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In Search of Imprints Left by the Impairment of Nephrogenesis

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Abstract
Clinical aspects dealing with the impairment of nephrogenesis in preterm and low birth weight babies were intensely researched. In this context it was shown that quite different noxae can harm nephron formation, and that the morphological damage in the fetal kidney is rather complex. Some pathological findings show that the impairment leads to changes in developing glomeruli that are restricted to the maturation zone of the outer cortex in the fetal human kidney. Other data show also imprints on the stages of nephron anlage including the niche, the pretubular aggregate, the renal vesicle, and comma- and S-shaped bodies located in the overlying nephrogenic zone of the rodent and human kidneys. During our investigations it was noticed that the stages of nephron anlage in the fetal human kidney during the phase of late gestation have not been described in detail. To contribute, these stages were recorded along with corresponding images. The initial nephron formation in the rodent kidney served as a reference. Finally, the known imprints left by the impairment in both specimens were listed and discussed. In sum, the relatively paucity of data on nephron formation in the fetal human kidney during the late phase of gestation is a call to start with intense research so that concepts for a therapeutic prolongation of nephrogenesis can be designed.

Introduction

The impairment of nephrogenesis is a clinical picture that causes a too early cessation of nephron formation in preterm and low birth weight babies [Black et al., 2012]. The resulting incidence rate of oligonephropathy is estimated to be between 8 and 24% of affected babies [Kandasamy et al., 2012]. The accompanying severe consequences for health in later life have been comprehensively communicated [Abitbol et al., 2016; Luyckx, 2017]. Clinical experiences further demonstrate that the impairment of nephrogenesis is evoked by intra- and extrauterine noxae that are quite different in molecular composition [Black et al., 2012; Stritzke et al., 2017]. These include restricted nutrition, particularly in terms of the protein or micronutrient intake, and poor antenatal perfusion with a lack of oxygen [Woods et al., 2001; Buchholz et al., 2016]. Also inflammatory cytokines, reactive oxygen species, and antiangiogenic factors are suspected to harm nephrogenesis [Sutherland et al., 2014; Nguyen et al., 2015]. The role of drugs administered to preterm and low

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birth weight babies is unexplained [Schreuder et al., 2014; Girardi et al., 2015]. To date, it is not known whether the mentioned noxae have diffuse targets or each of them interacts with a specific link in the chain of nephrogenesis [Barnett et al., 2017].

The damage to morphological structures in the fetal human kidney is complex. Pathological data demonstrate up to 18% morphologically abnormal glomeruli in the outer cortex of the kidneys in preterm and low birth weight babies [Gubhaju et al., 2009; Black et al., 2012]. Altered glomeruli are recognized by a dilated Bowman's space and a shrunken glomerular tuft [Sutherland et al., 2011]. Recently published literature reveals that prematurity leads not only to damage of developing glomeruli but also to a decrease in their total number [Callaway et al., 2018]. This finding is an important hint that noxae harm not only maturing glomeruli occurring in the maturation zone but also the stages of nephron anlage that are restricted to the overlying nephrogenic zone in the fetal human kidney.

During a search of relevant literature in the databases PubMed® and Google Scholar® it was noticed that the stages of nephron anlage in the rodent kidney had been intensively researched. In contrast, for the fetal human kidney no systematic description or corresponding illustrations were available. To contribute, the stages of nephron anlage in the fetal human kidney during the late phase of gestation were screened and illustrated. In addition, the reported sites of damage caused by the impairment of nephrogenesis were listed according to the frame of spatiotemporal nephron formation. This combination enables allocation of the described damage to concrete morphological structures.

Basics of Nephrogenesis in the Rodent Kidney

A broad spectrum of data was generated during the last decades with the help of rodent models dealing with acute kidney injury, chronic kidney disease, and congenital abnormalities of the kidney and urinary tract [Bao et al., 2018; Nigam et al., 2019]. A further input was obtained from related cell culture experiments [Rak-Raszewska et al., 2015; Little et al., 2019]. However, in these investigations mainly the initial kidney development was analyzed, while the process of nephrogenesis shortly before birth or a too early cessation was of only marginal interest [Wanner et al., 2019; Yermalovich et al., 2019].

The development of a nephron in the rodent kidney during early organogenesis starts with 6 different stages of nephron anlage, which is followed by the process of functional maturing.

Nephrogenic Niche

A nephrogenic niche is a transient construct that arises from the concomitence of competent $GDNF^+/Six2^+/CITED1^+$ nephrogenic mesenchymal progenitor cells and epithelial progenitor cells located at the tip of the branching ureteric bud [Carrol and Das, 2013; Chai et al., 2013; Combes et al., 2015; Lawlor et al., 2019]. During the subsequent nephron induction a reciprocal exchange of morphogens such as GDNF, Wnt, BMP, and FGF takes place.

Pretubular Aggregate

When the action of morphogens is successful, a group of induced mesenchymal progenitor cells separates, migrates, and aggregates to form a pretubular aggregate [Brown et al., 2013; O'Brien and McMahon, 2014].

Renal Vesicle

During the mesenchymal-to-epithelial transition, cells of the pretubular aggregate convert into a renal vesicle to develop characteristics of polar differentiation [Mah et al., 2000; Martinez et al., 2001; Liu et al., 2018].

Comma-Shaped Body

The comma-shaped body arises from cell multiplication and elongation of the renal vesicle [Georgas et al., 2008; Cui et al., 2015].

Early S-Shaped Body

The comma-shaped body further elongates, but at the same time through torsion it forms an early S-shaped body. Its proximal pole (medulla orientated) contains the presumptive glomerulus and proximal tubule, while the distal pole (renal capule orientated) forms the later intermediate and distal segments of the nephron [Wang et al., 2003; Heliot et al., 2013; Chung et al., 2017].

The pretubular aggregate, the renal vesicle, the comma-shaped body, and the early S-shaped body develop closely, spatially separated but in focal contact with the tip of a branching ureteric bud. Due to polar differentiation, the renal vesicle, the comma-shaped body, and the early S-shaped body are covered by a basal lamina.

Late S-Shaped Body

During development of the late S-shaped body the proximal, intermediate, and distal segments of the later nephron becoming established. At its proximal pole typi-

cal features of the glomerulus are formed. Very characteristically, at the distal pole the presumptive connecting tubule forms a functional connection with the related ureteric bud [Mah et al., 2000; Iino et al., 2001; Kao et al., 2012; Zhang et al., 2019].

Maturation

After formation of the late S-shaped body, succeeding steps of nephron development such as maturation of the glomerulus [Kreidberg, 2003; Schell et al., 2014], elongation of nephron segments [Jacobson, 1981; Kanwar et al., 2004; Little and McMahon, 2012; Yang et al., 2013], and functional differentiation [Murray et al., 2010; Gong and Hou, 2017] take place. The transition from the late S-shaped body to its maturation is locally and timely paralleled by the functional differentiation of the collecting duct (CD) tubule [Kloth et al., 1993].

Nephrogenesis Restricted to the Nephrogenic Zone

In the fetal human kidney during the period of late gestation the process of nephrogenesis is restricted to the outer cortex. However, the emergence of the nephron anlage and the process of nephron maturing are spatially separated. Consequently, the outer cortex consists of an outside positioned nephrogenic zone containing the stages of nephron anlage and an underlying maturation zone (Fig. 1; Table 1). Covered by the renal capsule, the nephrogenic zone lines, along the entire surface, respectively, each lobus of the fetal human kidney [Minuth, 2019a, b]. Sections stained, for example, with hematoxilin and eosin show it as a seam with a slightly pronounced color.

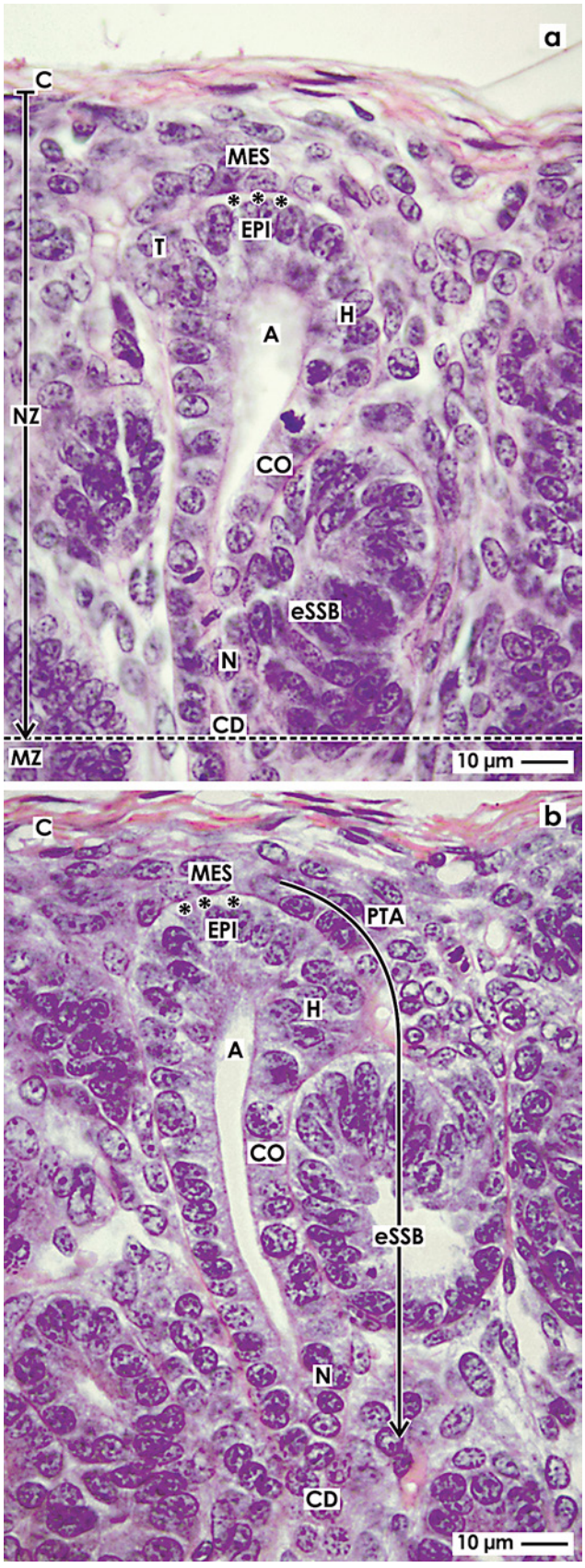


Fig. 1. a Nephrogenic niche (**a**) and initial pretubular aggregate (PTA) (**b**) in the nephrogenic zone (NZ) of the fetal human kidney seen by optical microscopy. **a** The outer border of the nephrogenic zone is covered by the renal capsule (C). A dotted line along the proximal pole (PP) of an early S-shaped body (eSSB) marks the inner border at the underlying maturation zone (MZ). The distal ending of a branched collecting duct (CD) tubule shows the formation of a CD ampulla (A). It is composed of a head (H), a conus (CO), and a neck (N) that opens into the CD tubule. A nephrogenic niche consists of epithelial progenitor cells (EPI) integrated into the tip (T) of a CD ampulla, an interface (asterisks), and overlying nephrogenic mesenchymal progenitor cells (MES). **b** When the process of induction was successful, some of the mesenchymal progenitor cells change their shape and become angular. Then they separate, aggregate, and migrate along the head of a CD ampulla. Further development (indicated by the arrow) of the nephron anlage takes place along the outer contour of the related CD ampulla.

Table 1. Identified publications dealing with the stages of nephron anlage in the fetal human kidney during the late phase of gestation

Stages of nephron anlage	Human kidney	Impairment	Damage caused by impairment of nephrogenesis (species)
Renal capsule/outer border of the nephrogenic zone	Minuth, 2019a, b	–	
Nephrogenic niche	Tank et al., 2012 Rosenblum, 2008 Oxburgh et al., 2017 Lindström et al., 2018a Menon et al., 2018 Minuth, 2018b	Abdel-Hakeem et al., 2008 Rumballe et al., 2011 Awazu and Hida, 2015 Rabadi et al., 2018	r r r r
Pretubular aggregate	Lindström et al., 2018b	Kispert et al., 1998 Tan et al., 2018	r r
Renal vesicle	Fanni et al., 2011	Barnett et al., 2017	r
Comma-shaped body	Faa et al., 2011	Almeida and Manda-rim-de-Lacerda, 2002	h
Early S-shaped body, no link to CD ampulla	Crisi et al., 2013	Rodriguez et al., 2004 Callaway et al., 2018	h pm
Late S-shaped body, anlage of glomer-ulus and nephron segments, link via the connecting tubule to the CD ampulla	Gröne et al., 2002 Batchelder et al., 2010 Dakovic Bjelakovic et al., 2018	–	
Inner border of the nephrogenic zone	Minuth, 2019b	Sutherland et al., 2011 Ryan et al., 2018	h h
Maturation zone			
Maturation of glomeruli including capillarization	Potter et al., 1965 Alpers et al., 1992 Naruse et al., 2000 Takano et al., 2007 Batchelder et al., 2013 Lindström et al., 2018c	Faa et al., 2010 Black et al., 2013 Gubhaju et al., 2014	h h h
Nephron segmentation	Ferre and Igarashi, 2019 Lindström et al., 2018d	Kandasamy et al., 2018	h
Differentiation	Baum et al., 2003	–	

h, human; r, rodent; pm, primate; –, not investigated.

The outer border of the nephrogenic zone is in contact with the inner side of the renal capsule (Fig. 1) [Minuth, 2019a, b]. It protects the developing kidney from harmful exogenous influences. The renal capsule consists of a tunica fibrosa with several strata and a rete capillare capsulare that guarantees the necessary supply of nutrition and respiratory gas. As the most inner layer of the renal capsule, the tunica muscularis makes contact with the outer border of the nephrogenic zone.

The inner border of the nephrogenic zone is artificial, since it is defined by a dotted line along parietal cells at the proximal (medulla orientated) pole of the S-shaped bodies (Fig. 1a) [Sutherland et al., 2011; Ryan et al., 2018]. This line also meets the branching sites of CD tubules [Minuth, 2019b]. In gestational controls the width of the nephrogenic zone is no more than 150 μm, while in the group of preterm babies it is significantly smaller (i.e., 100 μm) [Sutherland et al., 2011].

Thus, with an unexpectedly limited width of only 150 µm and sorted in vertical order, the process of nephron induction and the resulting stages of nephron anlage such as the pretubular aggregate, the renal vesicle, comma-shaped bodies, early S-shaped bodies, and late S-shaped bodies are located. The ureteric bud-derived ending of a CD tubule is essential for initial nephron formation [Rosenblum, 2008; Tank et al., 2012]. Each of them shows a bifid branching in the nephrogenic zone at its end [Al-Awqati and Goldberg, 1998]. On orientated microscopic slices one can recognize that not only the CD tubule but also its branch is orientated toward the renal capsule. Most importantly for nephron formation, an established branch dilates to form a collecting duct (CD) ampulla. As described later, the outer shape of a CD ampulla in the fetal human kidney is an important governing structure for the stages of nephron anlage.

The Stages of Nephron Anlage in the Fetal Human Kidney during the Phase of Late Gestation

To recognize the single stages of nephron anlage in a fetal human kidney, it is necessary to start systematically with a niche at the tip of a CD ampulla. It is located about 30 µm beneath the renal capsule (Fig. 1; Table 1) [Minuth, 2019a]. The resulting stages develop along a partially curved vector that goes along the tip, head, conus, and neck of the related CD ampulla (Fig. 1b). Compared to numerous investigations made in rodent kidneys, data on the stages of nephron anlage in the fetal human kidney is rare.

Nephrogenic Niche

The epithelial progenitor cells integrated into the tip of a CD ampulla and the overlying nephrogenic mesenchymal progenitor cells point to the center of a niche (Fig. 1a) [Rosenblum, 2008]. Data dealing with metric coordinates of niches in the nephrogenic zone of the fetal human kidney was recently published [Minuth, 2018a, 2019a]. Regarding a single niche, one must consider that it is a transient construct. In homology to the rodent kid-

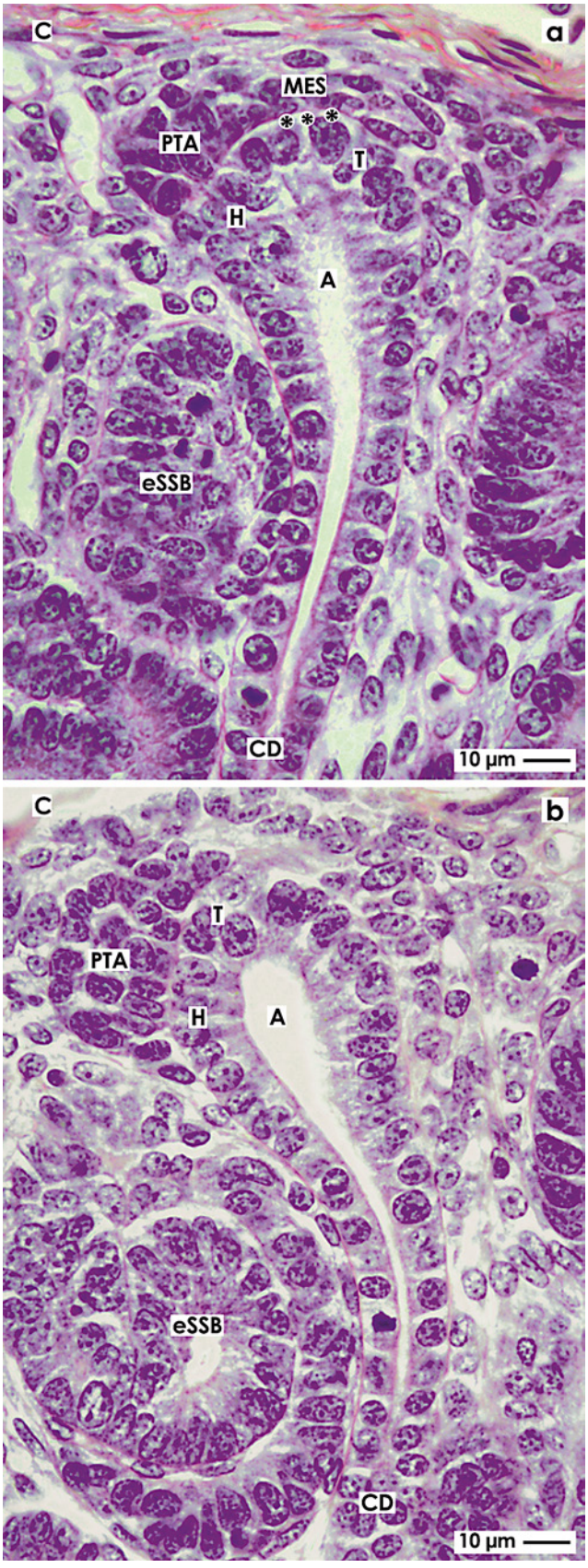
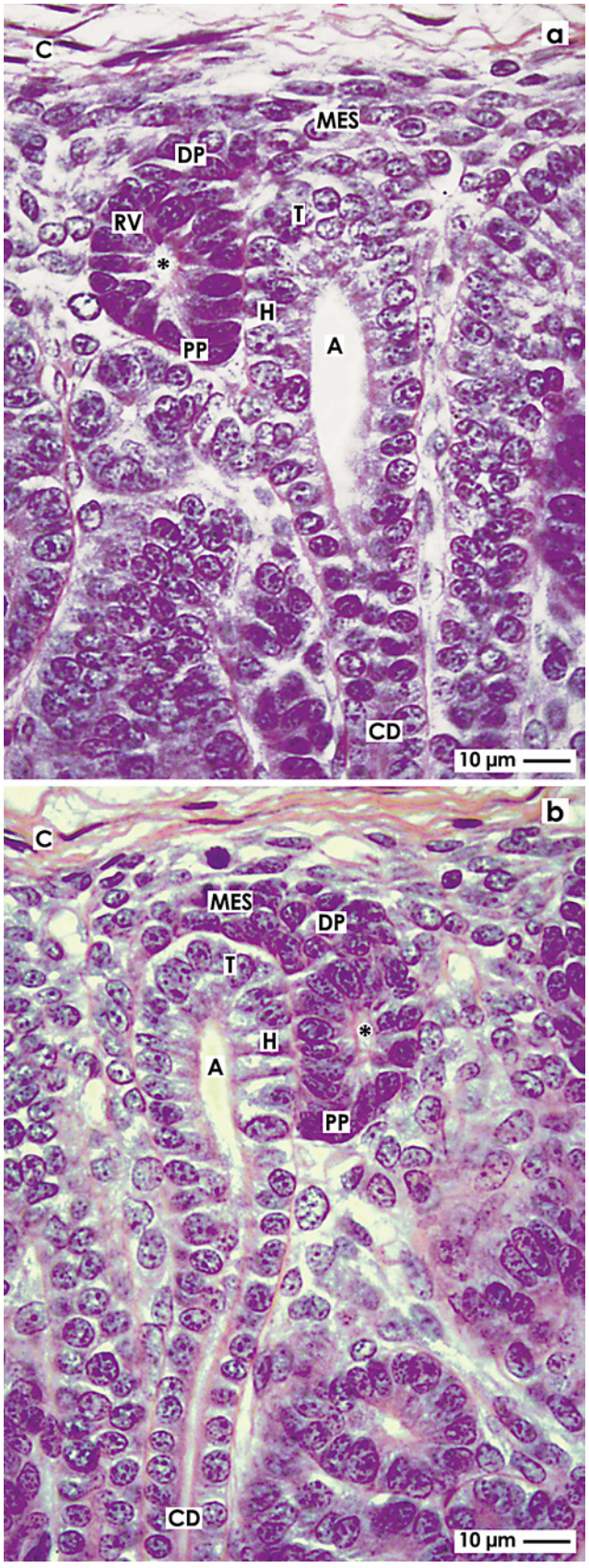


Fig. 2. Early (**a**) and advanced pretubular aggregate (PTA) (**b**) in the fetal human kidney demonstrated by optical microscopy. Induced mesenchymal progenitor cells form a strand. It extends first along the tip (T) (**a**) and then along the head (H) (**b**) of the related CD ampulla (A) to form a drop-like pretubular aggregate. (C) renal capsule, (eSSB) early S-shaped body, (CD) collecting duct.



ney, one also assumes for the fetal human kidney that for a successful nephron induction epithelial progenitor cells in the tip of a CD ampulla must first find and then remain vis-à-vis GDNF$^+$/Six2$^+$/CITED1$^+$ mesenchymal progenitor cells so that a reciprocal exchange of several morphogens can take place [Oxburgh et al., 2017]. Under an optical microscope one can observe that the basal aspect of epithelial progenitor cells at the tip of a CD ampulla does not touch the bodies of neighboring mesenchymal progenitor cells, but it is separated by an interface (Fig. 1). Orientated sections further exhibit that 2–3 layers of mesenchymal progenitor cells occur between the tip of a CD ampulla and the inner side of the renal capsule. Recently published literature shows that the biological profiles of progenitor cells in the niche exhibit similarities but also unexplained inequalities when rodent and human kidneys are compared [Lindström et al., 2018a, b; Menon et al., 2018].

Pretubular Aggregate

When the induction process is successful, a group of mesenchymal cells leaves the inner layer of GDNF$^+$/Six2$^+$/CITED1$^+$ mesenchymal progenitor cells to form a drop-like pretubular aggregate (Fig. 1b). During this process the shape of migrating cells becomes strikingly angular and interspaces between them appear.

Astonishingly, during further development the distal pole (renal capsule orientated) of the pretubular aggregate remains in contact with the inner layer of mesenchymal progenitor cells. By cell multiplication the broader proximal pole (medulla orientated) becomes elongated first along the tip (Fig. 2a) and then at the head (Fig. 2b) of the related CD ampulla. The lateral part of an establishing pretubular aggregate reaches the area of a vertically lining perforating radiate artery. The region between the head of a CD ampulla and the medial side of the pretubular aggregate is at that time marked by an interface. Only 1 article describing the recruitment of mesenchymal nephron precursors in the fetal human kidney was found [Lindström et al., 2018a].

Fig. 3. Primitive (**a**) and extending renal vesicle (RV) (**b**) in the fetal human kidney shown by optical microscopy. A pretubular aggregate transforms into the renal vesicle by elongation. Its proximal pole (PP) is found near the head (H), while its body is identified at the tip (T) of the related CD ampulla (A). The distal pole is in connection with nephrogenic mesenchymal progenitor cells near the tip of the CD ampulla. A renal vesicle exhibits a faint basal lamina and a lumen (asterisk). (C) renal capsule, (CD) collecting duct.

A renal vesicle was earlier described in the rodent kidney as a more or less stand-alone corpuscle with a central lumen and a basal lamina [Mah et al., 2000; Martinez et al., 2001; Liu et al., 2018]. Both characteristics reflect the mesenchymal to epithelial transition and the parallel occurrence of polar differentiation in the nephron anlage.

In contrast, when orientated sections of the fetal human kidney are regarded, it appears that a renal vesicle as a stand-alone vesicle does not exist (Fig. 3a). Instead, it is a fluent transition between the pretubular aggregate (Fig. 2b) and the later emerging comma-shaped body (Fig. 4a). Hence, a renal vesicle is recognized as an oval cell strand next to the head of the related CD ampulla (Fig. 3a). At its distal pole (renal capsule orientated) cells still make contact with the inner layer of mesenchymal progenitor cells. The cells of its proximal pole (medulla orientated) reach the border between the head and the conus of the related CD ampulla. Depending on the section plane, a lumen is visible near the proximal pole of a renal vesicle (Fig. 3b). Precise focusing further reveals that a faint basal lamina covers mainly the proximal pole of a renal vesicle. Astonishingly, only 1 article dealing with the transition of nephrogenic mesenchymal progenitor cells into a renal vesicle in the fetal human kidney was found [Fanni et al., 2011]. It was shown that MUC1 was not expressed in all of the renal vesicles.

Comma-Shaped Body

To understand the position of a comma-shaped body (Fig. 4), one has to imagine that the proximal pole (medulla orientated) of the renal vesicle is further elongated by migration and multiplication of cells (Fig. 3). During this process the medial aspect of the comma-shaped body makes contact first with the conus and then with the neck of the related CD ampulla (Fig. 4a). An interface of varying length between the comma-shaped body and the con-

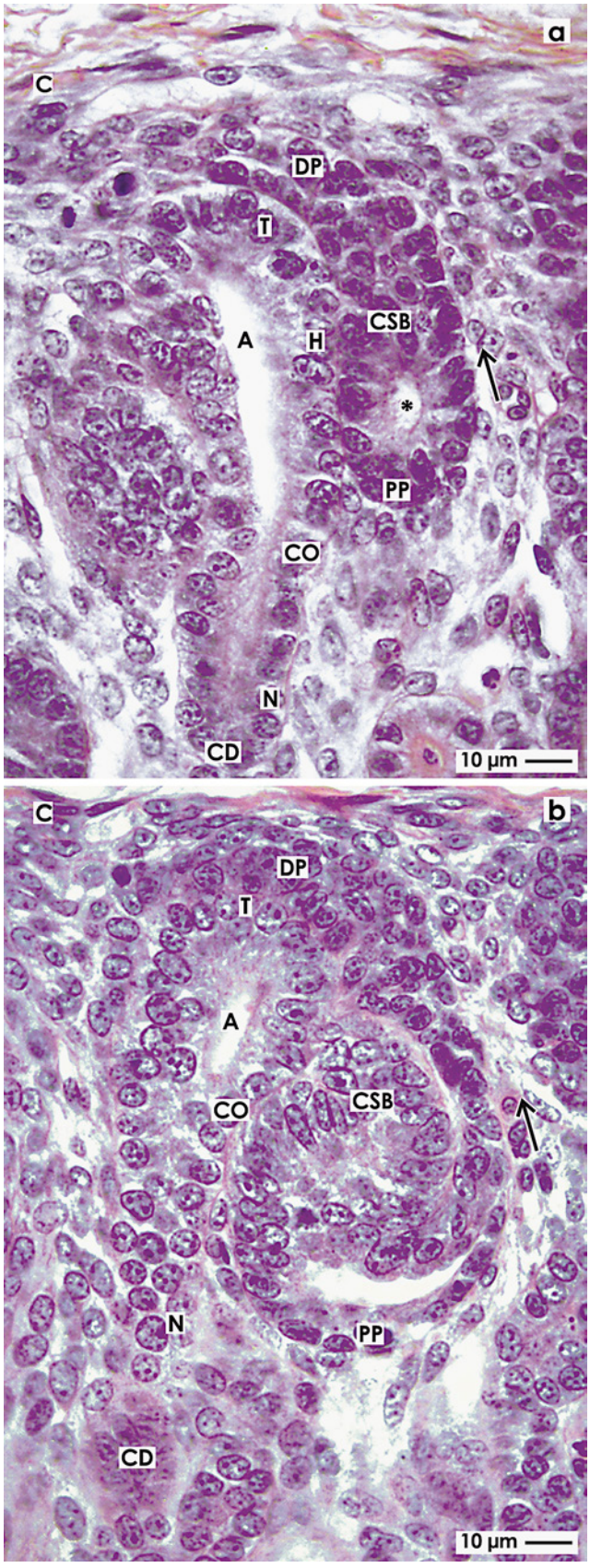
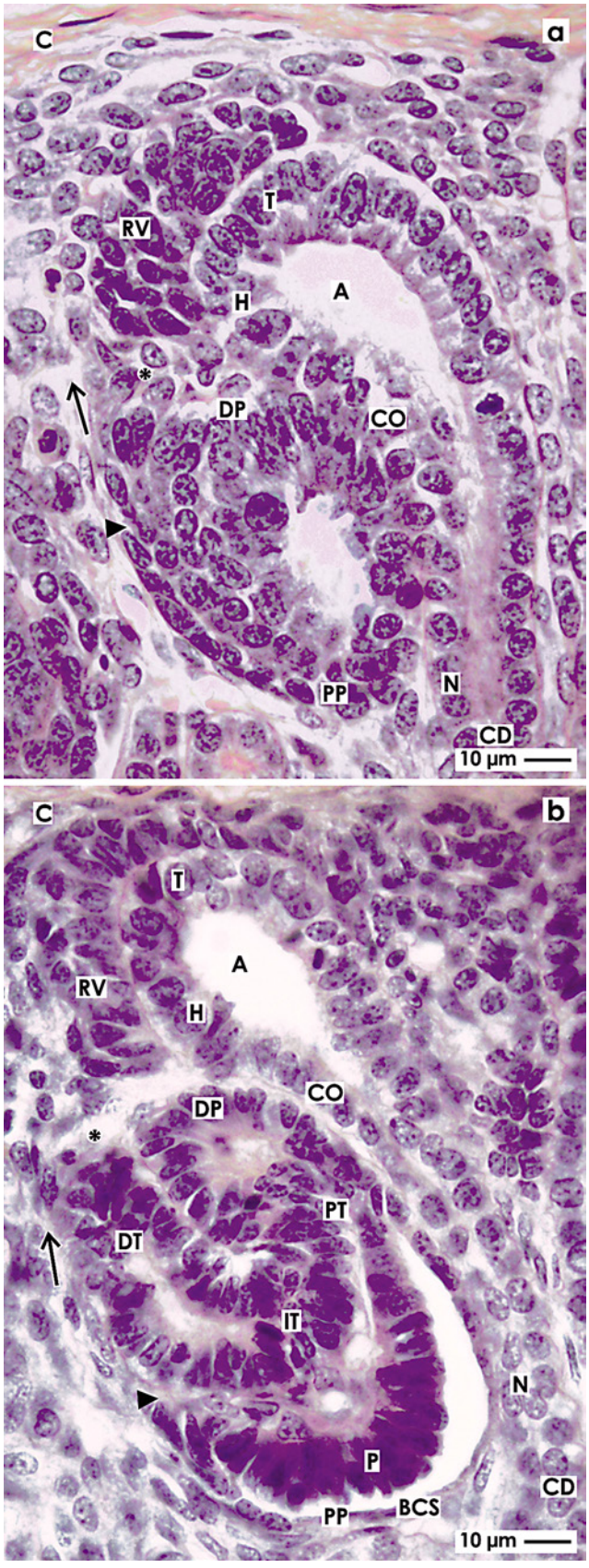


Fig. 4. Starting (**a**) and advanced comma-shaped body (CSB) (**b**) in the fetal human kidney shown by optical microscopy. **a** A comma-shaped body arises by elongation of the renal vesicle at its proximal pole (PP) along the conus (CO) and then the neck (N) of the related CD ampulla (A). At its proximal pole a lumen is visible. Its distal pole (DP) near the head (H) and the tip (T) of the CD ampulla is in contact with the mesenchymal nephrogenic progenitor cell layer. The lateral side is bordered by a perforating radiate artery (arrow), while its medial side contacts the CD ampulla (A). **b** The advanced comma-shaped body extends from the conus (CO) up to the neck (N) of the CD ampulla. At its proximal pole it exhibits broadening and curling. (C) renal capsule, (CD) collecting duct.



cavity along the head, conus, and neck of the CD ampulla is visible. Depending on the section plane, a lumen near the proximal pole (medulla orientated) of the comma-shaped body is visible. Its most extended position is identical to the proximal pole of the subsequently arising S-shaped body and, at the same time, to later developing parietal cells of the glomerulus [Minuth, 2019b]. One can further see that the cell strand of the comma-shaped body still makes contact with the inner layer of nephrogenic mesenchymal progenitor cells near the tip of the related CD ampulla. During the last phase of elongation the proximal pole of the comma-shaped body winds first around the neck and then retrograde along its conus (Fig. 4b). It is hardly to believe, but only a single article mentioning the comma-shaped body in the fetal human kidney was found [Faa et al., 2012].

Transition to the S-Shaped Body

A comma-shaped body converts into an early S-shaped body by elongation and curling at its proximal (medulla-orientated) pole (Fig. 5a). At this site the later glomerulus with its parietal (Bowman's capsule cells) and visceral (podocytes) epithelial cell layers and the future proximal tubule develops [Heliot et al., 2013]. At the distal (renal capsule orientated) pole a light district of cells is observed, which points to the initial obliteration and subsequent separation of the cell strand providing connection with nephrogenic mesenchymal cells (Fig. 4b). Thus, an attribute of the early S-shaped body is that the connection originally leading to the nephrogenic mesenchymal progenitor cells is interrupted (Fig. 5a). With time, in its middle the intermediate and the distal segments of the later

Fig. 5. Transition from the early (**a**) to the advanced (**b**) S-shaped body in the fetal human kidney demonstrated by optical microscopy. **a** The S-shaped body develops between a vertically lining perforating radiate artery (arrow) and the related CD ampulla (A) along its head (H), conus (CO), and neck (N). Typical for the very early S-shaped body is the zone of obliteration (asterisk) at the border between the head and conus of the CD ampulla. Here a separation between the forming S-shaped body and the nephrogenic mesenchymal cells takes place. As a result, the distal pole (DP) of the developing S-shaped body arises at this site. **b** The proximal pole (PP) of the early S-shaped body is orientated towards the medulla. Here the glomerulus starts to develop, including the parietal (Bowman's capsule cells, BCS) and visceral (podocytes, P) epithelial layers and the tubule segments. At the arising glomerular tuft a transverse cleft (arrowhead) indicates the ingrowth of endothelial cells. (PT) proximal, (IT) intermediate, and (DT) distal tubule segments, (C) renal capsule, (RV) rest of renal vesicle. (T) tip of the CD ampulla, (CD) collecting duct.

nephron are formed. This process happens near the conus of the related CD ampulla. Furthermore, one can observe a transverse cleft on the lower lateral side of the S-shaped body (Fig. 5b). Due to invasion of endothelial cells towards the here developing glomerular tuft, it appears that the entry of this cleft is orientated toward a vertically lining perforating radiate artery. With ongoing development, a second cleft is noticed which develops between the intermediate and distal tubule segments.

Astonishingly, only a single article dealing with physiological features of the early S-shaped body in the fetal human kidney was found [Crisi et al., 2013]. It shows that the tips of the ureteric bud (CD ampulla) do not express the calcium-sensing receptor, while on S-shaped bodies a first faint immunoreaction is detected.

Late S-Shaped Body

At the distal (renal capsule-orientated) pole of the developing S-shaped body a prominence invades the related CD ampulla at the border between its head and conus (Fig. 6a) [Iino et al., 2001]. Thereby a functional connection is formed which links the nephron anlage to the related CD ampulla via the future connecting tubule.

Some on the development of the late S-shaped body in the fetal human kidney is available. One of these articles shows the spatiotemporal expression of chemokines and chemokine receptors on the late S-shaped body containing the presumptive glomerulus [Gröne et al., 2002]. A further paper describes the binding of developmental markers especially on S-shaped bodies not in the fetal human but in the kidney of the rhesus monkey as a nonhuman primate model [Batchelder et al., 2010]. A current article informs about ultrastructural features of arising glomeruli in the late S-shaped body of the fetal human kidney [Dakovic Bjelakovic et al., 2018].

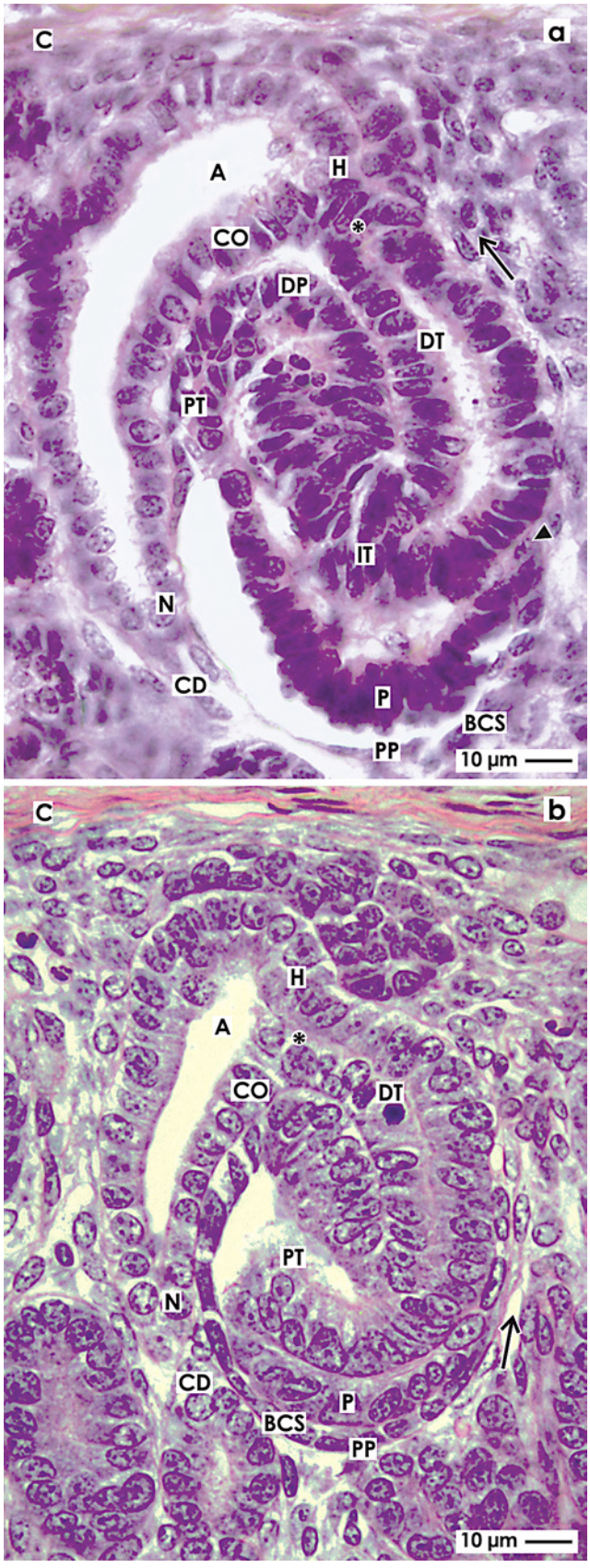


Fig. 6. Position and orientation of an earlier (**a**) and later S-shaped body (**b**) in the fetal human kidney seen by optical microscopy. These extend along the CD ampulla (A) between its head (H), conus (CO) and neck (N). **a** The proximal pole (PP) of the S-shaped body is orientated towards the medulla. Here the glomerulus develops including the parietal (Bowman's capsule cells; BCS) and visceral (podocytes, P) epithelial layers. Furthermore, the segments of the proximal tubule (PT), the intermediate tubule (IT), and the distal tubule (DT) are establishing. At its distal pole (DP) a prominence (asterisk) forms a connection at the border between the head and conus of the related CD ampulla. **b** The late S-shaped body is linked (asterisk) via the future connecting tubule with the related CD ampulla. (C) renal capsule, (CD) collecting duct (arrow) vertically lining perforating radiate artery.

Maturation

The stages of nephron anlage develop from the outer border (Fig. 1) towards the inner border of the nephrogenic zone (Table 1; Fig. 6). Yet, the late S-shaped body as the last stage of nephron anlage matures to become a functional nephron.

A series of articles is available which shows the transition of the late S-shaped body into the maturing glomerulus. Path-breaking morphological results were presented decades ago by Dr. Potter [1965]. In immunohistochemical experiments the primary expression of PDGF B-chain, PDGF receptor, and α-actin was investigated [Alpers et al., 1992]. Years later, a comprehensive immunohistochemical profile during glomerulogenesis was elaborated [Naruse et al., 2000; Takano et al., 2007]. Sound information dealing with the number and spatial distribution of glomeruli was obtained not in the fetal human but in the developing rhesus monkey kidney [Batchelder et al., 2013].

Concrete data dealing with segmentation of the nephron in the fetal human kidney is rare. A current investigation shows that hepatocyte nuclear factor-1β is an essential transcription factor that regulates the development of renal epithelia [Ferre and Igarashi, 2019]. Basic data on the proximal-distal axis of the developing nephron in the human kidney was recently presented [Lindström et al., 2018c, d]. Only 1 paper provides information about the peri- and postnatal development of the nephron [Baum et al., 2003].

The Imprints Left by Damage in Human and Rodent Kidneys

In order to make a differentiated pathological diagnosis, find the molecular break(s) in the chain of nephrogenesis, and develop reliable therapeutic concepts to prolong nephrogenesis, it is important to know about the morphological imprints left by the impairment. To inform about the different sites of damage, the available data was listed according to the frame of nephron formation (Table 1). This strategy enables assignment of pathological findings either to the maturation zone or to the nephrogenic zone and to the here contained stages of nephron anlage. For example, the occurrence of morphologically abnormal glomeruli [Gubhaju et al., 2009] and/or glomeruli with a dilated Bowman's space and/or with a shrunken tuft [Sutherland et al., 2011] point out that damage occurs in the maturation zone. Also an increase in abnormally developed glomeruli indicates that it is not the formation of the S-shaped body within the nephrogenic zone but rather the maturing of the glomerulus within the maturation zone that is affected. In contrast, a decrease in the total number of glomeruli exhibits that not solely the formation of glomeruli in the S-shaped body but also the previous stages of nephron anlage located within the nephrogenic zone can be harmed [Callaway et al., 2018]. The main problem in the current situation is that only few articles describing the concrete damage in the stages of nephron anlage are available.

Nephrogenic Niche

Detailed data on nephron induction and morphogen signaling in the nephrogenic zone of the rodent kidney is available, while related information about the fetal human kidney is lacking [Oxburgh et al., 2017].

For the process of induction it was shown that maternal food restriction in rats leads to an increase in mRNA for morphogenic molecules such as WT1, FGF2, and BMP7, while mRNA for Pax2, GDNF, FGF7, BMP4, Wnt4, and Wnt11 is decreased [Abdel-Hakeem et al., 2008]. Furthermore, it was demonstrated that cessation of nephrogenesis in the mouse alters the expression of genes in nephrogenic progenitor cells and decreases their amount and activity for proliferation [Rumballe et al., 2011]. In a further investigation it was shown that maternal nutrient restriction in rats decreases ureteric bud branching by up to 50% but surprisingly does not affect the duration of nephrogenesis [Awazu and Hida, 2015]. A current paper illustrates that maternal undernutrition during pregnancy increases fetuin-B in the developing mouse kidney [Rabadi et al., 2018]. In turn, an increase in fetuin-B limits nephrogenesis by reducing the number of $SIX2^+$ progenitor cells, stimulating their apoptosis via NF-κB upregulation and inhibiting their proliferative renewal via p21 control.

Pretubular Aggregate

Information about the pretubular aggregate in the fetal human kidney is not available. However, for the mouse kidney it was shown that morphogen Wnt4 is required for the condensation of induced mesenchymal progenitor cells and for the development of a pretubular aggregate [Kispert et al., 1998; Tan et al., 2018]. Interestingly, the necessary Wnt4 signaling is based on intact cell-to-cell contacts and sulphated glyoaminoglycans.

Renal Vesicle

Concrete data on the formation of the renal vesicle in the fetal human kidney was not found. However, for

mouse neonates it was shown that in comparison to controls malnutrition produces 76% fewer Six2$^+$ progenitor cells in the nephrogenic zone urgently needed for the induction and formation of nephron anlage [Barnett et al., 2017]. Furthermore, a decrease in the locally synthesized morphogens Wnt9b and Fgf8, essential for nephron formation, was measured. This again resulted in 64% fewer developed renal vesicles and 32% fewer nephrons than in controls. However, it was not discussed whether the decrease in Six2$^+$ progenitor cells limits the process of nephrogenesis or specifically the process of renal vesicle formation was affected.

Comma-Shaped Body

Only little information about the comma-shaped body in the fetal human kidney is available. One article showed that from the second to the third semester a significant reduction of comma-shaped bodies can take place [Almeida and Mandarim-de-Lacerda, 2002].

Early S-Shaped Body

Some more data was found regarding the early S-shaped body in the fetal human kidney. It was shown that basophilic S-shaped bodies were missing in longer-surviving preterm infants [Rodriguez et al., 2004]. In premature baboons it was demonstrated that a decrease in glomerular generation is paralleled by an increase in renal corpuscle area including S-shaped bodies [Callaway et al., 2018].

Late S-Shaped Body

Although it is clearly visible in the optical microscope, not a single article found describing the late S-shaped body or discussing whether disturbance of the link between the S-shaped body and the related CD ampulla is a signal that blocks the further progress of nephrogenesis in the fetal human kidney.

Maturation

A series of pathological results dealing with glomerulogenesis and tubulogenesis in the fetal human kidney were found. These have to be allocated to the maturation zone. For example, the number and spatial distribution of the here occurring glomeruli are among the basic parameters for recognition of impairment of nephrogenesis [Faa et al., 2010; Black et al., 2013; Gubhaju et al., 2014]. New insights into the functional maturation of nephrons were recently published [Kandasamy et al., 2018].

Finally, altered glomeruli and damaged stages of nephron anlage immediately raise the question of whether a strategy can be found for a therapeutic prolongation of nephrogenesis in preterm and low birth weight babies. The available literature summarized in Table 1 is the present answer. Unambiguously, it reflects an unexpected lack of knowledge on normal and pathophysiological aspects of the nephrogenic zone, stages of nephron anlage, and maturation of the nephron in the fetal human kidney. Furthermore, considering the incomplete vessel system, it is obvious that administration of an eligible drug must be adapted to the peculiar structural and functional features of the nephrogenic zone [Minuth, 2018b]. The less considered molecular interaction between the renal capsule and the nephrogenic zone is also important [Minuth, 2019a]. Most relevant for a therapeutic prolongation of nephrogenesis are morphogens and related agonists that influence the prospective nephron endowment [O'Brien et al., 2018].

Methodological Aspects

The here presented contribution is a guide that facilitates the identification of structures in the nephrogenic zone of the fetal human kidney. In this context, some hints for an optimal histological preparation are necessary. The general problem is that accidentally cut sections of the fetal kidney do not help to analyze the stages of nephron anlage. In order to investigate them in a repeatable manner, kidneys must be orientated for histological cutting. Consequently, one should keep in mind that the nephrogenic zone and contained stages of nephron anlage extend along the entire surface, respectively, of each lobus of the fetal human kidney (Fig. 1). Due to its exposed position, one has to prevent a damage to the kidney surface during histological preparation [Minuth, 2019b]. Consequently, one should best hold a fetal kidney only on its hilum and avoid touching the renal capsule with fine forceps.

To obtain repeatable perspectives, blocks of parenchyma have to be orientated before embedding and during histological cutting as was earlier described [Minuth, 2019b]. Following this advice, a fixed kidney is cut from the capsule towards the papilla of a lobus. Then the medulla is separated from the cortex. Embedding of the tissue block is performed so that the axis of CD tubules lines perpendicular to the capsule. After trimming the lateral sides of the block, sections with a comparable perspective can be produced by the microtome. Following this strategy, the nephrogenic zone and contained collecting tubules, branching sites, CD ampullae, and nephrogenic

mesenchyme, as well as all of the stages of nephron anlage, become visible in a regular spatial relation to the renal capsule.

For the here shown illustrations, fetal human kidneys of gestational age between weeks 16–18 and later were selected from the stock of preparations used for the Course of Microscopic Anatomy for Medical Students at the University of Regensburg. According to routine methods, specimens were fixed in paraformaldehyde solution and embedded in paraffin wax. Then, sections (5-µm thickness) were produced and stained with hematoxylin and eosin for analysis using an optical microscope. Screening of the stained sections was performed using a Leica DM750 microscope (Leica Microsystems, Wetzlar, Germany) equipped with a Basler Microscopy Pulse 5.0 camera (Basler AG, Ahrensburg, Germany). The here shown illustrations of histological sections are originals without any reworking. The images were processed with CorelDRAW X7 (Corel Corporation, Munich, Germany) only for inserting of the labels shown. To obtain information about metric parameters, images were analyzed with the same program.

Conclusion and Perspectives

The impairment of nephrogenesis in preterm and low birth weight babies is an unresolved biomedical issue. It is caused by several noxae, which cause in the outer cortex of the fetal kidney a too early termination of nephrogenesis. The damage results in oligonephropathy with severe consequences for health later in life. While abundant data on the development of the rodent kidney is available, the lack of knowledge about nephrogenesis in the fetal human kidney is the basic obstacle to find a concept for a therapeutic prolongation of nephrogenesis. To contribute from a microanatomical point of view, the stages of nephron anlage were described and recorded. The resulting take-home messages are:

During the phase of late gestation, the formation of a nephron in the fetal human kidney starts with the 6 stages of nephron anlage that are restricted to the nephrogenic zone.

During normal development the nephrogenic zone has a width of 150 µm and extends along the entire organ surface, respectively, each lobus.

The induction of a nephron as the first stage of nephron anlage takes place at the tip of a CD ampulla.

The stages of nephron anlage are the nephrogenic niche, the pretubular aggregate, the renal vesicle, the comma-shaped body, the early S-shaped body, and the late S-shaped body.

The sequence of nephron anlage proceeds in a spatiotemporal frame that lines from the inner side of the renal capsule to the inner (artificial) border of the nephrogenic zone.

The stages of nephron anlage develop in close spatial relation with the related CD ampulla from its tip, head, and conus and finally to its neck.

Each stage of nephron anlage has a special orientation, position and shape.

Statement of Ethics

The author declares that this paper is in accordance with ethical standards.

Disclosure Statement

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