cell-lineage labeling have led to a revision of this theory. It was established that the ureteric bud at the site of fusion with the mesonephric duct does not differentiate into urinary bladder structures but regresses under the influence of regulated apoptosis, which is a prerequisite for successful separation of the ureter from the mesonephric duct and normal morphogenesis of the sphincter complex. Despite the morphogenetic similarity of urinary system formation among mammals and substantial progress in morphological, immunohistochemical, and molecular-genetic studies, obtaining new data in comparative embryology of humans and animals remains relevant [13–16].

The aim of the study: to determine the main regularities and chronological sequence of prenatal ontogenesis of the ureterovesical junction in the laboratory mouse.

MATERIAL AND METHODS

The study was performed on 15 series of histological sections of laboratory mouse embryos. The material was obtained from the collection of the Department of Histology, Cytology and Embryology of Bukovinian State Medical University. A complex of morphological research methods was applied (morphometry, microscopy, three-dimensional computer reconstruction, and statistical analysis).

The Biomedical Ethics Commission of Bukovinian State Medical University (Protocol No. 5 dated 19.02.2026) found no violations of moral and legal norms in the conduct of the scientific study.

The study is a fragment of the research work of the Department of Histology, Cytology and Embryology of Bukovinian State Medical University, "Regularities of morphogenesis, structural and functional organization, and anatomical variability of organs and formations of different regions of the body and systems of the human organism and experimental animals", state registration number: 0126U003125. Implementation period: 01.2026–12.2030.

RESULTS AND DISCUSSION

In the early stages of mammalian development, the mesonephric (Wolffian) ducts open into the cloaca, which separates into the caudal part of the hindgut and the urogenital sinus, the primordium of the urinary bladder and urethra. This period covers days 10–15 of gestation (stages E10.5–14.5) in the laboratory mouse, corresponding to weeks 4–8 of gestation in humans (Fig. 1). The caudal part of the mesonephric duct is the anlage of the upper urinary tract. In the laboratory

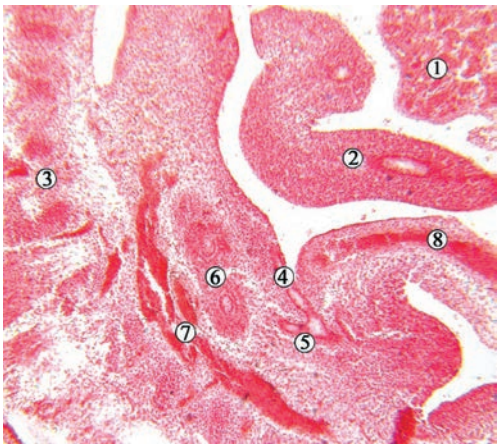

Fig. 1. Parasagittal section of a laboratory mouse embryo at stage E11. Hematoxylin and eosin staining. Photomicrograph. Magnification x70: *1 – liver; 2 – midgut; 3 – vertebral column primordia; 4 – mesonephric duct; 5 – ureteric bud; 6 – metanephric primordium; 7 – dorsal aorta; 8 – allantois.*

mouse, at stage E10.5–11.5, the cranial part of the ureteric bud connects with the renal mesenchyme and forms the renal collecting system, whereas the caudal part of the ureteric bud differentiates into the ureter. During E10.5, the ureters connect with the urinary bladder via the common nephric duct. By stage E14.5, the ureters separate from the mesonephric ducts and fuse with the structures of the urinary bladder, in particular with the anlage of Lieutaud's trigone (Fig. 2).

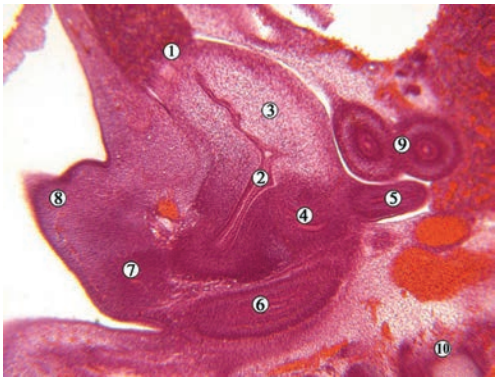

Fig. 2. Parasagittal section of a laboratory mouse embryo at stage E14.5. Hematoxylin and eosin staining. Photomicrograph. Magnification x70: *1 – allantois; 2 – anlage of Lieutaud's trigone; 3 – urinary bladder; 4 – intramural segment of the ureters; 5 – common nephric duct; 6 – hindgut; 7 – cloaca; 8 – genital tubercle; 9 – midgut; 10 – primordium of the vertebral column.*

The architectonics of the position of the intramural segment and the ureteral orifice in Lieutaud's trigone depends on normal morphogenesis of the common nephric duct, ureter, and mesonephric duct.

Expansion of the common nephric duct is the first step in remodeling of the distal part of the ureter. This process occurs during E11–E13 with the formation of a multilayered epithelium lining it. Its histological pattern differs from the epithelial plate of the mucosa of the ureters and mesonephric ducts. At stage E14, cells of the common nephric duct undergo regression or may differentiate into the structures of Lieutaud's trigone.

Discussion. Studies emphasize that the common nephric duct probably regresses during ureteral maturation by stage E13 rather than differentiating into Lieutaud's trigone [12, 17]. This is confirmed by data on signs of apoptosis of the common nephric duct at E11, whereas signs of regression were absent in the caudal part of the Wolffian duct and in the ureter [12, 18]. Programmed cell death was observed in the ureteral lumen at later stages, before the formation of a functional junction with the urinary bladder. At E15, apoptotic cells were detected in the caudal part of the ureter, which was blocked up to this stage by Chwalla's membrane. This is a temporary two-layered epithelial septum that, in the early stages of mammalian embryogenesis, separates the internal lumen of the common nephric duct from the cavity of the urogenital sinus. Theoretically, apoptosis in the caudal segment of the ureter may be important for the formation of its lumen. The process of local apoptosis in the ureteral lumen at stage E14–E15 may represent degeneration of Chwalla's membrane [12, 19].

Expansion of the common nephric duct and its subsequent apoptosis are important processes for separating the ureter from the Wolffian duct; however, it has not been definitively clarified how, after separation, the ureter assumes its definitive position in the urinary bladder. Analysis of studies suggests two hypotheses. According to the first, the intramural segment of the ureter reaches its definitive position by migrating along the urogenital sinus. According to the second, the ureter is displaced as it is encompassed by the enlarging urogenital sinus. In both hypotheses, a cascade of morphological events is observed: apoptosis between E11 and E12, which permits separation of the ureter from the Wolffian duct; fusion of the ureteral epithelium with the bladder epithelium, which occurs at E13; and accelerated growth of the urinary bladder, which is observed between E12 and E14.

In addition to the stages of normal embryonic development of the urinary system, regularities in the development of pathological morphogenesis have been identified. The Weigert – Meyer law is one of the fundamental rules in embryology and urology that describes the anatomical position of the ureters in cases of complete duplication of the renal pelvis and ureters [2, 12]. Thus, if two separate ureters are formed, they do not open into the urinary bladder randomly but according to a clear rule: the ureter from the upper pole of the kidney passes lower and enters the urinary bladder more caudally and medially than normal. The ureter from the lower pole of the kidney enters the urinary bladder more cranially and laterally relative to the upper ureter. Its position is closer to normal, but its anatomical course is shorter. This anatomical paradox is accompanied by a prevailing pathology for each ureter. The ureter from the upper pole often has pathology of the intramural segment with development of ureterocele or obstruction with hydronephrosis of part of the kidney. The ureter from the lower pole enters the urinary bladder more cranially and at a more direct angle, resulting in vesicoureteral reflux [5]. We also observed this feature in studies of human fetuses (Figs. 3, 4).

The theoretical model of development of this anomaly assumes that when two branches of the ureteric bud form on the Wolffian duct, the ureter that appears first and corresponds to the lower end of the organ occupies its position more rapidly. The second ureteric anlage from the upper pole shifts together with the Wolffian duct caudally and more medially,

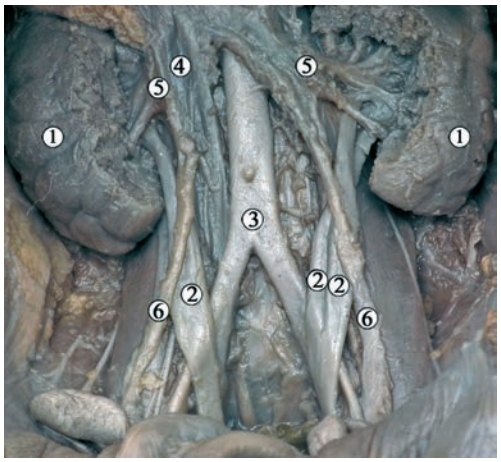

Fig. 3. Retroperitoneal organs of a 6-month-old male human fetus. Photograph of a macrospecimen. Magnification x3: *1 – kidneys; 2 – ureters; 3 – aorta; 4 – inferior vena cava; 5 – renal veins; 6 – testicular veins.*

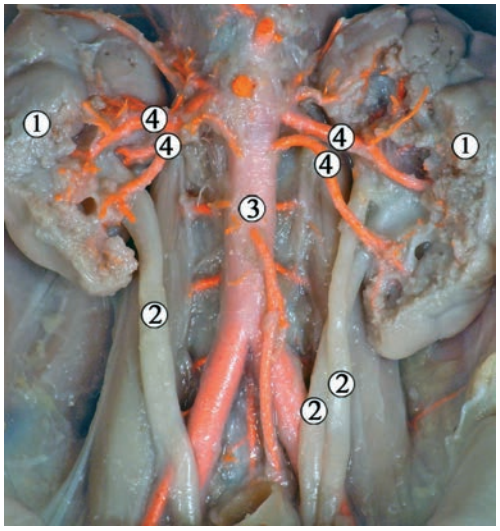

Fig. 4. Retroperitoneal organs of a 6-month-old female human fetus. The arteries are filled with a lead-based mixture. Photograph of a macrospecimen. Magnification x3.0: *1 – kidneys; 2 – ureters; 3 – aorta; 4 – renal arteries; 5 – accessory renal arteries.*

causing the ureters to change places. Studies indicate that apoptosis of the common nephric duct depends on signals from bladder tissues and occurs only in close proximity to these signals. To confirm this, a model of formation of an accessory ureteric bud in the laboratory mouse was reproduced, induced by exposure to high levels of retinoic acid during ureteric bud formation. These studies show that formation of the ureteric bud in a position close to the urogenital sinus may be crucial for receiving signals that induce programmed cell death in structures of the common nephric duct, whereas tissues of the common nephric duct associated with ureteric bud branches that form at higher positions on the Wolffian duct may persist because they are outside the range of signals arising from the urinary bladder, which normally induce apoptosis [12].

Summarizing these data, it should be noted that formation of the ureterovesical junction has features of both normal and abnormal development. Its proper anatomical architectonics ensures unobstructed urine passage and plays a decisive role in maintaining urodynamics, forming a reliable sphincter complex in the mature organism. Disruption of normal embryogenesis of this region causes the development of anomalies included in the structure of CAKUT syndrome. Therefore, further study of the molecular-genetic mechanisms of formation of this segment is one of the most relevant tasks of modern experimental embryology.

CONCLUSIONS

1. The normal architectonics of the intramural segment and ureteral orifice in the laboratory mouse directly depends on coordinated remodeling of the common nephric duct through local apoptosis at stage E11–E13.

2. Differentiation of the ureter from the mesonephric duct and its connection with the urinary bladder in the laboratory mouse are ensured by a sequence of morphological transformations: apoptosis of the common nephric duct at stage E11–E12, fusion of the epithelial layers of the ureter and urinary bladder at stage E13, and accelerated growth of the urogenital sinus during E12–E14.

3. Disturbance of urinary system development, according to the Weigert – Meyer law, is caused by disorders of apoptosis of the common nephric duct and leads to ureterocele, obstruction, and vesicoureteral reflux.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Особливості морфогенезу сечової системи миші лабораторної

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Анотація. Процес закладки та формування сечової системи є подібним серед ссавців. Експериментальні моделі з використанням миші лабораторної слугують ефективним інструментом для розкриття механізмів розвитку сечовидільного тракту, оскільки аналогічні дослідження на ембріонах людини супроводжуються серйозними методичними та біоетичними обмеженнями. Важливою ділянкою, що забезпечує функціонування верхнього та нижнього відділів сечової системи, є сечовідно-міхурове сполучення. У дефінітивному стані воно виконує функцію фізіологічного клапана, що забезпечує безперешкодний односпрямований пасаж сечі. Вивчення його формування є фундаментальним для розуміння етіології аномалій цієї ділянки. Метою роботи було з'ясувати основні закономірності та хронологічну послідовність пренатального онтогенезу сечовідно-міхурового сполучення миші лабораторної. Дослідження проведено на 15 серіях гістологічних зрізів препаратів зародків миші лабораторної. Матеріал використано із колекції кафедри гістології, цитології та ембріології Буковинського державного медичного університету. Застосовано комплекс методів морфологічного дослідження (морфометрія, мікроскопія, тривимірне комп'ютерне реконструювання, статистичний аналіз). На ранніх стадіях розвитку ссавців мезонефричні (Вольфові) протоки відкриваються в клоаку, яка розділяється на каудальний відділ задньої кишки та сечостатеву пазуху, зачаток сечового міхура та сечівника. Цей період охоплює 10–15 дні гестації (стадії E10.5–14.5) миші лабораторної, що відповідає 4–8 тижням гестації у людини. Зачатком верхніх сечових шляхів є каудальна частини мезонефричної протоки. У миші лабораторної на стадії E10.5–11.5 краніальна частина сечовідного зачатка з'єднується з мезенхімою нирки та утворює порожнинну систему нирки, тоді як каудальна частина сечовідного зачатка диференціюється у сечовід. Під час E10.5 сечоводи з'єднуються з сечовим міхуром через загальну нефральну протоку. Вже на стадії E14.5 сечоводи відокремлюються від мезонефричних проток і зливаються зі структурами сечового міхура, зокрема із закладкою трикутника Льєто. Отже, нормальна архітектоніка інтрамурального відділу та вічка сечовода миші лабораторної безпосередньо залежить від координованого ремоделювання загальної нефральної протоки шляхом локального апоптозу на стадії E11–E13. Диференціація сечовода від мезонефричної протоки та його з'єднання з сечовим міхуром у миші лабораторної забезпечуються послідовністю морфологічних перетворень: апоптозом загальної нефральної протоки на стадії E11–E12, злиттям епітеліальних шарів сечовода та сечового міхура під на стадії E13, а також пришвидшенням росту сечостатевої пазухи у терміни E12–E14.

Ключові слова: анатомія; ембріологія; мікроанатомія; порівняльна анатомія; сечова система; м'язи-замикачі; миша лабораторна; людина.