Immune processes at the level of the nephron. The immune system and its compartmentalization

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Abstract

The immune system, although regarded as a functional aggregate that acts as a whole, is compartmentalized at the level of many organs, allowing a division of labour during an immune response. The concept of compartmentalization has been recently highlighted in the lymphoid organs and signalled at the level of the digestive and the respiratory tracts.

The immune processes take place at the level of the nephron in well-defined compartments, corresponding to the morpho-functional compartments of the nephron: glomerular, tubulo-interstitial and juxtaglomerular.

The activation of the nephron compartments during immune processes is related to the immune receptors, especially Toll-like receptors. An important role during immune processes in these compartments is played by ATII receptors.

The immune compartmentalization of the nephron is based on the compartment specificity of chemokines, dendritic cells and T and B cells and complement. The immune-mediated diseases follow the immune compartmentalization of the nephron: glomerular, tubulointerstitial and vascular diseases.

The proposed compartmentalization concept of the nephron comes within the general compartmentalization of the immune system in lymphoid organs and in other organs and tissues.

Key words: glomerulonephritis, tubulo-interstitial disease, vascular disease.


Introduction

The pathological processes taking place in various organs have sometimes an important immune component. In some organs antigens preferentially locate in certain morpho-functional compartments. Thus, in the kidney some antigens will locate at the level of the glomerulus, while others will locate at the level of the interstitium. In organs like bowel, lung and kidney, the conflict between the multitude of antigens and the immune system will develop in an organized manner that respects their morpho-functional units.

The conflict between antigens and the immune system does not take place chaotically, the functioning of it requires a good organization. The immune system, although regarded as a functional aggregate that acts as a whole, is compartmentalized at the level of many organs that allow a division of labor during a normal or pathological response. Thus, at the level of lymphoid organs, the immune cells from this compartment will be directed towards the affected organ. At the same time an organisation of the immune system is discussed at the level of nonlymphoid organs.

Recently, Crivellato et al. [1] have reviewed the compartmentalization of the immune system at the level of the lymph nodes, spleen, and thymus, both anatomically and functionally. At the lymph node level, there is a cortical region where B-cells prevail and a paracortical region where...
T-cells predominate. Between the two zones, there is an interconnection, the third region being the medullar section. The thymus displays a lobular pattern with distinct cortical and medullary compartments. The spleen shows compartmentalization as well.

The question of the compartmentalization of the immune system has also been raised for other organs. Brandtzæg et al. [2] mention the regional specialization of the immune system at the level of the digestive tract with the formation of microcompartments. Becker et al. [3] describe the compartmentalization of the immune response to inhaled grain dust.

The compartmentalization of the immune system ensures better functionality with regard to the pathological processes that take place in different tissues or organs. According to Crivellato et al., antigens, antigen-presenting cells, and T cells are subject to anatomical constraints in their movement. Specialized sub-compartments may facilitate the contact between cells and the recognition process. At the same time, this could ensure the most favorable conditions for signaling and induction mechanisms [2].

From a morphofunctional point of view, the nephron is divided into two zones: the glomerular and the tubulointerstitial one. From the immunological point of view, the diseases of the nephron are divided into immune glomerular, and tubulointerstitial nephropathies. This suggests the existence of a specialization of the immune system within a glomerular or tubulointerstitial zone that delineates these two distinct immune compartments.

Both clinical and immunological observations create the premises for the compartmentalization of the immune system at the level of the nephron. This is reflecting the current clinical practice, such as glomerular nephropathies, tubulointerstitial diseases, and vascular nephropathies. The immune-mediated diseases of the nephron closely follow the anatomical and clinical division. Immune compartments will define well structured morphofunctional zones where an individualized immune activity takes place. Intrarenal immune processes take place in morphofunctional compartments of the nephron, that become compartments with immune quality: glomerular, tubulo-interstitial and juxtaglomerular compartments.

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**Fig. 1.** Immune compartments of the nephron.
The paper sets itself to discuss:
• the intrarenal immune system, how it is manifested in normal conditions and in the conditions of an immune aggression at the level of the nephron,
• the compartmentalization of the immune system at the level of the nephron, and what are the arguments that sustain it,
• the third objective of the paper is represented by a synthetical view of the first two, of the compartmentalization at the level of the nephron respectively.

Intrarenal immune system of the nephron

In normal conditions in the lack of an immune aggression in the morphofunctional compartments of the nephron, there are resident cells as well as a reduced number of bone marrow derived immune cells. Resident cells, besides their organ-specific function, express some immune properties. The typical example is represented by mesangial cells that possess contractile properties, but also immune ones, having the capacity for phagocytosis.

The resident cells have immune properties more or less well defined and can constitute an immune defense component of the immune system of the organism, not strictly immunologically specialized, with bivalent functions, a main one related to the organ and the structure from which they originate, and an optional immune function that becomes active when they interact with an antigen.

It is worth mentioning that a macrophagic system is described at the level of tissues formed of mesangial cells in the kidney, Kupffer cells in the liver, alveolar macrophages in lung, microglial cells in brain etc.

We believe that the participation of resident cells in different organs is not limited only to phagocytic processes but is more complex because other tissular resident cells, including the kidney, participate to immune processes through a complex of factors.

It is considered that besides the classical immune system with specialized structures organized a tissue level, resident cell of different organs and tissues display alongside their functional specialization also immune properties. By means of this a defense system of the body takes shape.

These cells will allow appropriate immune defense mechanisms in the kidney, as resident cells in the nephron, although endowed with immune properties, cannot face an immune aggression. In these conditions bone marrow derived cells are needed to complete immune defense processes.

Immune cells originating from the bone marrow: polymorphonuclears, dendritic cells, T-cells, B-cells, stem cells occupy morphofunctional compartments of the nephron and display a professional immune activity.

During renal diseases, at the level of the interstitium, an inflammatory infiltrate with B cells is found, forming follicular aggregates together with T cells. B cells are located in the center of aggregates, being surrounded by T cells. They have been considered as remains of follicles in lymph nodes [4].

These structures, with a complex microarchitecture similar to that of lymphoid organs, present in chronically inflamed organs, have been referred to as tertiary lymphoid organs [6]. Steinmetz et al. characterised intrarenal lymphoid clusters of patients with lupus nephritis and ANCA associated nephritis. They identified four increasingly organized levels of intrarenal aggregates from scattered B cells to highly compartmentalized B cell clusters with central follicular dendritic cell networks [7]. Intrarenal immune processes take place in morphofunctional compartments of the nephron, that become compartments with immune quality.

As is the case with several immune organs (thymus, spleen, lymph nodes), in order to act properly the nephron displays component cells in well defined immune compartments. The kidney, at the level of the nephron, like other organs (bowel) – will delineate functional compartments. Resident cells from these compartments that have also immune capacities will develop an immune activity collaborating with other resident cells, as well as with bone marrow-derived immune cells. This is the reason why we
have considered that these morphofunctional compartments of the nephron can be defined from the point of view of these activities as immune compartments when we refer to the immune processes that take place in the nephron. These observations delineate an immune compartmentalization of the nephron.

**Compartmentalization of the immune system of the nephron**

There are many arguments pleading for the fact that immune processes occur in well-defined compartments in the nephron.

They are based on observations regarding:

- chemokines,
- immune cells: dendritic cells, B and T cells,
- local synthesis of the complement system components and disposition of circulating complement,
- clinical pathology: immune-mediated renal diseases: glomerular, interstitial and vascular,
- receptors.

**Chemokines**

Organ or compartment specificity of single chemokine receptors of CCR is a common finding in chemokine biology [8]. At the level of the nephron the chemokines secreted by local cells, from their morphofunctional compartments, trigger infiltration of leukocytes. According to Anders et al. [9] several chemokines specifically mediate the recruitment of leukocytes in the initial phase of renal injury, depending on the compartment involved. The local production of chemokines initiates the recruitment of immune cells into the glomerular compartment during consecutive glomerulonephritis; the production of chemokines at the tubulointerstitial level has the same effect in the tubulointerstitial compartment during interstitial nephritis. CCR1 mediates leukocyte recruitment and subsequent renal fibrosis, renal TGF-β1 mRNA expression being significantly reduced of the interstitial fibroblasts CCR1 deficient mice [10].

Application of CCR1 antagonist BX471 in the MRL/lpr mouse model of lupus nephritis reduced the amount of macrophage and lymphocyte migration into the interstitium, but not in glomeruli. Ninichuk et al. also observed that treatment with CCR1 antagonist, BX471, improved survival of COL4A3 deficient mice. These mice present less interstitial macrophages, apoptotic tubular epithelial cells, tubular atrophy, interstitial fibrosis and less globally sclerotic glomeruli [9].

In an immunohistochemical study of renal biopsies from different forms of glomerulonephritis, Segerer observed a different distribution of positive cells for CCR5 in the infiltrate at the level of the nephron. These cells were well represented at the level of the interstitium, while the number of CCR5 positive cells within glomeruli was very low [11].

Experimental studies have proven that chemoattractant protein 1 promotes macrophages, mediates tubular but not glomerular injury in nephrotoxic serum nephritis [12].

Compartment – specific expression and function of the chemokine IP-10/CXCL-10 in a rat model of renal endothelial microvascular injury was reported by Panzer et al. [13]. They have discussed the hypothesis of the heterogeneity of endothelial cells from different vascular sites, that may mediate compartment-specific T cell and monocyte recruitment in inflammatory renal disease.

**Dendritic cells, B and T cells**

Immune compartmentalization at the level of the nephron is also supported by the differential distribution of dendritic cells at the level of the nephron. At the level of the glomerulus, dendritic cells are scarce. In the normal kidney in mice, dendritic cells are well represented in the interstitium, while in the glomerulus they are rarely present (1/50 of the glomeruli) [14]. In human renal biopsies, a similar distribution of dendritic cells has been observed.

Concerning the specific compartment expression of dendritic cell markers in human glomerulonephritis, Segerer et al. [15] have proven that, in proliferative glomerulonephritis, numerous myeloid dendritic cells were found in both glomeruli and the tubulointerstitial space, but myeloid dendritic cell markers (DC-SIGN) were identified only in the interstitium.

It has to be noted that, in inflammatory renal diseases, at glomerular level, not only dendritic cells are rarely present but also B and T cells [6].

One explanation for this would be the absence of lymphocytes draining the glomerulus. Segerer considers that the absence of dendritic cells from the glomerulus, the lack of glomerular lymphatics, and the very rare glomerular T cell infiltrates may indicate that the glomerulus represents a special immunological niche [15]. According to Segerer et al. the glomerulus might therefore react predominantly by an innate response site; the tubulo-interstitium with its resident dendritic cells would be the site of an acquired immune response [15].

The distribution of B cells predominantly at the level of the interstitium has been observed in lupus and ANCA-associated nephritis. Steinmetz et al. have identified intrarenal aggregates from scattered B cells to highly compartmentalized B cell clusters with central follicular dendritic cell networks [7].

B and T cell compartmentalization has been found in IgA nephropathy. Thus, CD20 positive B cells and CD3 positive T cells were rarely found in glomeruli in IgA nephropathy, while in interstitial inflammation, both B and T cells, which can form lymphatic nodules, are present [6].

**The complement system**

The complement system has some characteristics in relation to the morphofunctional compartments of the
kidney, related to the immune processes taking place in the nephron. The elements of the complement system may have dual origin: they may be synthesized at the level of some renal cells or they may come from the circulation, with the depositing of them at the level of renal structures.

Expansion of complement genes in glomerular mesangial and epithelial cells has been observed in glomerular diseases. In interstitial diseases complement synthesis occurs predominantly in the tubular epithelium [16].

However, in glomerular diseases, the locally synthesized complement seems to be playing a small part in the accumulation of immune complexes. According to Sheerin et al., accumulation of immune complexes in glomerular diseases is independent of locally synthesized C3 [17-18].

Experimental data and clinical evidence seem to indicate that the circulating pool of complement underlies much of the pathology traditionally associated with glomerular injury [19]. At the glomerulus level, in pathological processes, the main role is played by circulating complement, with a different disposition of the complement in the two compartments of the nephron. The renal tubulo-interstitium is the main domain of local synthesis of complement, mainly C3, principally expressed by the tubular epithelium. Experimental studies in mice suggest that local synthesis of complement from renal epithelial cells is a critical mediator of tubular damage proteinuria – associated renal disease [17].

Clinical pathology

Clinical pathology of the nephron brings important arguments regarding the compartmentalization. The pathology of renal glomerular and tubulo-interstitial immune mediated diseases is well structured. Primary glomerulonephritis (GN), as well as secondary ones in which immune processes are very important are the expression of immune pathology in the glomerular compartment. Some diseases, such as minimal change disease, are restricted to this compartment.

1. The glomerular immune compartment can be involved in different ways:
   • it can be the only manifestation of a glomerulopathy: such as in minimal change GN [20],
   • the glomerular immune compartment can secondarily affect the tubulo-interstitial one: in membranous GN [21],
   • the glomerular immune compartment can be affected concomitantly with the tubulo-interstitial one: in lupus nephritis,
   • a glomerular involvement can rarely follow a tubulo-interstitial one. In reflux nephropathy a glomerular injury can follow the tubulo-interstitial one with production of focal segmental glomerulosclerosis [22-23],
   • an important injury of the glomerular immune compartment is associated with tubulo-interstitial involvement due to a large communication between the two compartments: in rapidly progressive GN [24].

In the glomerular immune compartment there are the following cells:

• Resident immune cells:
   The mesangial cell represents the main element of the local immune system in the glomerular immune compartment. It presents complex immune properties but is not a specialized immune cell. It also presents other properties, such as contractile or phagocytic ability. During the process of phagocytosis, mesangial cells can take up immune complexes that are deposited in the mesangial region.

   Endothelial cells possess adhesion molecules that permit the attachment of circulating immune cells [25]. Endothelial cells have endocytosis capacity. Tykocinski et al. suggest that endothelial cells may function as semiprofessional or optional antigen presenting cells [26].

   The epithelial cell (podocyte) has receptors for C3b and C5 that permit attachment and possible activation of the complement system. Epithelial cells intervene in the uptake of macromolecules that have passed through the glomerular basement membrane and reach the subepithelial space [27-28].

• Bone marrow derived cells:
   T and B cells – Hooke et al. have shown through monoclonal antibodies at the level of normal glomeruli 1-2 leukocytes, primarily monocytes and rarely granulocytes.

   Dendritic cells (DC) – at the level of the glomerulus, dendritic cells are rarely observed. With relation to the interstitium, where they are numerous, they would be 50 times less numerous.

We present the main glomerular diseases in relationship with the immune compartmentalization of the nephron:

A. Glomerular nephropathies in which the immune process is limited primarily to the glomerular immune compartment

   Minimal change disease (MCD) represents a glomerular disease in which the glomerular immune compartment is affected but the tubulo-interstitial one is spared. The involvement of the glomerular immune compartment arises due to circulating T cells, which produce a glomerular permeability factor that causes podocytic lesions with foot processes effacement [29-30].

   Tubular epithelial cells are not affected by the permeability factor produced by T cells. An explanation can be that tubular cells present reduced NF-κB activation in comparison to other cells, such as podocytes [20].

   The participation of the tubulo-interstitial immune compartment should be present because of proteinuria, which can be regarded as an independent risk factor for poor outcome in most types of glomerular disease [31]. In MCD, inflammatory processes at the level of the glomerulus are usually absent. It is possible that the absence of factors in the urine
that participate in the inflammatory process (e.g., such as cytokines, chemokines, complement system components, and growth factors) explains both the absence of tubulointerstitial lesions and the favorable outcome of this disease.

**B. Glomerular nephropathies in which the immune process takes place in the glomerulus with consecutive involvement of the tubulointerstitial immune compartment**

In focal segmental glomerulosclerosis (FSGS), the immune processes initially take place in the glomerular immune compartment. Alterations of T cells have been described, and these alterations have a role in the production of glomerular lesions. They produce vascular permeability factors. The permeability factors in FSGS are different from those in MCD [32] and are associated with both foot processes effacement and the production of the nephrotic syndrome [33-34].

The presence of glomerular immune deposits, such as IgM, IgG, and C3, may be due to the trapping of immune complexes from the circulation at injured zones. An important role is played by TGF beta, which intervenes in fibrogenesis. TGF beta is involved in glomerular sclerosing lesions. The glomerular lesion takes place in the glomerular immune compartment and extends into the tubulointerstitial compartment, which is secondarily affected.

Tubulointerstitial lesions in FSGS may be primarily attributed to two elements: misdirection of the glomerular filtrate and proteinuria. Misdirection of the filtrate of the glomerular capillaries adherent to Bowman’s capsule into the paraglomerular space has recently been demonstrated [35]. In FSGS, proteinuria with urinary elimination of TGF-beta may be involved in the production of tubulointerstitial lesions. Also glomerular ultrafiltration of complement system components and intratubular C5b-9 formation regulates peritubular myofibroblast accumulation [36-37].

**Membranous GN** is a GN mediated through immune complexes (IC), especially those formed in situ. These are located on the external side of the GBM with complement deposits. Couser suggests that Ig and C3 deposits associated with formation of C$_{5b-9}$ produce large alterations in glomerular protein permeability [38]. Activation of the alternate pathway and C$_{5b-9}$ generation on the podocyte in relation to complement regulatory protein (Cry, CDS9) dysfunction takes place [39]. Couser describes the pathogenic role of sublytic C$_{5b-9}$ in the occurrence of podocytic lesions [40]. According to Nangaku C$_{5b-9}$ in sublytic quantities stimulates podocytes to produce proteases, oxidants, prostanoids, extracellular matrix components, and cytokines including TGF-beta [41].

In MGN, the glomerular immune compartment can affect the tubulointerstitial immune compartment and result in tubulointerstitial lesions. These are closely related to proteinuria. The increased elimination of complement factors could participate in the production of tubulointerstitial lesions that are correlated with the evolution of MGN.

Ronco and Debiec discusses a novel pathomechanism of MGN represented by alloimmunization against neutral endopeptidase, a podocyte antigen that can digest biologically active peptides. They have transferred a membranous nephropathy to the rabbit by injection of mothers’ immunoglobulin. Fetomaternal alloimmunization is considered a novel mechanism of renal disease that may apply to other organs [42].

Anti-inflammatory drugs, especially corticotherapy, and immunosuppression may include the tubulointerstitial inflammatory process as an important target.

**C. Glomerulonephritides mediated through inflammatory mechanisms**

According to Couser, the second type of mechanism of glomerular lesion is inflammatory: such as in mesangial proliferative GN, primary IgA nephropathy, mesangiocapillary GN, and a large group of secondary GNs, including poststreptococcal GN, lupus nephritis, and others [38]. It is important to note that the inflammatory process in the glomerular immune compartment is associated with an inflammatory process that takes place in the tubulointerstitial immune compartment. An immune cell infiltrate of variable intensity is present there.

The immune process in the tubulointerstitial immune compartment takes place mainly secondary to proteinuria. Proteinuria is an essential factor by which inflammation in the glomerular compartment affects the tubulointerstitial compartment in an immune GN to produce inflammatory lesions.

Proteinuria follows inflammatory processes that take place in the glomerular immune compartment. It will act on the tubulointerstitial region through:

- overload of the capacity of metabolism of the tubular lysosomal system; a rupture of lysosomes with a flow of enzymes at the site of tubular cells takes place, leading to their alteration and destruction,
- protein overload induced NF-kB activation in proximal tubular cells [43-44],
- the elimination of cytokines and chemokines produced during the course of the inflammatory process at the level of the glomerulus and other mediators of inflammation [45],
- the elimination of elements of the complement system in the urine [46],
- the synthesis and release of chemokines by tubular cells that will attract macrophages [47-48],
- filtered proteins in the glomerulus that lead to the proliferation of proximal tubular cells associated with an increased synthesis of vasoactive and proinflammatory substances [49]; albumin acts during reabsorption as a carrier of inflammatory mediators [50].

The immune process can take place concomitantly in both the glomerular immune compartment and the tubulointerstitial immune compartment in anti-GBM-mediated GN. Anti-GBM antibodies react with the GBM, frequently
determining a crescentic GN. At the same time, they react with tubular BM to produce lesions and an interstitial neighboring reaction. These antibodies can also react with the pulmonary BM [51].

The concomitant involvement of the two immune compartments, glomerular and tubulointerstitial, in inflammatory GNs reflects the complexity of the immune process in these diseases.

Hill et al. suggest that tubular epithelial lesions in chronic glomerulonephritis are usually secondary to proteinuria and not tubulointerstitial immune deposits, which appear to play only a minor role [52].

D. Crescentic glomerulonephritis: an obvious example of important involvement of the glomerular and tubulointerstitial immune compartments

Crescentic GNs are mediated through three mechanisms: anti-GBM antibodies, circulating immune complexes, and anti neutrophil cytoplasmic antibodies (ANCAs) [53]. They will lead to important lesions of the nephron. In crescentic GN there is an interrelation of the glomerular immune compartment with the tubulo-interstitial one, both being severely affected.

Crescentic GNs present severe lesions evidenced at two important levels of the glomerulus:
• lesions at the GBM involve the glomerular immune compartment and the passage of fibrin towards the filtration space [54]
• lesions in Bowman’s capsule permit direct communication between the glomerular and the tubulointerstitial compartments [55].

The presentation of immune changes in this type of glomerulonephritis permits a better understanding of immune processes that occur in the glomerular and tubular compartments.

The glomerular immune compartment is severely affected by holes within the GBM at both the capillary level and the level of Bowman’s capsule. The leakage of fibrin into the glomerular filtration space is followed by an intense cellular reaction of the existing epithelial cells with marked proliferation. Both parietal and visceral epithelial cells participate. Crescents are formed, and they occupy the filtration space. Podocyte bridges between the tuft and Bowman’s capsule are built. Le Hir et al. suggest that the bridges between the capillary tuft and Bowman’s capsule create spaces between the epithelial cells of Bowman’s capsule that allows fibrin to spill into the interstitium [24]. This determines an important involvement of the tubulo-interstitial compartment in RPGN.

The passage of fibrin and other mediators (e.g. cytokines and chemokines) from the glomeruli, where an important inflammatory process occurs, to the interstitium will trigger an inflammatory process at that level. At the same time, the elimination of mediators from the glomeruli into tubules may influence interstitial inflammatory processes as well. Later
on, interstitial macrophages will pass through holes of Bowman’s capsule into the glomeruli and contribute to the inflammatory processes (i.e. formation of crescents) that take place at that level. A lesion of the capsule can also be produced through the action of periglomerular mononuclear cells. So, experimental studies performed by Lan et al. in mice in which an antiGBM antibody mediated GN has been produced have shown macrophages and T lymphocytes periglomerular at the site of lesions of Bowman’s capsule [56]. An important role is played by chemokines, that were expressed mainly by CD68-positive macrophages and parietal epithelial cells in crescents [57].

Other chemotactic factors and cytokines may also pass along with cells and chemokines through the ruptured Bowman’s membrane to amplify the inflammatory process [48]. In addition to the extracapillary proliferation, there is also endocapillary proliferation. Lesion of the GBM is produced by polymorphonuclears and monocytes through proteolytic enzymes and oxidative products [58-63].

T cells in crescentic glomerulonephritis play an important role. T cells play a major role in the initiation of adaptive immune responses that lead to crescentic injury. The main role is played by T helper cells. According to Tipping and Holdsworth, the presence of T cells and macrophages in crescentic glomeruli, frequently in the absence of humoral mediators of immunity, suggests a dominant role for T cells in crescentic glomerulonephritis [64].

The interrelation between the glomerular and tubulointerstitial immune compartments is also very important during the evolution of RPGNs. Fibroblasts can penetrate through holes in Bowman’s capsule and will participate in the production of crescents [65, 66]. Lesions in rapidly progressive glomerulonephritis (RPGN) are characterized by a great diversity of involvement of one or both immune compartments. Cases with ANCA-positive vasculitis – related RPGN in which some glomeruli are normal and some glomeruli are severely affected with crescents have been reported [67]. Gluhovschi et al. observed such a patient, that had 11 glomeruli on the kidney biopsy specimen, 3 without modifications, while the others showed important lesions with crescent formation. It is worth mentioning that around these glomeruli there was a rich interstitial inflammatory infiltrate. In the same patient they found diffuse and nodular interstitial lymphocytic infiltrate [68]. We can discuss here of lymphatic-like nodules which can be present during chronic inflammation in RPGN-vasculitis like those signaled by Heller [6].

Crescentic RPGN represents the prototype of severe involvement of the glomerular immune compartment. It is followed by severe involvement of the tubulointerstitial immune compartment, which will in turn influence the glomerular compartment to amplify the lesions. In conclusion, the components of the glomerulus delineate a glomerular immune compartment that has complex implications for immune processes. Important immune processes occur at this level, and they are reflected in several types of primary and secondary glomerular nephropathies. In most immune mediated glomerular diseases, immune changes from the glomerular immune compartment are associated with the involvement of the tubulointerstitial compartment.

The tubulointerstitial immune compartment during inflammatory processes localized at that level

The interstitium and tubules are affected concomitantly during immune inflammatory processes. There is a strong interrelation between the interstitium and tubules. Together, they form the compartment defined as the tubulointerstitial compartment. We should remember that resident cells like lymphocyte-like and fibroblast-like cells are present in the interstitium. Under pathophysiologic conditions, circulating immune cells include polymorphonuclears, monocytes, and lymphocyte infiltrates. These cells will participate in the initial phase of the inflammatory process. In the late phases after the resolution of the inflammatory process, the fibroblast will participate in remodeling processes. Hematopoetic stem cells and dendritic cells are also present at this level. The normal interstitium contains an extensive population of dendritic cells which function as antigen-carrier cells. Dendritic cells present a dense network around glomeruli and tubules [69]. Dendritic cells are considered to represent a complex sentinel network in the kidney, that serves to detect infectious pathogens. This seems possible in pyelonephrites. Dendritic cells would be positioned to capture antigens from bacteria ascending through the tubule. Dendritic cells take molecules from the tubular lumen. Segerer et al. found a population of

Fig. 4. Rapidly progressive glomerulonephritis in vasculitis (Wegener granulomatosis). Rich interstitial inflammatory infiltrate with nodular aspect. Two glomeruli with disorganised glomerular structure with the presence of an acidophilic material.
Langerin positive dendritic cells (a marker of Langerhans cells) which surround the tubular epithelial layer. They can be incorporated in the tubular epithelial layer [15]. The participation of resident interstitial cells in interstitial inflammation has not yet been clarified.

**Tubular cells** are located between the interstitial and urinary spaces. They belong to the tubulointerstitial compartment; there is a strong relationship between tubular cells and the interstitium. They participate in immune processes in the interstitium. Therefore, they show many similarities to resident glomerular cells that participate in inflammatory processes that occur in the glomerulus.

During inflammatory processes, tubular cells react with immune cells like T cells and monocytes that are present in the interstitium and constitute the interstitial inflammatory infiltrate. During passage through tubules, urinary leukocytes express adhesion molecules that permit their attachment to tubular cells [70]. As a result, an inflammatory process is produced. Tubular cells are resident cells that present numerous immune properties in addition to their specific functions. Following stimulation, they can produce various cytokines and chemokines [71].

According to Segerer and Schlondorff the initiation of an inflammatory response in the tubulointerstitium may occur by activation of tubular epithelial cells and DCs. Here from some of them migrate to regional lymph nodes, activating and priming lymphocytes to elicit a response to the specific antigenic stimuli. After that they return to initial place in the tubulointerstitium. Renal DCs may not traffic out of the kidney after taking up antigen. Schlondorff and Segerer consider that DCs may take and present antigen for recognition in the renal interstitium. After that chronic antigenic stimulation may initiate the formation of lymphoid-like folicules, if lymphocytes meet these DC [4].

The inflammatory interstitial process is frequently encountered in renal diseases. It may occur in interstitial renal diseases or secondary to other diseases [72-73].

**The inflammatory process can take place:**
- Only in the tubulointerstitial compartment; this situation occurs in urinary tract infections and drug-related tubulointerstitial nephropathies.
- In other previously-mentioned situations, the immune process occurs in the glomerular immune compartment.
and extends into the tubulointerstitial immune compartment (membranous GN).

- The immune process can take place concomitantly in the glomerular and tubulointerstitial immune compartments. The most typical example of this is lupus nephritis.

The concomitant presence of a common nephritogenic antigen in the glomeruli and interstitium could trigger an inflammatory tubulointerstitial process in the two compartments. Proteinuria plays an important role in the production of tubulointerstitial lesions [74].

The tubulointerstitial immune compartment can influence the glomerular compartment

This occurs in RPGN with crescents [75]. Although hypothetical, this could be possible in reflux nephropathy, where glomerular lesions of FSGS accompany tubulointerstitial lesions [23].

We will present the main diseases in which the inflammatory process takes place only in the tubulointerstitial immune compartment; other situations have been presented above.

Immune compartments in urinary tract infections (UTIs)

UTIs represent the clearest example of tubulointerstitial immune compartment involvement without concomitant involvement of the glomerular immune compartment. In UTIs, a wide range of immune cells, including PMNs, macrophages, T and B cells, plasma cells, and NK cells, are mobilized inside the tubulointerstitial immune compartment. The participation of resident interstitial cells, especially lymphocyte-like cells, has not yet been proved. It is possible that round cells similar to lymphocyte-like cells play a role.

During tubulointerstitial inflammation, numerous mediators like cytokines and chemokines (IL6 and IL8) are produced [76]. The lack of involvement of the glomerular immune compartment could be due to the absence of antigenic stimulation; in contrast, antigenic stimulation of the tubulointerstitial compartment does occur.

Glomerular involvement can sometimes be observed in UTIs that are associated with reflux nephropathy. In these cases, it is possible for proinflammatory cytokines and chemokines to reach the glomerular immune compartment via tubulo-glomerular reflux. During the late progression towards chronic renal failure in UTIs, a process of initial periglomerular fibrosis is initiated that later affects the glomerulus.

Acute drug-induced tubulointerstitial nephritis

An inflammatory reaction accompanied by the presence of immune cells, such as PMNs, eosinophils, lymphocytes, plasma cells, and macrophages, in the interstitium is produced in this disease [77].

Increased levels of eosinophils are found in the blood and urine. The immune inflammatory process takes place in the tubulointerstitial compartment and leads to acute tubulointerstitial nephritis. Involvement of the glomerular immune compartment is observed only in very rare cases. Thus, NSAIDs can produce tubulointerstitial lesions with an eosinophilic infiltrate in the interstitium [78, 79]. During the reaction to NSAIDs, glomerular involvement characterized by the production of minimal changes (foot processes effacement) is noticed by electron microscopy [80, 81].

The relationship between the two compartments is produced primarily through proteinuria, through the passage of molecules through Bowman’s capsule and possibly by “downstream” diffusion of mediators along peritubular capillaries.

Proteinuria represents an important element in the cross-talk between the two immune compartments. Glomerular proteinuria influences the tubulo-interstitial immune compartment quantitatively, by overrunning the metabolization capacity of the tubule, as well as through qualitative elements. From the inflammatory process that takes place in the glomerular immune compartment come factors of the complement system, cytokines, chemokines, etc., that can influence the tubulo-interstitial immune compartment [44-50].

The communication through Bowman’s capsule is obvious in crescentic RPGN, where there are holes at this level [55]. This mechanism is discussed in other glomerular nephropathies as well.

Immune mediated distinct pathology of the kidney represents an important argument in the delimitation of morpho-functional compartments as well as immune compartments.

An immune process is present at the level of the juxtaglomerular apparatus of the nephron. This process primarily affects the afferent arteriole and the juxtaglomerular mesangium that delineate a third compartment closely related to the nephron. Immune vascular nephropathies affect vessels in that region [82].

The juxtaglomerular apparatus of the nephron. Implications for the immune processes of the nephron

The juxtaglomerular apparatus participates in immune processes: by cells of the extraglomerular mesangium and by means of arterioles, that are involved in immune processes alongside other vessels in the body.

Glomerular mesangial cells have phagocytosis capacities as regards immune complexes. By analogy, the extraglomerular mesangium, being in close connection with the glomerular mesangium, might also have such properties. This could explain the presence of immune complexes at this level.

The inflammatory cellular infiltrate as well as the settling of immune complexes at the level of JGA may...
perturb the latter’s functioning, especially the transmission of information between the macula densa and the afferent arteriole.

Ren et al. have experimentally proven the possible involvement of a lesion subsequent to immune processes in JGA function. By administration of Thy 1-1 antibody and complement to rabbits, the tubuloglomerular feedback was completely eliminated [83]. Alteration of JGA structures subsequent to an immune process pales for their involvement in some immune mediated nephropathies, mainly in glomerular nephropathies.

In immune-mediated diseases, deposits of immune complexes have been observed in the extraglomerular mesangium.

In IgA nephropathy [84], systemic lupus erythematosus (SLE), immune deposits in the extraglomerular mesangium have been described by Silva et al. and Hvala et al. [85, 86].

The presence of immune cells arising from the bone marrow in the extraglomerular mesangium has been described in some immune-mediated diseases. For example, the presence of T cells has been indicated in diabetic nephropathy during the course of the autoimmune disease type I diabetes mellitus. The JGA has a role in regenerating the affected glomerular mesangium during immune-mediated nephropathies.

In experimental studies Hugo et al. have demonstrated the migration of mesangial cells from the extraglomerular mesangium to the mesangium, fact in favor of a role for the juxtaglomerular apparatus in the maintenance of the mesangial cell population [87]. Haseley et al. suggest that these cells may play an important role in the repair of mesangial lesions [88].

In a recent study Gluhovschi et al. have signaled the presence of a CD34 marker in the glomerular mesangium, as well as in the extraglomerular mesangium. The presence of this marker can be attributed either to stem cells or to mesangial cells in the process of transition, that shows the role of the extraglomerular mesangium of the JGA in immune mediated glomerular diseases [89].

The juxtaglomerular apparatus vessels are implicated in some immune processes during humoral-mediated acute rejection of renal grafts [90], vasculitides [82]. (Such as Wegener granulomatosis, Henoch-Schönlein purpura microscopic polyangiitis, essential cryoglobulinemia). It has also been shown to be present in other diseases with inflammatory vascular infiltrate such as disseminated SLE, scleroderma and uremic hemolytic syndrome.

In antibody-mediated rejection, the immune reaction is not limited only to vessels from the juxtaglomerular apparatus. According to Nast and Cohen, a frequent form of antibody-mediated acute rejection is characterized by diffuse peritubular staining for the complement component C4d [90]. The presence of this component is considered to indicate the presence of humoral rejection. This finding suggests that there is an interrelation with the tubulointerstitial immune compartment.

Receptor of Angiotensin II and toll-like receptors and compartmentalization of the nephron

Regarding the morphofunctional compartmentalization, Navar describes the compartmentalization of intrarenal angiotensin II. He notes that angiotensin II is compartmentalized in both a regional and a segmental manner [91]. The density of both AT1 receptors and ATII itself is higher in the medulla than in the cortex [92].

Recently, Guzic et al. have underlined the relation between T lymphocytes and angiotensin II. They have proved that mice lacking T and B cells do not develop hypertension in two models of hypertension (with high angiotensin II or with low angiotensin II (DOCA salt). Transfussion of T but not B cells restores that abnormality [93]. These experiments plead for the important role of T lymphocytes in arterial hypertension [94].

Proteinuria produced by the glomerular lesions in GNs can induce tubulointerstitial lesions and the activation of local RAS, which is involved in the regulation of glomerular circulation. One clinical observation regarding the relationship between the tubulointerstitial infiltrate and HT is as follows: in minimal change disease that lacks inflammatory infiltrate, HT is not present; GN diseases where this infiltrate is present are usually associated with HT.

Therefore, the control of proteinuria via ACEIs or ARBs may prevent the negative effects of proteinuria and halt the progression of GN [95]. Recently, Ruiz-Ortega et al. have suggested that ACE-inhibitors and ARBs offer an organ-protective effect through their pleiotropic mechanisms, such as the blockade of the proinflammatory response induced by angiotensin II [96].

ACEI and ARBs can also act on immune cells to influence their immune function and produce an immunosuppressive effect [97].

Due to their presence in all three immune compartments (glomerular, tubulointerstitial, and, especially juxtaglomerular) of the kidney, AT1 receptors play an important role in the functioning of these compartments. They also permit a closer interrelation between these compartments during immune processes.

At the level of the tubulointerstitial compartment, TLRs seem to play a very important role [98]. There is a relationship between TLR and the renin-angiotensin system. Angiotensin II upregulates Toll-like receptor 4 on mesangial cells. Through this it can participate in the development of inflammation in many non-infectious renal diseases [99].

Toll-like receptors (TLR) are present in the glomerular immune compartment at the level of mesangial cells (TLR 3 and 4) and in the tubulointerstitial compartment at the level of tubular cells (TLR 1, 2, 3, 4 and 6). Immune cells that originate in the bone marrow and infiltrate the nephron express TLRs at the level of monocytes, macrophages (TLR 1, 2, 4, 6), and dendritic cells (TLR 4, 7, 8, 9) [100].
Synthetic view

Immune compartments define well-structured morpho-functional zones where an individualized immune activity takes place.

This compartmentalization of the nephron shows some similarities to that described by Crivellato et al. In the case of several immune organs (e.g. thymus, spleen, and lymph nodes), the immune organs restrict component cells to well-defined immune compartments in order to ensure proper functionality. On the contrast to lymphoid organs, where there is a permanent concentration of immune professional cells in order to ensure the distribution in different organs and tissues, in the kidney, at the level of the nephron, as well as in other organs this concentration of immune professional cells is produced during immune diseases when immune aggregates are formed, taking the shape of small lymphoid follicles, developing into tertiary lymphoid organs. In normal physiological conditions, in morpho-functional compartments there is a small number of such cells, the immune compartments are resting or have a minimal necessary functionality that ensures the necessary immune protection. Therefore the immune compartmentalization at the level of the kidney is a dynamic structure, with few resting immune specialized cells in the compartments, and many in inflammation. According to Segerer and Schlondorf, tertiary lymphoid follicles are also considered dynamic structures [23].

Through immune compartmentalization of the nephron, we can understand that immune processes in the nephron take place in well-defined spaces that overlap with the glomerular, tubulointerstitial, and juxtaglomerular morpho-functional regions. Two types of cells, immune cells that originate in the marrow and resident cells that express immune properties, participate in this process.

In lymphoid organs, these compartments are constituted predominantly by immune cells; in other organs like the kidney, resident cells with primary functions specific to the organ also participate in the immune response. As we mentioned above, in the kidney, in the course of the inflammatory process, besides interstitial diffuse infiltrate, lymphoid-like structures have been found. These could represent according to Heller an intrarenal immune system [6].

The resident cells have immune properties that are more or less defined, and they can constitute an immune defense component of the organism. These cells are not strictly immunologically specialized, and so they have bivalent functions. Their main function relates to the organ and structure in which they originate, and their optional immune functions become active when they interact with an antigen. The mesangial cell represents the main residential element of the local immune system in the glomerular immune compartment [101-103]. In the tubulointerstitial compartment tubular cells play an important role in immune processes [104-107]. In the immune compartments of the nephron, specialized cells, such as T, B cells or dendritic cells, are usually present in relatively small numbers [6, 108]. During immune processes, a larger amount of immune cells originating in the bone marrow infiltrate the area [27]. During an important aggression, therefore, morpho-functional compartments become true functional immune compartments [109, 110]. A similar process is found in the liver, that is presently mentioned as a lymphoid organ [111].

After the immune process, immune cell counts typically return to initial levels. During chronic persistent disease, however, immune cells originating in the bone marrow persist in the compartments of the nephron. In addition to the classical immune system, with its specialized structures organized at the tissue level, resident cells of different organs and tissues display immune properties along with their functional specializations, pointing to the existence of a defense system of the body.

It is to be noted that under normal conditions, the immune activity at the level of the immune compartments of the nephron is confined to the constitutive elements endowed with properties that place them into innate immune defence and to the rare immune professional cells present. Under these conditions, the term of “immune compartment” of the nephron has little significance. Under the conditions of immune pathological processes, in the morpho-functional compartments, an important activity takes place, with formation of lymphoid follicles, assimilated to a tertiary lymphoid organ.

The kidney is one of the organs with a well represented morpho-functional compartmentalization, in which the concept of compartmentalization of the immune system seems to be well expressed. The aim of this paper has been to present data concerning immune renal pathology through a new concept – that of compartmentalization of the immune system (first described by Crivellato). This cannot be confined to the kidney; it may provide a new perspective for the understanding of the immune system, both as a unitary whole and through its regional features.

References