The significance of reciprocal induction relations between the derivates of nephrogenic mesoderm. Implications in pathology and regeneration

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Abstract: Functional capacity of renal excretory biosystem is assured by remarkable complex structures: glomerular basal membrane for ultrafiltration of blood plasma, tubular system of the nephron for resorption-secretion processes and juxtaglomerular complex for self-balancing. The purpose of the paper is to draw the attention of histopathologists over the phenotypic transformation of metanephrogen mesenchyme and over the relations between derivates of this mesenchyme in the ontogenesis process, with implications in pathology and regeneration. Authors conducted this study and, by classical microanatomic methods, they highlighted the structural heterogeneity of renal cortex, the phenotypic variability of glomerular capillary network, the spatial distribution and the relations of intraglomerular mesangial matrix. Based on personal observations, authors notice the fact that only a proper acknowledgement of reciprocal induction relations consequences between ureteric bud emerged from mesonephros and metanephrogenic blastema allows the understanding of renal parenchyma structural particularities and the determinant factors in anatomical-functional disposition of renal excretory biosystem, as well as the implications in pathology and regeneration.

Key Words: nephron, renal glomerulus, metanephrogenic mesenchyme, ureteric bud, reciprocal induction, kidney stem cells.

The functional structures of renal excretory system are determined during ontogenesis by the phenotype changes of metanephrogen mesenchyme, in the presence of reciprocal induction relations between the derivates of nephrogenic mesoderm (Mesoderma intermedium). The structural heterogeneity of renal parenchyma and the phenotype variability of its elements raised many problems regarding their genesis and evolution:

How is achieved the formation of many structural elements of renal parenchyma from the mesenchyme of nephrogenic mesoderm that is initially a homogenous structure?

Is it possible that the elements of renal parenchyma have another origin beside primordial mesenchyme of nephrogenic mesoderm?

What are the determining factors for the competence of metanephrogenic mesenchyme to specifically respond to the inductive action of ureteral bud derived from mesonephros mesenchyme?

What are the topographic, anatomic and functional relations between the derivates of metanephrogenic mesenchyme?

What are the necessary and sufficient conditions for the phenotype differentiation of the elements of metanephrogenic mesenchyme into the endothelial, epithelial and mesangial structures?

Are there any stem cells present inside completely differentiated renal parenchyma and what is their location?

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Is there a genetic control over the phenotype changes undergone by metanephrogenic mesenchyme?

What is the practical importance for the knowledge of relations between the derivatives of metanephrogenic mesenchyme in pathomorphogenesis and/or in nosologic classification of elementary renal lesions?

We proposed ourselves to perform a microanatomic analysis of the relations between the derivatives of metanephrogenic mesenchyme, that is necessary for the rigorous evaluation in optic microscopy of the structures involved in filtration, resorption and secretion inside renal excretory system. The purpose of the paper is to draw the attention on the phenotype changes undergone by metanephrogenic mesenchyme and on the relations between the derivate of this mesenchyme during ontogenesis dynamics; we also deal with their implications in pathology and regeneration processes.

Problems raised by semantic content and use of terms in the structural anatomy of renal parenchyma. There are numerous difficulties in understanding the anatomic descriptions in some books, due to the confusing semantic content of terms or their wrong use while nominating different structures. The international homologation of the terms used in the description of renal parenchyma was achieved on the following organization levels: macroanatomic, micro-anatomic and embryologic. The terms that nominate anatomic structures involved in time and space progress of renal functions such as filtration, resorption and secretion, still need to the emphasized: nephronum, corpusculum renale, glomerulus, mesangium, mesoderma intermediate, mesonephros, metanephros, induction, vasculogenesis.

a. Nephron (Nephronum) is an anatomic and functional system made of renal corpuscle (corpusculum renale) and tubular subsystem (tubulus renalis). The collecting duct (ductus colligen) and papillary duct (Ductus papillaris) are not parts of nephron Histologic Terminology (2008) incorporate them [1].

b. Renal corpuscle (Corpusculum renale) is a subsystem of nephron, made of renal glomerulus discovered by Malpighi (1666) [2] and glomerular capsule (capsula glomerularis) described by Bowman (1842) [3].

c. Renal glomerulus (glomerulus) is the structural unit of renal corpuscle and it is made of arterial blood capillaries (Vas capillare glomerulare) that form the glomerular capillary network (Rete capillare glomerulare) and intraglomerular mesangium located in the spaces between capillaries. The term of renal glomerulus is frequently used as a synonym to renal corpuscle. But facts related to vasculogenesis and tubule-genesis plead against it. Because of the contiguity relations that establish between the metanephrogenic mesenchyme derivatives – glomerular arterial capillaries network and proximal convoluted tube – there is a capsular space (Spatium capsulare; Spatium urinarium) limited by an external wall made of epithelial cells (Epithelioctyus parietalis) and an internal wall made of capsular visceral cells (Podocytus; Visceral cell of capsule). One can easily notice that the walls of the capsular space belong to proximal convoluted tube derived from metanephrogenic mesenchyme after tubule-genesis processes. The glomerular capillary network is also derived from metanephrogenic mesenchyme after vasculogenesis processes, offering a structural autonomy to renal glomerulus. Between the two derivatives from metanephrogenic mesenchyme establish contiguity relations after the adhesion of internal wall of capsular space to the glomerular arterial capillaries network. Thus, the anatomic and functional unit of glomerular filtration is formed; it is known as basal glomerular membrane (membrana basalis) that also includes intraglomerular mesangium.

d. Mesangium forms aglomerular stroma and is a supportive structure for glomerular arterial capillaries. In the structure of mesangium we find mesangial cells (Mesangiocytus) and a mesangial matrix (Matrix mesangialis) that play important roles in the regulation of blood flow and glomerular filtration.

e. Nephrogenic mesoderm, known as mesoderm intermedium, contains mesenchyme that will form the nephrogenic chord that will metameric segment and achieve two ephemeral structures in the superior and middle parts of embryo: pronephros and mesonephros. At the caudal part of embryo, still remains a non-segmented sector from the nephrogenic chord – metanephros. By metanephrogenic bud (Massa metanephrogenica, Metanephrogenic blastema), metanephros will contribute to the formation of definitive kidney after reciprocal induction to ureteral bud (Diverticulum metanephricum) developed from Wolff canal [6]. The absence of ureteral bud lead to the non-differentiation of metanephrogenic blastemal and consequently to renal agenesis.

f. Induction is a process involved in organogenesis; an embryonic region interacts with another region in order to influence its differentiation or behavior. There are two types of induction: 1. Primary embryonic induction that is at the basis of the formation of embryo dorsal axis; 2. Secondary induction – a group of cells respond to the action of another group of cells (example: epithelium-mesenchyme); it has a regional and genetic specificity.

g. Vasculogenesis is the process of blood vessel formation that take place by the production “de novo” of endothelial cells. It takes place during the embryonic development of blood vessels and during tumor growing in adults. Another process of blood vessels formation is angiogenesis that is different from vasculogenesis and consists of the burgeoning of preexistent vessels.

MATERIALS AND METHODS

The microanatomic study of the effects generated by reciprocal induction processes between the structures of nephrogenic mesoderm, was achieved on fragments of kidney harvested from three seven months old fletes, from adults aged 25 and 35 years old and from three embryos aged 8 weeks old. The fragments were fixed in 8% formaldehyde solution buffered at pH 7.2 and then embedded in paraffin using classical methods. 5 microns serried sections were
stained with Hematoxiline Eosine for general topographic orientation and MacManus Periodic Acid Schiff stain for the visualization of PAS positive neutral mucopolysaccharides. Four fetus, new born and adult kidneys were injected intrarterial with China ink to study the anatomic and structural variability of capillary networks and glomerular loops.

The sections were examined using Nikon Eclipse 80i research microscope. The images were captured by Nikon Digital Sight DS-Fi1 High Definition Color Camera Head, using Nis Element Basic Research software. Photos were processed in Adobe Photoshop CS5 software.

RESULTS

The study of relations between derivates of nephrogenic mesoderm (Mesodermo intermedium) was achieved through: microanatomic analysis of structures location within renal cortical, analysis of glomerular capillary networks phenotypic variability and the analysis of distribution and relations of intraglomerular mesangial matrix.

A. Microanatomic analysis of renal cortex

The study was performed on seriate sections, in frontal plane, through kidneys obtained from Homo Sapiens fetuses, aged 7 months and through metanephros of 8 weeks embryo. When examining with the 4X objective, we identified the cortical (Cortex renalis), medullar (Medulla renalis) and columnar (Columna renalis) regions of renal parenchyma, as well as sectors of cortical region (Labyrinthus corticis with Cortex corticis, Radius medullaris and Lobulus corticalis) (Fig. 1). When examining with the 10X and 20X objectives, within cortex corticis, we noticed the fibrous capsule of the kidney (Capsula fibrosa), ”spheroïd” shaped condensations of metanephrogenic mesenchyme (Massa metanephrogenica) which contribute to the formation of nephrovascular (Glomerulus) and secretory nephrotubular (Tubulus secretorius) structures. (Fig. 2 A, B). The examination with 20X and 40X objectives allowed the visualization of renal glomerular capsular primordium, as structural part of proximal tubular system that, within spaces, has the shape of italic “S” letter. (Fig. 2 B, C). From the analysis of seriate sections, we noticed the volumetric increase of glomerular primordium, by two simultaneous processes: numeric increase of blood capillaries by vasculogenesis process, the differentiation of mesangial cells and matrix on one side and the phenotypic transformation of glomerular capsule visceral layers cells into podocytes, on the other side. (Fig. 2 F-H).

B. Analysis of glomerular capillary networks phenotypic variability

The study of phenotypic variability of arterial glomerular capillary network was achieved on seriate sections through 7 months fetus kidney, new born and adult, with and without injecting chromatic tracer (China ink). When examining with the 4X objective, we identified the interlobar arteries within Bertin columns, which have parallel trajectory with longitudinal axis of renal pyramids. At the level of renal pyramids’ basis, they divide in order to form the arcuate arteries, with arcuate trajectory at the basis of pyramids (Fig. 1). On seriate sections of renal fragments injected with China ink, the presence of interlobular arteries located along Ferrein pyramids is easily noticeable (Fig. 1 and 3A). They form the afferent arteries of renal glomeruli (Fig. 3 A-D). The angles under which these arteriolas detach from interlobular arteries are variables: sharp angle with medial opening in its inferior third, right angle in the middle third and sharp angle with lateral opening in the superior third, underneath fibrous capsule. Glomerular afferent arteriolas, after a short path, spread in order to form a plexiform capillary network (Fig. 3 G-O). Between glomerular blood vessels, it is noticed the presence of various spaces of intraglomerular mesangial location (Fig. 3 I-O). When examining with 40X and 60X objectives, we visualized glomerular blood with sinusoidal trajectory and through their connection to the efferent arteriole, they form vascular loops (ansa) (Fig. 3 I-M) which branch off extraglomerular, achieving an important capillary network around convoluted tubules and Henle loop (Fig. 3 B, C, E,F).

C. Analysis of spatial distribution and relations of intraglomerular mesangial matrix

When examining with the 40X and 60X objectives the seriate sections of renal cortex stained/coloured with Mac Mannus Periodic Acid Schiff stain, we identified the presence of PAS-positive material, both at the level of parietal sheet of glomerular capsule, as well as the level of glomerular capillary networks (Fig. 4). Capillaries of glomerular network, grouped inside lobules, are sectioned under various angles and delineated by PAS-positive subendothelial membrane, with circumferential trajectory. The geometrical shape of glomerular arterial capillaries depends on the sectional plane: transverse, oblique or longitudinal. Within the dihedral angle determined by two planes that contain capillaries, we visualized a remarkable accumulation of PAS-positive, neutral mucopolysaccharides, in contiguity relations with subepithelial basal membranes of peripheral capillaries (Fig. 4 A/D; I J). This distribution of mucopolysaccharides determines the aspect of “angular mesangium”. When examining longitudinal sections from glomerular vascular lobules, it is easily noticeable the presence of PAS-positive mesangial matrix within the space between two arteriolar capillaries that determine a radial spatial distribution (Fig. 4 K-N).

DISCUSSIONS

Evolution in time and space of nephrogenic mesoderm mesenchyme determines the appearance of two fundamental structures which represent the basis of renal parenchyma morphogenesis: ureteric bud, developed within the inferior extremity of mesonephrotic duct and metanephrogenic blastema (Masa metanephrogenica), differentiated from caudal extremity of nephrogenic cord. The acknowledgement of reciprocal induction relations between ureteric bud and metanephrogenic blastema allows the understanding of renal parenchyma structural particularities and of determinant factors in anatomical-
Figure 1. Structural heterogeneity of renal cortex in a 7 months old human fetus. Underneath the "fibrous capsule", in "cortex corticis" area, one can visualize subcapsular nephron primordia that differentiate from metanephros mesenchyme by phenotype changes. 1. Fibrous capsule; 2. Cortex corticis; 3. Labyrinthus corticis; 4. Radii medulares (Ferrein); 5. Arcuate artery; 6. Pyramis renalis. Paraffin section. Hematoxyline Eosine stain. Micro-photos taken by Digital Sight DS-Fi1 High Definition Color Camera Head. X28.
Figure 2. Sequential imagery for the morphogenesis of structural elements forming renal corpuscle inside metanephros mesenchyme by vasculogenesis (glomerulus) and tubule genesis processes (capsula glomerularis). 1. Fibrous capsule; 2. Cortex corticis; 3. Metanephros mass; 4. Primordia of proximal convoluted tube and of glomerulus; 5. Nephron loop; 6. Tubulus proximalis; 7. Capsula glomerularis – stratum viscerale; 8. Capsula glomerularis – stratum parietale; 9. Primordia for renal glomerulus; 10. Capsular space; 11. Rete capsulare glomerulae. Paraffin section. Hematoxylin Eosine stain. Micro-photos taken by Digital Sight DS- Fi1 High Definition Color Camera Head. x70 (A); x140 (B-D); x280 (E, H); x420 (F, G).
Figure 3. The variable shape of renal glomerulus, the variable angles of afferent arteries branching from interlobular arteries, the variable trajectory of capillaries and capillary networks around tubules. 1. Glomerulus; 2. Interlobular artery; 3. Peritubular capillary plexus; 4. Arteriola glomerulus afferens; 5. Capillary blood vessel inside glomerulus; 6. Glomerular intercapillary space. Paraffin section. Intra-arterial injection with China ink. Micro-photos taken by Digital Sight D - Fi1 High Definition Color Camera Head. x70 (A); x140 (B-D); x280 (E, H); x420 (F, G).
Figure 4. Location and relations of PAS positive “matrix mesangialis” inside renal glomerulus and glomerular capsule. It is located inside the spaces between glomerular arterial capillaries near glomerular basal membrane. 1. Capsula glomerularis – stratum parietale; 2. Spatium capsulare; 3. Rete capillare glomerulare; 4. Glomerular capillary blood vessel; 5. Matrix mesangialis; 6. Vascular pole. Paraffin section. MacManus stain. Micro-photos taken by Digital Sight DS-Fi1 High Definition Color Camera Head. x140 (A, C, D, F); x280 (G-L); x420 (M, N).
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Table 1. Contribution to the knowledge of renal glomerulus structures and its homologation

<table>
<thead>
<tr>
<th>Authors</th>
<th>English Terms</th>
<th>International Anatomical Terminology</th>
<th>Eponyms</th>
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<tr>
<td>Antoine Ferrein (1693-1769)[4]</td>
<td>Renal medullary ray</td>
<td>Radius medullaris</td>
<td>Ferrein’s pyramids</td>
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<tr>
<td>Euxpere Joseph Bertin (1712-1781) [5]</td>
<td>Renal column</td>
<td>Columna renalis</td>
<td>Bertin’s columns</td>
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<tr>
<td>Gospar Friedrich Wolff (1735-1794) [6]</td>
<td>Mesonephric duct Mesonephros (1759)</td>
<td>Ductus mesonephricus Mesonephros</td>
<td>Wolffian duct Wolffian body</td>
</tr>
<tr>
<td>Sir William Bowman (1816-1892) [3]</td>
<td>Glomerular capsule (1842) Capsular space (Urinary space)</td>
<td>Capsule glomerularis Spatium capsulare (Spatium urinaria)</td>
<td>Bowman’s capsule Bowman’s space</td>
</tr>
<tr>
<td>Karl Wilhelm Zimmermann (1861-1935) [7]</td>
<td>Connective tissue for supports glomerular capillaries (1933) (Mesangium)</td>
<td>Mesangium</td>
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The study of microanatomic relations between the derivates of nephrogenic mesoderm mesenchyme determines the expansion of anatomical researches in the area of nephron’s structures morphogenesis and mostly of blood vessels genesis from renal glomerular capillary network. Our study, achieved through classical microanatomic methods highlighted the structural heterogeneity of renal cortex, the phenotypic variability of glomerular capillary network, the spatial distribution and the relations of intraglomerular mesangial matrix.

Felix (1912) [12] stated that, in order to understand the structural anatomy of renal glomerulus, the morphogenesis of glomerular capillary network most be known. The origin of renal parenchyma blood vessels was highly controversial. Sabin (1917) [13] promoted the idea of renal vessels development direct from mesoderm through burgeoning (angiogenesis). Edward (1951) [14] described terminal buds of renal artery branches which grow and occupy Bowmann capsule invagination, where they form glomerular capillary network.

Nowadays, it is considered that the evolution of metanephrogenic mesenchyme is determined by the interactions between ureteric bud and metanephrogenic blastema. The simultaneous development of renal blood vessels and differentiation of nephroblastic structures epithelium through vasculogenesis (differentiation in situ, from angioblasts) and/or angiogenesis (sprouting from the preexisting vessels) has been demonstrated (Saxen, 1987 [15]; Coffin et al., 1991 [16]; Hyink et al., 1996 [17]). Researches on culture organs and interspecies transplant experiments demonstrated the extrarenal origin of renal glomerular endothelial cells, through angiogenesis mechanism (Saxen 1987 [15]; Pinson et al. 1995 [18]; Berstein et al. 1981 [19]; Ekblom et al. 1982 [20]; Sariola et al. 1983 [21]). Although, studies of transgenic mice experiments suggested that glomerular endothelium develops through vasculogenesis (Hyink et al., 1996 [17]; Potter, 1965 [22]; Robert et al., 1996 [23]; Abrahamson et al., 1998 [24]). The presence of angioblasts, materialized by Flt-1 and Flk-1 in prevascular metanephrogenic blastema sustains the idea of vasculogenesis contribution to the development of renal blood vessels. The cells of metanephrogenic mesenchyme (Metanephritic mesenchimal cell) migrated within the depression of proximal convoluted tubule, through vascularogenesis, can organize the glomerular capillary network. This is achieved by the coalescence, in situ, of endothelial precursory cells (endothelial precursor cells; synonym: angioblasts) and then by connection to large vessels (Risau and Flamme, 1995) [25].

Molecular basis of genesis and the organization of renal vascularization are unknown. Still, the role of angiogenic factors was accepted (Saxen, 1987 [15]; Kloth et al., 1995 [26]). The presence of angioblasts with Fk1 and Fp11 within metanephrogenic blastema suggests that the vasculogenesis is involved in the development of renal vessels. In tissular metanephros cultures, the VEGF manifestation is weak. The addition of rhVEGF induces
the differentiation and proliferation of angioblasts within endothelial cells. VEGF and receptors play a key role in the development process of the kidney, through differentiation of endothelial cells, capillary formation and tubular epithelium proliferation.

An important role in the maintenance of structure and function of glomerular capillary ultrafiltration was assumed by a pericapillary interstitial tissue, named, according to Zimmermann (1933) [7] "supportive conjunctive tissue of glomerular capillaries" and homologated by International Anatomical terminology as mesangium [42]. Mesangial cells (Mesangiocytes) are incorporated within mesangial matrix (Matrix mesangialis). They are similar to muscular cells, possess a great variability in shape and volume and accomplish various functions: contractility, fagocitosis, synthesis of mesangial matrix and basal membrane, storage and transport of some complex chemical substances and not the least, they participate in the scarring process of glomerular lesions (Beregi, 1978)[27]. Mesangial matrix contains collagen fibers, mucopolysaccharides and participates in the balance of blood flow inside glomerular capillaries (Georgescu L, 1978)[28]. Mesangial cells contract under the influence of endothelins, control the blood flow inside capillaries and influence glomerular filtration (Mente, 1996)[29]. Sakai and Kriz (1987) [30] named "mesangial angle" the direct relation between mesangial matrix and glomerular basal membrane. It has a mechanic role, applying traction onto the glomerular basal membrane, counterbalancing the hydraulic force which determines ultrafiltration (Kriz et al., 1990) [31]. Proliferation of mesangial cells was noticed in glomerulosclerosis diabetes (Idaka et al., 1968) [32], in compensatory hypertrophy (Olivetti et al., 1980) [33], in immunologic glomerulonephritis (Couser, 1990) [34]. Similarly, was noticed the growth of mesangial matrix in different types of glomerulosclerosis and proliferative membranous glomerulonephritis (Heptinstall, 1983 [35]; Spargo et al., 1980 [36]).

Structural and functional anatomy of renal parenchyma was added a new subsystem, named Goormaghtigh juxtapaglomerular apparatus (Goormaghtigh's juxtapaglomerular apparatus) and homologated as Complexus juxtapaglomerarius. It was identified at the level of glomerular hilum, between afferent and efferent arterioles and glomerulus. Three structures have been included within this complex: macula densae, tunica media arteriolarum glomerularum and insula perivascularis mesangii (Table 1). Juxtapaglomerular complex inside renal cortex represents the major structure of rennin-angiotensin system and the most important place for hydroelectrolythic balance and preservation. Three populations of cells have been identified within juxtapaglomerular complex: Epitheliocytus maculae densae, Myocytus juxtapaglomerarius and Mesangiocytus extraglomerarius. Miocytus juxtapaglomerarius, located inside middle tunica of afferent arteriola, secrets rennin, as a response to Beta-1 adrenergic stimulation, to the decrease of renal perfusion pressure and to the decrease of NaCl concentration. Epitheliocytus maculae densae controls sodium (Na+) concentration in glomerular filtrate within proximal convoluted tubule. Mesangiocytus extraglomerarius has an agranular cytoplasm and phontotypical is similar with mesangiocytus intraglomerarius, but the functional role is still unknown.

The complexity of renal parenchyma morphogenesis processes by involvement of stem cells populations raise questions about the existence and localization of stem cells within adult kidney. Recent studies have identified locations of stem cells inside renal parenchyma in adults.Oliver (2004) demonstrated that the main location of stem cells is renal papilla, where the oxygen tension is low. Herzlinger (1994) [38]; Meshina et al. (2003) [39] and Challer et al. (2006) [39] consider that stem cells exist also at the level of cortical tubular system. Park et al. (2010) [41] also identified nests of stem cells within renal capsule. The presence of these cells in adult kidney, through their capacity of creating renal parenchyma cells, raises the question about their contribution in hemostasis, in tissue regeneration and renal failure therapy.

CONCLUSIONS

1. Anatomic, rigorous assessment of renal parenchyma, which has a heterogeneous structure, requires the systematic examination of embryo derivates from nephrogenic mesoderm mesenchyme (Mesoderma intermediate) existing within renal cortical and medullary.

2. Genesis and evolution of renal structures depend on reciprocal interactions and interductions between two embryonic conjunctive tissues emerged from nephrogenic mesoderm: mesonephros mesenchyme (Mesonephros) by "ureric bud" (Diverticulum metanephricum) and metanephros mesenchyme (Metanephros) by metanephrionic bud (Massa metanephrogenica, sin: Metaneprogenic blastaema).

3. Metaneprogenic bud assures the synchronic genesis of two renal structures groups: one nephrovascular (Glomerulus) through vasculogenesis processes and other nephrotubular, secretory (Tubulus secretarius) through transdifferentiation processes of metanephrogenic bud mesenchyme into tubular epithelium.

4. The junction between nephrovascular and secretory nephrotubular structures determines the shaping of two anatomic-functional compartments: one for filtration (capillary-podocytes barrier) and other for reabsorption-secretion (vascular-epithelial barrier)

5. Disturbances in genesis and evolution program of renal structures lead to the occurrence of congenital malformations.

6. Pathological processes, inflammatory and/or degenerative may determine side effects at the level of anatomic-functional embryologic compartments, through which a nosological classification of renal pathology can be achieved.
References


