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EDITORIAL

Renewal of FSP1: A marker of fibrogenesis on human renal biopsies

Renal biopsy remains the gold standard for the diagnosis of renal diseases. Indeed, the prognosis and the treatment broadly depend on the type of nephropathy determined on renal biopsy. However, within a given nephropathy in an individual patient, it may be difficult to draw up the prognosis from renal biopsy. Reliable histologic predictors of renal function outcome are still needed. In this issue of *Kidney International*, Nishitani et al present a contributive work to meet this requirement [1]. Using a "from bench to bedside" approach, the authors performed for the first time on human tissues what was done in mice 10 years ago, when a fibroblast specific marker, namely fibroblast-specific protein 1 (FSP1), was characterized [2]. FSP1 was identified by comparing murine cDNA libraries obtained from cell cultures of renal tubulointerstitial fibroblasts versus that of proximal tubular epithelial cells. This new marker of fibroblasts was not restricted to renal interstitium, but also labeled fibroblasts in other organs except brain and liver. FSP1 belongs to the S-100 superfamily of small Ca^{2+}-binding proteins implicated in several cellular and extracellular functions, including cytoskeletal-membrane interactions, Ca^{2+}signal transduction, cell growth, differentiation, and motility, cancer metastasis, and angiogenesis [3]. Furthermore, cDNA encoding FSP1 is similar to *mts1* (*S100A4*) gene, previously described and implicated in cancer development and metastasis [4].

FSP1 and α-smooth muscle actin, two markers of profibrotic cells

As soon as it was initially described [2], FSP1 was used to label the cells involved in fibrosis in mouse renal interstitium: therefore, these cells deserved the name of fibroblasts. FSP1-positive cells coexpressed HSP47, a chaperone molecule indicative of collagen synthesis, demonstrating that FSP1-positive cells were actually involved in fibrosis [5]. Whereas scanty interstitial fibroblasts were found in normal renal interstitium, their number increased in fibrotic conditions. Although FSP1 represent a significant progress in our knowledge in fibrogenesis, all the questions about renal interstitial cell types involved in renal fibrosis are not answered. In the paper by Nishitani et al [1], the dogma of myofibroblast as the major interstitial cell type responsible for fibrosis is challenged and the complex heterogeneity of interstitial cell population is underlined. The myofibroblast was defined as a fibroblast in a reversible activated state involved in scarring and exhibiting contractility for scar retraction and strong expression of α-smooth muscle actin (α-SMA) [6]. In wound healing phenomenon, α-SMA–positive cells are clearly demonstrated as profibrotic cells. That latter myofilament protein isoform became the trademark of activated fibroblasts and their usual easy marker, allowing fibrosis cellular phenomenons in many tissues from many species to be studied. It fit well for interstitial fibroblasts as well as for epithelial cells engaged in epithelial-mesenchymal transition (EMT). Nishitani et al [1] suggest the hypothesis that most of α-SMA–positive cells would originate from vascular cells, reducing the importance of α-SMA–positive cells originating from fibroblasts or from epithelial cells transformed by EMT. This opinion should be moderated. First, Nishitani et al [1] reported that about 10% of interstitial cells coexpress FSP1 and α-SMA: therefore, a significant number of interstitial cells are clearly myofibroblasts expressing the fibroblast specific marker FSP1. Second, in cell culture experiments under given conditions, tubular epithelial cells can acquire α-SMA [7]: this EMT phenomenon cannot involve vascular cells because it develops in a pure epithelial cell population. Finally, one can wonder what is a fibroblast and what does FSP1 represent. Fibroblasts are interstitial spindle cells, constantly but nonspecifically expressing the intermediate filament vimentin in the cytoskeleton, producing interstitial collagens. In steady state conditions, they are scanty cells considered as residual resting mesenchymal cells. In fibrosis, the number of interstitial collagen-producing cells is increased and the interstitial cell population is made of interstitial fibroblasts, most of them resulting from epithelial cells transformed by EMT, whereas colonization by circulating bone marrow cells is a minor phenomenon [5]. FSP1 and/or α-SMA are expressed by these cells. In this respect, it is difficult to consider FSP1 exclusively as

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a lineage marker. FSP1 appears more as marker of cells engaged in fibrogenesis, at least in epithelial cells undergoing EMT, because FSP1 expression precedes complete EMT [7], transfection of FSP1 induces EMT [2], and inactivation of FSP1 reduces fibrosis [7].

Pathogenic role of EMT: EMT as a mechanism of tubular destruction and fibrosis

Since the seminal publication of FSP1 [2], several studies have taken advantage of this fibroblast marker to explore renal fibrosis in mouse models. All of these studies on the development of renal fibrosis pointed out both types of FSP1-positive cells: interstitial fibroblasts and tubular epithelial cells, the phenotype of which was transformed into a mesenchymal cell [5, 8]. This change in phenotype and in cell type is EMT. Besides interstitial fibrosis, EMT of glomerular epithelial cells has been implicated in glomerulosclerosis [9]. That EMT from tubular epithelial cells is on par with interstitial fibroblasts is now definitely established in renal fibrosis. Furthermore, this phenomenon yields a major component in interstitial cells responsible for fibrosis [5]. EMT is a fascinating cellular phenomenon emphasizing the plasticity of cells in renal tissue, where initially during nephrogenesis the opposite phenomenon is observed. Except for the collecting duct cells, the rest of the nephron results from the transformation of the metanephric mesenchyme at the tip of the ureteral bud into epithelial cells, either tubular or glomerular. EMT in renal fibrosis appears as a reversal of cell transformations associated with nephrogenesis and generates interstitial cells from destroyed tubules. EMT is under the control of extracellular milieu and of growth factors, TGF-β_1, EGF, and FGF_2, classically involved in fibrosis, whereas it is inhibited by bone morphogenic protein-7.

Role of glomerular disease in renal fibrosis

A major goal in the Nishitani et al study [1] was to correlate the renal function decline in IgA nephropathy with interstitial fibrosis as it appears after FSP1 immunohistochemistry. Such a study design assumes that the prognosis of glomerular diseases relies on the tubulointerstitial compartment of the kidney, which is a classic opinion [10]. Nevertheless, from recent experimental results, it appears that most of the renal tissue damage is under the control of glomerular lesions both as starters and as progression factors of renal tissue fibrosis [11]. Indeed, massive proteinuria from glomerular origin is a classic downstream mechanism of tubulointerstitial damage. But Kriz and LeHir [11] have recently proposed additional mechanisms that seem more active in nephron loss and development of fibrosis. One consists of misdirected filtration at the glomerulotubular junction with spreading of the filtrate between the tubular epithelium and the tubular basement membrane, resulting in the formation of proteinaceous crescents. The second is the involvement of the origin of the proximal tubule by obstructive overgrowth of crescent cells. Both mechanisms lead to secondary tubular damage, nephron loss, and interstitial fibrosis. Importantly, from serial sections it was determined that tubule degeneration was localized only downstream of glomeruli, with crescents obstructing the origin of proximal tubules, whereas tubules depending from nonobstructed or normal glomeruli were spared. This pattern of lesion distribution emphasized the major role of diseased glomeruli in tubulointerstitial involvement. In Nishitani et al's paper [1], severe glomerular lesions with crescents were not described and only mesangial proliferation and sclerosis were scored. That latter type of glomerular lesion does not fit with the model of tubulointerstitial fibrosis proposed by Kriz and LeHir [11].

To shift from experimental to human pathology is the goal of most research works: the study by Nishitani et al [1] is a good example of that. Because the spectrum of the pathophysiology of renal fibrosis in human renal diseases is wide, many research teams should be interested in testing the useful tool FSP1, unless it remains of confidential use.

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