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Invited Review

The possible role of colligin/HSP47, a collagen-binding protein, in the pathogenesis of human and experimental fibrotic diseases

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Summary. Colligin or heat shock protein 47 (HSP47) is a stress protein that resides in the endoplasmic reticulum and is thought to participate in intracellular processing, folding, assembly and secretion of procollagens. Irrespective of the tissue site and organ, induction of colligin/HSP47 expression is always noted during the process of fibrosis, particularly in and around the fibrotic lesions in both humans and experimental models. Its expression is highly tissue- and cell-specific, and restricted to mostly phenotypically altered collagen-producing cells. These observations suggest that up-regulation of this collagen-specific chaperone-colligin/HSP47 may play an important role in the subsequent fibrotic process, possibly by regulating increased synthesis/assembly of collagens.

Key words: Colligin/Heat shock protein 47, Collagen, Glomerulosclerosis, Fibrosis, Human, Rat

Introduction

Colligin, a collagen-binding protein, was first identified by Kurkinen et al. (1984) from murine parietal endoderm cells, and found to bound specifically to gelatin, type I and type IV collagens. Subsequently, species-specific forms of colligin were characterized in humans and rats as gp46 (Clarke and Sanwal, 1992; Cates et al., 1984), in the chick as HSP47 (Hirayoshi et al., 1991), and in the mouse as J6 (Wang and Gudas, 1990). All these proteins were later found to have a common collagen binding ability.

Colligin/HSP47, a 47 kDa protein with a unique collagen binding ability (Cates et al., 1984, 1987; Kurkinen et al., 1984; Nagata et al., 1986; Nagata and Yamada, 1986; Saga et al., 1987), is localized exclusively in the endoplasmic reticulum (ER) (Kambe et al., 1994; Nagata and Yamada, 1986; Nandan et al., 1988). This protein can bind native collagens (Nagata et al., 1986; Nagata and Yamada, 1986; Natsume et al., 1994). It is thought that colligin/HSP47 binds to the procollagen immediately after it enters the ER, forms a triple helix, proceeds to Golgi complex where colligin/HSP47 dissociates from it and procollagen is secreted to the cell surface (Satoh et al., 1996). In vitro studies have shown that dissociation of procollagen from colligin/HSP47 is pH-dependent (Saga et al., 1987; Nakai et al., 1992). In addition, this 47 kDa stress protein is thought to be involved in the processing and secretion of collagens with correct conformation, while it prevents the secretion of abnormally conformed procollagens, raising the possibility of an additional function of colligin/HSP47, i.e., as a quality control system for procollagens (Nakai et al., 1992).

Recently, several excellent multi-author reviews have provided a clear explanation of the possible role(s) of colligin/HSP47 as a collagen-specific molecular chaperone in the intracellular processing, folding and assembly of procollagens (Nagata, 1996, 1998; Ball et al., 1997). Most of these reviews were based on in vitro studies. In this brief review, based on in vivo animal models, we will summarize our understanding of the possible involvement of colligin/HSP47 in various animal models of fibrotic diseases; in addition to its expression, distribution, and possible function in various human renal and pulmonary fibrotic disorders.

Fibrotic/sclerotic process

A common feature of fibrosis/sclerosis is increased deposition of extracellular matrix (ECM) proteins, which is due to uncontrolled synthesis and/or degradation. Extensive research has been carried out to elucidate the mechanism of fibrosis/sclerosis, and one of the molecules that have received most attention is collagen.

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This molecule belongs to an ECM protein family, present in almost all normal tissues in both humans and multicellular animals. Collagens form the architectural framework of the vertebrate body and are an essential component for the maintenance of structural integrity of cells and tissues. However, in certain disease states, proliferation of collagen-producing cells with subsequent overexpression of collagens results in fibrosis/sclerosis. In most cases, fibrosis/sclerosis is a progressive pathological process, and a gradual expansion of the fibrotic mass ultimately leads to destruction of the normal tissue. Diseases associated with fibrosis/sclerosis present one of the major challenges in clinical practice. Although the exact mechanism of fibrosis/sclerosis is not yet known, increased levels of collagen have previously been demonstrated in numerous studies in generalized connective tissue disorders and/or organ-specific fibrosis/sclerosis. These studies showed very convincingly that increased synthesis with excessive deposition of collagens are mainly responsible for fibrotic/sclerotic changes in the human and animal lung, liver and kidney (Bateman et al., 1981; Takiya et al., 1983; Oomura et al., 1989; Woodrow et al., 1992; Arthur, 1994; Razzaque et al., 1994b, 1997a; Zhang et al., 1994; Takahara et al., 1995; Deheinzelin et al., 1997; Regoli et al., 1998; Shiba et al., 1998). Although increased synthesis and deposition of various collagens are thought to be responsible for fibrosis/sclerosis in various experimental and human diseases (Bateman et al., 1981; Zhang et al., 1994; Razzaque et al., 1997a, 1998a), very little is known about the intracellular processing of the collagen molecules during fibrosis/sclerosis. Recent in vivo studies found a close association between colligin/HSP47 and collagen deposition in various experimental and human fibrotic diseases. We will briefly discuss in this review the possible involvement of colligin/HSP47 in various experimental and human diseases associated with fibrosis based on the existing data.

Expression of colligin/HSP47 in animal models of fibrosis

1. Experimental glomerulonephritis

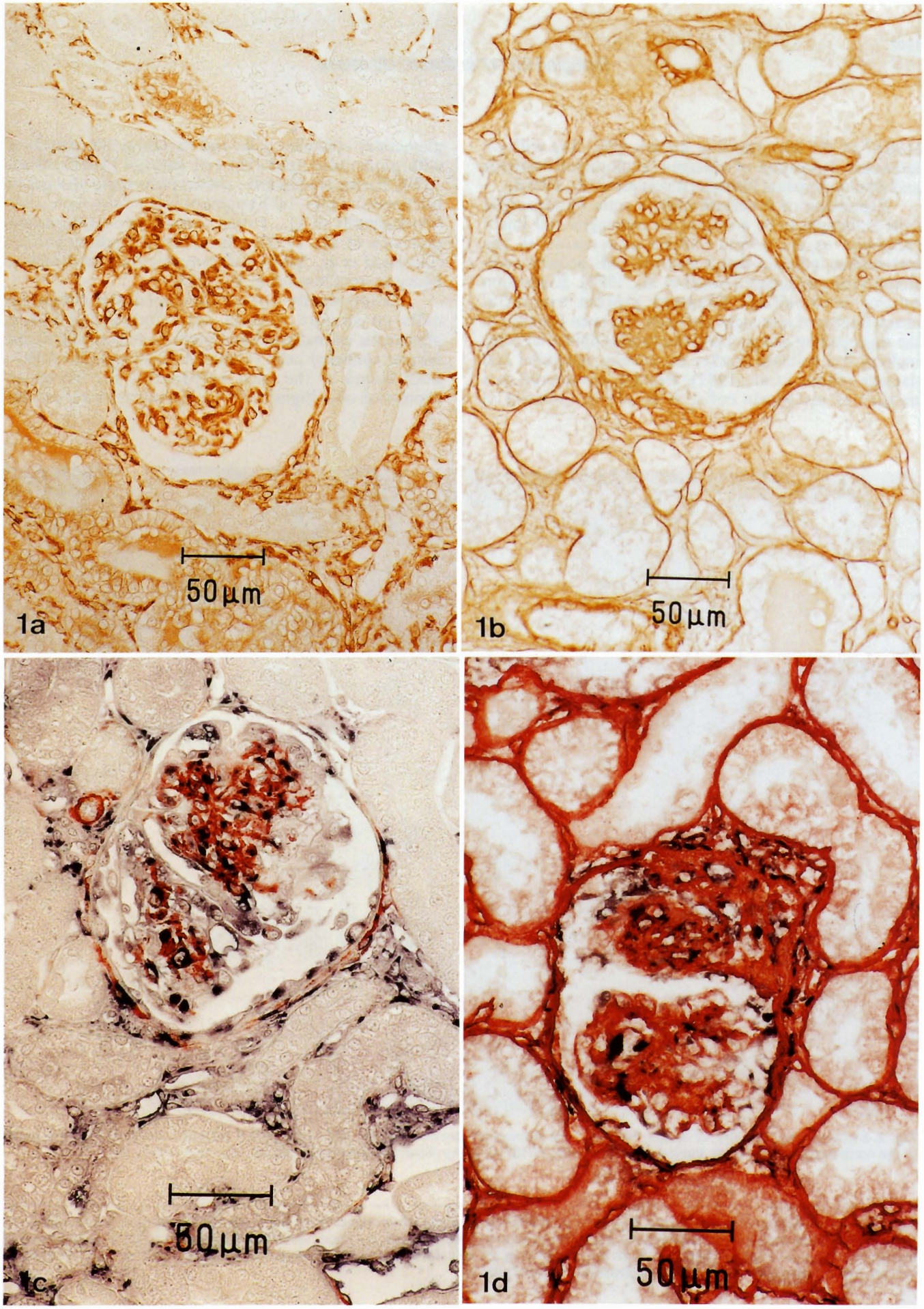
Glomerulosclerosis is the end result of various known and unknown renal disorders, in which excessive amounts of ECM, including various types of collagens, are deposited in a disorganized manner in the glomeruli, resulting in renal dysfunction which gradually leads to an irreversible end-stage renal failure. A number of animal models have been developed to investigate the pathogenesis of glomerulosclerosis, the most common of which is that induced by injecting anti-Thy-1 antibody in rats. In this model, early mesangiolytic changes are followed by diffuse glomerulosclerotic changes in the kidney (Yamamoto and Wilson, 1987). Immunohistochemical staining shows that overexpression of colligin/HSP47, relative to the control (Fig. 1a) (Razzaque and Taguchi, 1997) is associated with increased deposition of type IV collagen in the proliferative and sclerotic glomeruli (Fig. 1b). Two important features of Thy-1 nephritis have been described; increased proliferation of phenotypically altered α-smooth muscle actin-positive mesangial cells and infiltration of monocytes/macrophages (Bagchus et al., 1990; Johnson et al., 1991). Using double staining, α-smooth muscle actin-positive mesangial cells (Fig. 1c) are usually the major element responsible for increased expression of colligin/HSP47 in sclerotic glomeruli, while ED-1-positive monocytes/macrophages are negative for colligin/HSP47; colligin/HSP47 expressing cells in the sclerotic glomeruli are colocalized with increased deposition of type IV collagen (Fig. 1d). Similar results are also found on western-blot analysis, where almost no visible band is seen in the control kidney while a distinct band appears at 47kDa in the Thy-1 kidney, demonstrating up-regulation of colligin/HSP47 in the glomerulosclerotic kidney.

A similar study in another rat model of glomerulonephritis induced by anti-GBM antibody showed parallel up-regulation of both collagens and colligin/HSP47 in the sclerotic glomeruli and in regions of interstitial fibrosis. In addition, most of the peri-glomerular cells around fibro-cellular crescents were immunopositive for colligin/HSP47 expression and all colligin/HSP47-expressing cells in the kidney were collagen-producing cells (Ceol et al., 1996; Razzaque et al., 1997a, 1998b).

2. Hypertensive nephropathy

Dahl rats are a useful model for investigating the mechanisms involved in the development of hypertensive renal damage (Rapp and Dahl, 1971). In this model, progressive glomerulosclerosis with marked tubulointerstitial damage is noted in Dahl salt-sensitive rats fed a high salt diet, while no histological changes are present in Dahl salt-resistant rats fed a high salt diet. The exact mechanism of hypertensive renal damage Dahl salt-sensitive rats remains mostly unknown, but, earlier studies suggested that abnormal collagen metabolism plays a crucial role in the pathological process (Hamaguchi et al., 1995; Tamaki et al., 1996). As anticipated, compared to the normotensive kidney (Fig. 2a), there is increased expression of colligin/

Fig. 1. Immunohistochemistry for colligin/HSP47 **(a)** and type IV collagen **(b)** in experimental glomerulonephritis in rats. Note overexpression of colligin/HSP47 and increased deposition of type IV collagen in the proliferative and sclerotic glomeruli. Double staining showed that colligin/HSP47-expressing cells were mostly α-smooth muscle actin-positive myofibroblasts **(c)**, which colocalized type IV collagen **(d)**. Colligin/HSP47 is stained dark-purple while α-smooth muscle actin or type IV collagen is stained intense red in figures c and d.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HSP47 in the hypertensive kidney (Fig. 2b) with an increased deposition of collagen in glomerulosclerosis and tubulointerstitial fibrosis (Razzaque et al., 1998d).

Expression of α-smooth muscle actin by mesangial cells is thought to be a marker for mesangial cell injury (Johnson et al., 1991) and its expression in the interstitium indicates that interstitial cells acquire myofibroblastic phenotype (Nagel et al., 1973). Expression of the intermediate filament protein vimentin, characteristic of mesenchymal cells, has been detected in the regenerating and proliferative tubular epithelial cells, making it a suitable marker for tubular epithelial cell damage (Grone et al., 1987). Desmin, considered as a marker of myogenic cells, is weakly expressed in glomerular epithelial cells and its expression correlates with glomerular epithelial cell damage (Yaoita et al., 1990). Earlier studies have shown phenotypic changes of intrarenal cells in hypertensive nephrosclerosis (Hamaguchi et al., 1995), experimental nephritis (Johnson et al., 1991), experimental hydronephrosis (Diamond et al., 1995) and gentamicin-induced tubular injury in rats (Nouwen et al., 1994).

Phenotypically altered mesangial and interstitial cells (α-smooth muscle actin-immunopositive), glomerular epithelial cells (desmin-immunopositive) and tubular epithelial cells (vimentin-immunopositive) have been found as the cells responsible for increased expression of colligin/HSP47 in hypertensive kidney and

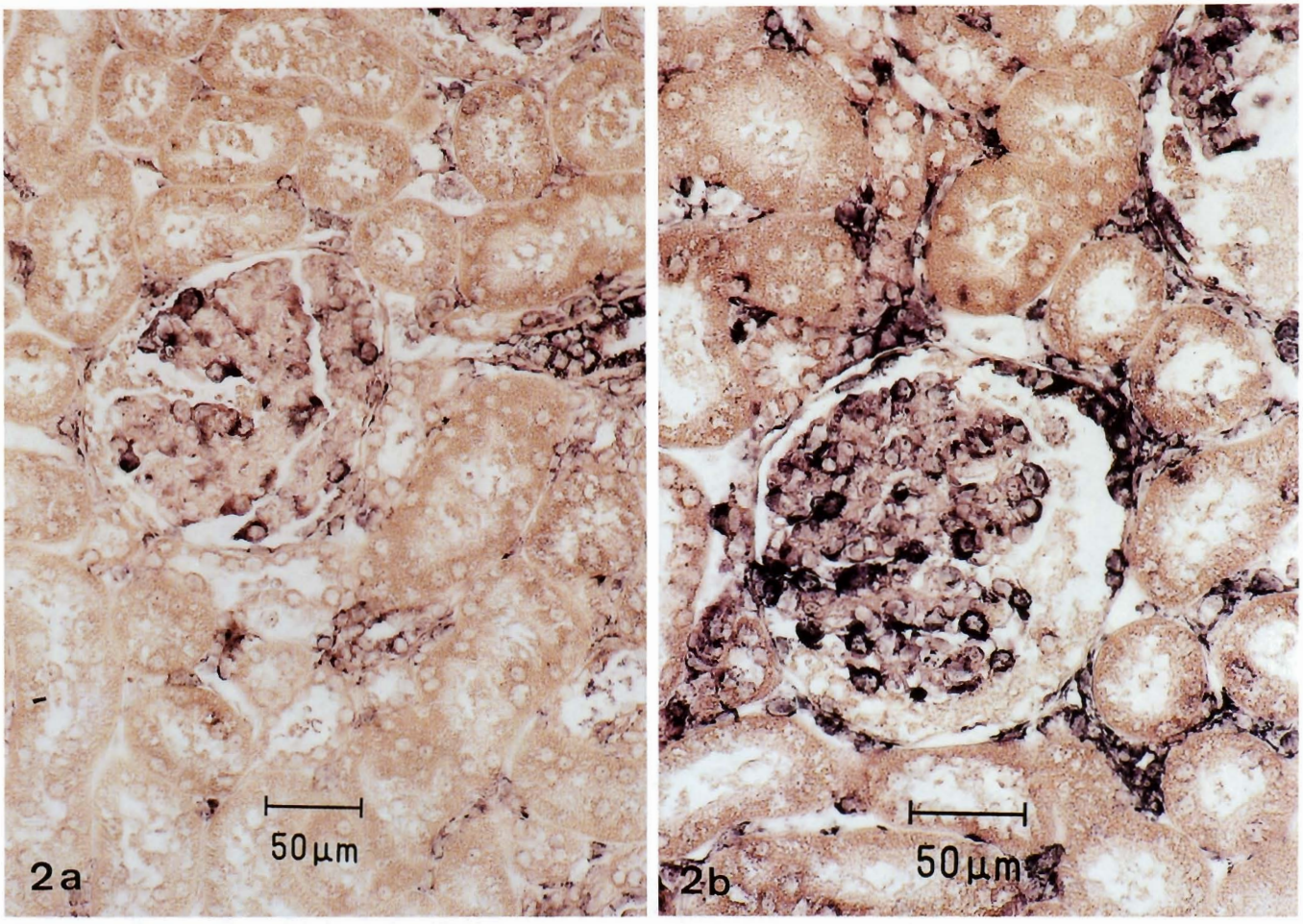

Fig. 2. Immunohistochemistry for colligin/HSP47 in the kidneys of normotensive **(a)** and hypertensive **(b)** Dahl rats. Note that in contrast to the normotensive kidney (a), the expression of colligin/HSP47 is significantly increased in the hypertensive kidney (b).

Fig. 3. Immunohistochemistry for desmin **(a, b)** and colligin/HSP47 **(c, d)** in the control kidney (a, c) and in dietary-induced hypercholesterolemic rat kidney (b, d). Note the phenotypic change in glomerular epithelial cells as shown by strong desmin-immunopositivity (b) in dietary-induced hypercholesterolemic rat kidney. Compared to the control rat kidney (c), note the increased expression of colligin/HSP47 in the hypercholesteromic rat kidneys; with a predominant expression in the glomerular epithelial cells (d).


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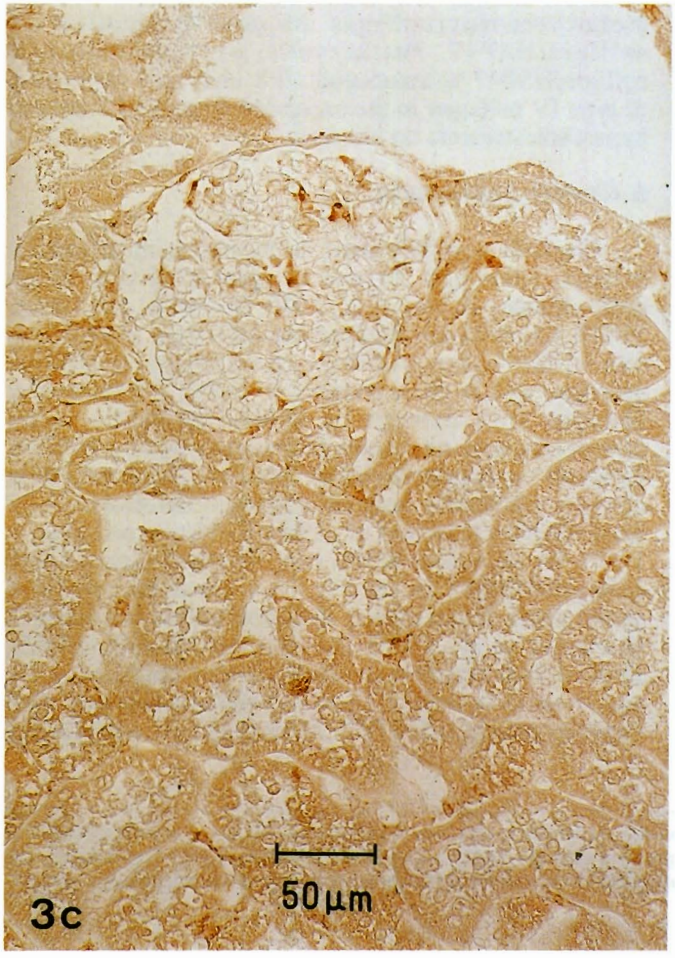
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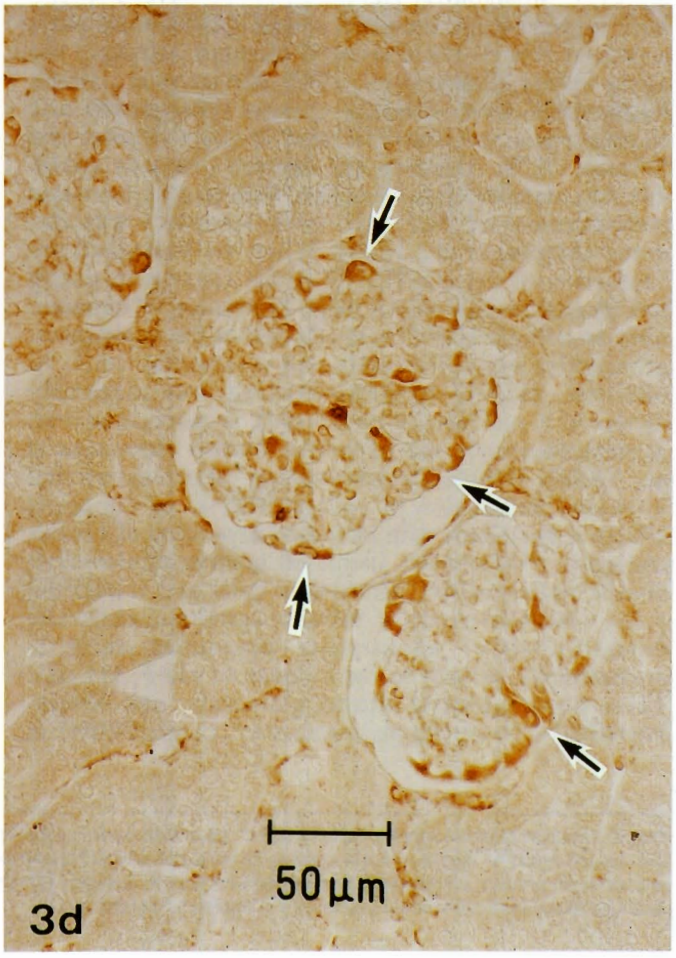
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colocalize collagens in the sclerotic glomeruli and fibrotic interstitium (Razzaque et al., 1998d).

3. Remnant kidney model

The remnant kidney (5/6 nephrectomy) model is widely used to study progressive glomerulosclerosis. Unlike Thy-1 nephritis, which is an immune-mediated disorder, the remnant kidney model is a non-immunological disorder; however, glomerulosclerosis ultimately develops in both models. Similar to Thy-1 nephritis (Razzaque and Taguchi, 1997), upregulation of colligin/HSP47 is associated with increased collagen biosynthesis in the rat remnant kidney model (Sunamoto et al., 1998a); most intra-glomerular cells were found to express colligin/HSP47. These results demonstrated that regardless of the pathogenic mechanism of the disease process, glomerulosclerosis is associated with up-regulation of colligin/HSP47.

4. Age-related nephropathy

The Fischer 344 (F 344) rat, which has often been used in aging research, spontaneously develops nephropathy in advanced age, associated with progressive glomerulosclerosis and interstitial fibrosis (Coleman et al., 1977; Montgomery and Seely, 1990). Several studies have suggested that abnormal collagen metabolism plays a crucial role in the structural changes affecting the aging kidney (Peleg et al., 1993; Abrass et al., 1995). Furthermore, these structural changes subsequently lead to proteinuria and impaired renal function (Couser and Stilmant, 1975; Anderson and Brenner 1986). In aged F 344 rats, impaired renal function, indicated by increased concentrations of BUN and serum creatinine was also noted (Maeda et al., 1985). When we examined the expression of colligin/HSP47 in the kidneys of young rats (6-month-old), only a weak expression of immunoreactive colligin/HSP47 was detected in the mesangium, glomerular epithelial cells and interstitial cells. In contrast, HSP47 immunostaining was markedly increased in old rats (24-month-old), in association with glomerulosclerosis and interstitial fibrosis (Razzaque et al., 1998e). Double-immunostaining clearly shows that increased expression of colligin/HSP47 in the aging kidney is associated with increased deposition of various collagens. Furthermore, increased number of α-smooth muscle actin-positive glomerular cells and interstitial cells, vimentin-positive tubular epithelial cells and desmin-positive glomerular epithelial cells is preferentially present in the kidneys of old F 344 rats. These phenotypically altered glomerular and tubulointerstitial cells are the main source of colligin/HSP47 in the aging kidney.

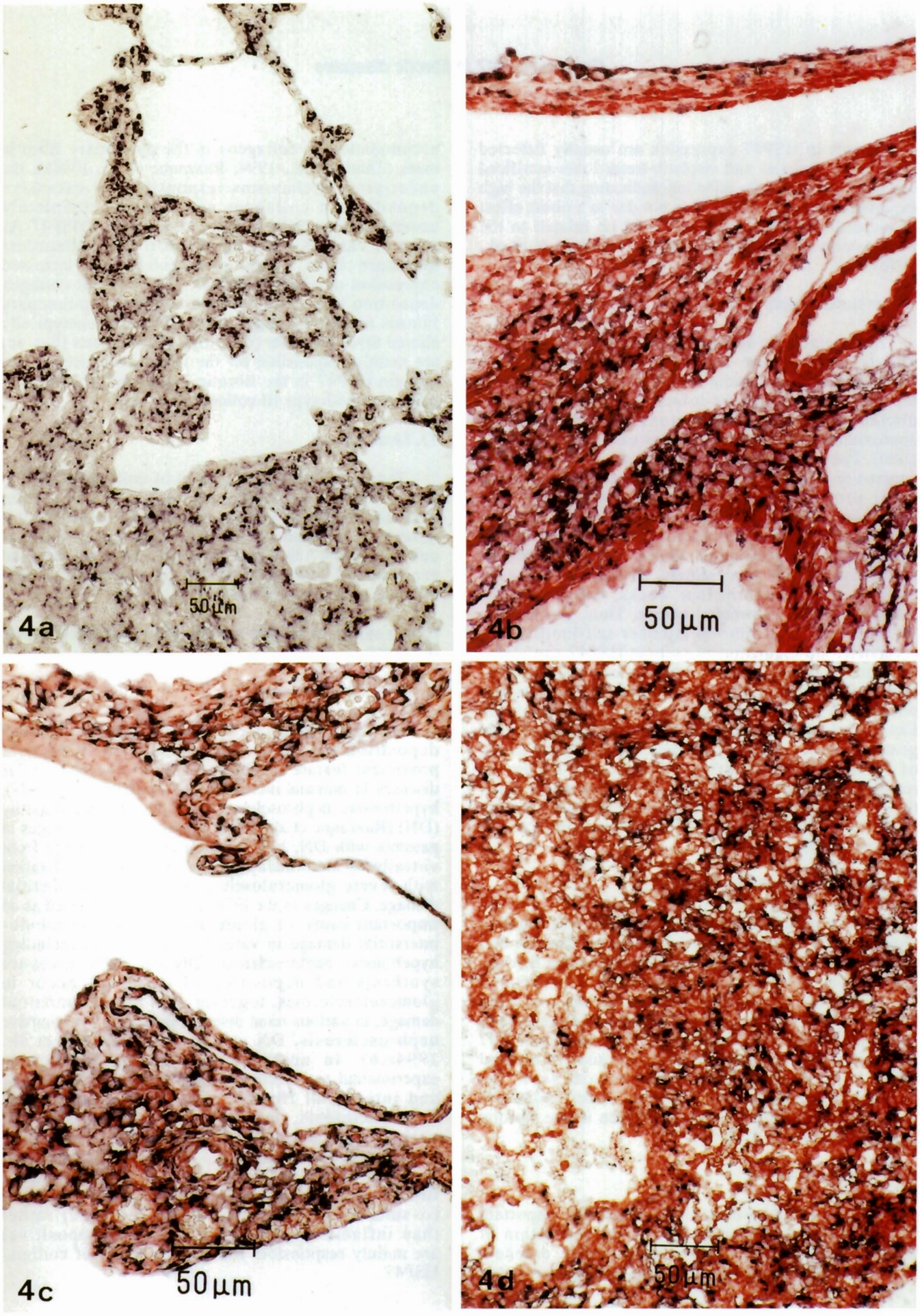
5. Lipid nephropathy

Previous studies have shown that long-term dietary-induced hypercholesterolemia results in a variety of glomerular injuries, including mild glomerular hypercellularity, expansion of mesangial matrix, glomerular infiltration of foam cells and inflammatory cell infiltration; which lead to mild renal dysfunction and proteinuria (Keane et al., 1988; Kasiske et al., 1990; Guijarro et al., 1995). Furthermore, glomerulosclerosis in high cholesterol-fed rats is known to be associated with increased glomerular accumulation of ECM including type IV collagen (Guijarro et al., 1995). In addition, compared to the control kidney (Fig. 3a), there is a phenotypic change in glomerular epithelial cells as shown by the presence of desmin-immunopositivity (Fig. 3b) (Yaoita et al., 1990) in the kidney of rats with dietary-induced hypercholesterolemia. Compared to the control rat kidneys (Fig. 3c), overexpression of colligin/HSP47 is noted in hypercholesteromic rat kidneys; with a predominant expression in the glomeruli (Fig. 3d) (Razzaque and Taguchi, 1999). The phenotypically altered glomerular epithelial cells are the main colligin/HSP47-expressing cells in the hypercholesteromic rat kidneys while, mesangial cells and infiltrating monocytes/macrophages are mostly negative for colligin/HSP47. Furthermore, overexpression of colligin/HSP47 is associated with increased deposition of type IV collagen in the expanded mesangial matrix in hypercholesteromic rat kidneys.

6. Cisplatin nephropathy

Cisplatin is widely used in the treatment of various tumors, although its use is restricted due to its nephrotoxicity (Choie et al., 1980; Goldstein and Mayor, 1983). Cisplatin-induced tubulointerstitial nephritis is one of the major problems encountered in clinical practice, and is characterized by early inflammatory changes with damage to tubular epithelial cells (apoptosis and necrosis) (Razzaque et al., 1997b), followed by tubulointerstitial fibrosis. These structural changes ultimately lead to a gradual deterioration in renal function (Choie et al., 1980; Goldstein and Mayor, 1983). We have also shown that increased expression of colligin/HSP47 in the fibrotic areas of cisplatin nephropathy is associated with deposition of collagens (Razzaque et al., 1996). Furthermore, double-staining showed that vimentin-positive tubular epithelial cells and α-smooth muscle-positive-myofibroblasts also express colligin/HSP47. However, no significant

Fig. 4. Immunohistochemistry for colligin/HSP47 **(a)** in bleomycin-induced pulmonary fibrosis in rats showing increased expression of colligin/HSP47 in and around areas of fibrosis. Double staining reveals that colligin/HSP47 expressing cells are mostly α-smooth muscle actin-positive myofibroblasts **(b)** and vimentin-positive fibroblasts **(c)** and colocalize type III collagen **(d)**. Colligin/HSP47 is stained dark-purple, while α-smooth muscle actin, vimentin and type III collagen are stained intense red in figures b, c and d.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differences in HSP47 expression are usually detected between control rats and cisplatin-treated rats sacrificed one hour after cisplatin injection, indicating that the high expression of colligin/HSP47 is not due to a direct effect of cisplatin as a stressor, but could be related to the progression of interstitial fibrosis (Razzaque et al., 1996).

7. Gentamicin nephropathy

Aminoglycoside antibiotics including gentamicin are widely used in the treatment of gram-negative infections; and gentamicin is still widely prescribed for the treatment of serious infection despite the well-documented acute nephrotoxicity occurring in approximately 10% of all clinical cases (Smoth et al., 1980). The specificity of gentamicin for renal toxicity is apparently related to a preferential accumulation in the renal proximal convoluted tubules (Humes and Weinberg, 1986). Gentamicin nephrotoxicity is associated with tubular necrosis in the early stages followed by regeneration of tubular epithelial cells and interstitial fibrosis. Interestingly, all these pathological changes resolve within four weeks, and the kidney returns to almost normal structure. Thus, gentamicin-induced interstitial fibrosis is rather self-limiting and reversible. Up-regulation of colligin/HSP47 expression is identified during fibrosis, while its expression returns to almost normal level when fibrotic changes resolve within 4 weeks (Cheng et al., 1998). Although the factors that regulate the expression of colligin/HSP47 in gentamicin-treated kidney are not clear, the upregulation of colligin/HSP47 during fibrosis and its down-regulation during the resolution of fibrosis might allow the design of potentially useful therapeutic interventions to reduce the expression of colligin/HSP47 in progressive fibrotic diseases.

9. Unilateral ureteral obstruction model

Unilateral ureteral obstruction is a well studied experimental model of renal interstitial fibrosis and earlier studies have convincingly demonstrated that up-regulation of collagen synthesis with excessive deposition of interstitial collagens are the two main changes responsible for fibrosis. Similar to other models of interstitial fibrosis, the expression of colligin/HSP47 is significantly upregulated after the onset of ureteral obstruction and gradually increases up to one week. The expression of colligin/HSP47 is also closely related to increased deposition of type I collagen in the fibrotic mass (Moriyama et al., 1998).

10. Pulmonary fibrosis

Pulmonary fibrosis is also a clinically important disorder, characterized by increased deposition of various ECM including collagens. However, despite a large number of publications describing increased accumulation of collagens in the pulmonary fibrotic mass (Zhang et al., 1994; Razzaque et al., 1998a), the underlying mechanisms responsible for excessive deposition of collagens are still not completely understood, especially with regard to colligin/HSP47. As seen in various renal sclerotic/fibrotic disorders mentioned above, a close association between increased expression of colligin/HSP47 (Fig. 4a) and collagen deposition is seen in bleomycin-induced pulmonary fibrosis in rats (Razzaque et al., 1998a). Phenotypically altered myofibroblasts (Fig. 4b) and fibroblasts (Fig. 4c) are mainly responsible for the increased expression of colligin/HSP47 in the fibrotic lungs, and are found to colocalize with type III collagen (Fig. 4d).

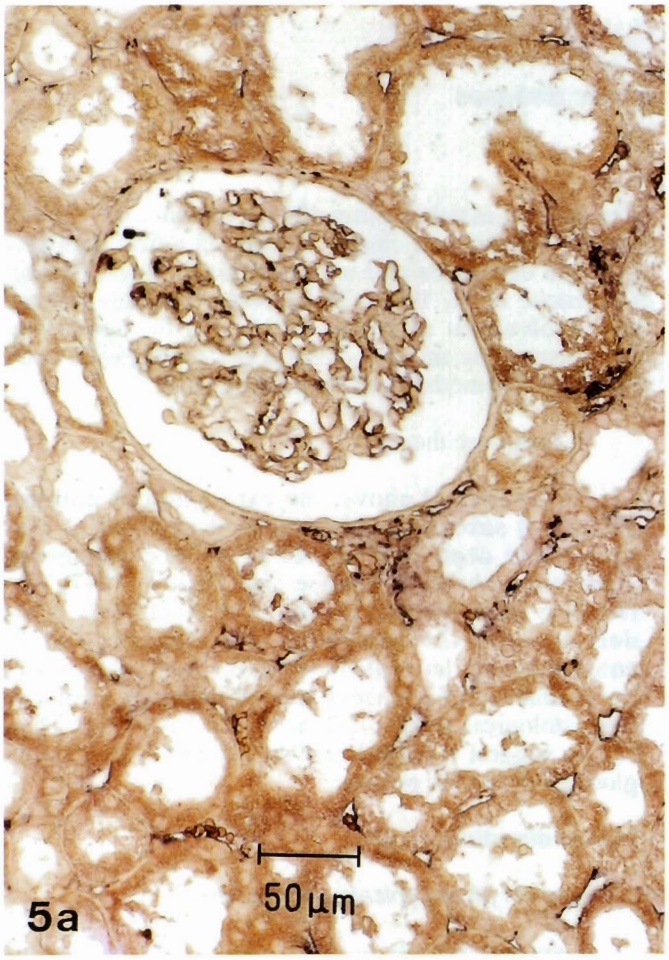
11. Liver fibrosis

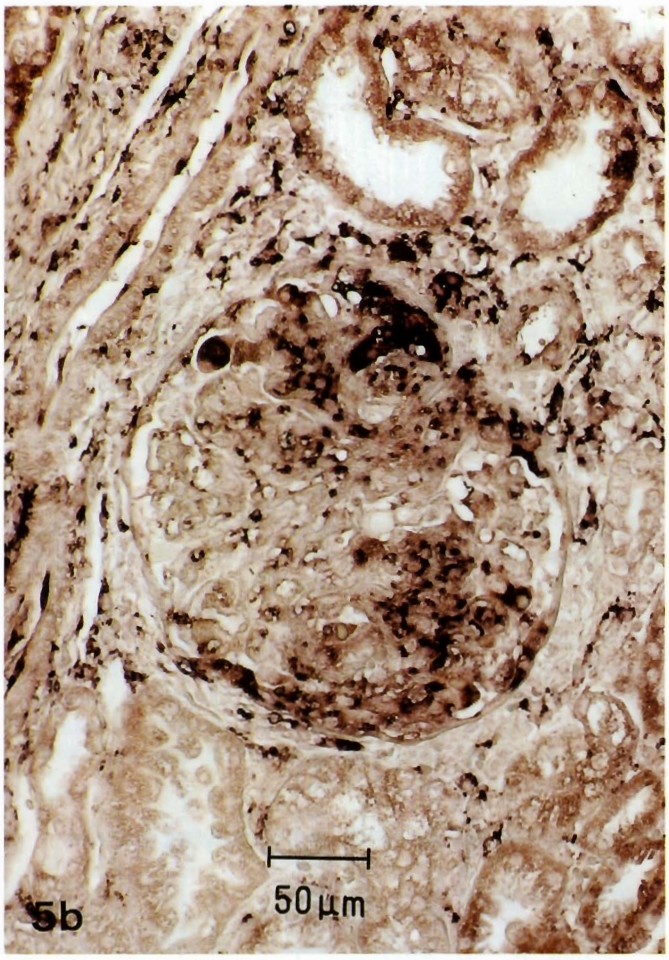
The possible in vivo role(s) of colligin/HSP47 in liver fibrosis was initially suggested in carbon tetrachloride (CCl_4)-induced liver fibrosis model. In this model, a marked increase in the expression of colligin/HSP47 is noted, in parallel with increased expression of collagen during the progression of fibrosis (Masuda et al., 1994; Kawada et al., 1996).

Expression of colligin/HSP47 in human fibrotic diseases

1. Renal fibrotic diseases

Mesangial matrix expansion, due to increased deposition of various components of ECM, is a prominent feature of chronic progressive glomerular diseases in humans including IgA nephropathy (IgAN), hypertensive nephrosclerosis and diabetic nephropathy (DN) (Razzaque et al., 1994a,b). Histological changes in patients with DN, hypertension and IgAN range from virtually no abnormality to mesangial cell proliferation with severe glomerulosclerosis and tubulointerstitial damage. Changes in the ECM have been suggested as an important cause of glomerulosclerosis and tubulo-interstitial damage in various renal diseases including hypertensive nephrosclerosis, DN and IgAN. Excessive synthesis and deposition of collagens occur in glomerulosclerosis, together with tubulointerstitial damage, in various renal diseases including hypertensive nephrosclerosis, DN and IgAN (Razzaque et al., 1994a,b). In accordance with the findings in experimental renal fibrotic diseases, glomerulosclerotic and interstitial fibrotic changes in hypertensive nephrosclerosis, DN and IgAN are associated with upregulation of colligin/HSP47 expression (Fig. 5a-c) (Razzaque et al., 1998b). Furthermore, as seen in various animal models of renal sclerotic/fibrotic diseases, phenotypically altered renal cells (α-smooth muscle actin-immunopositive) rather than inflammatory cells (CD68 immunopositive) are mainly responsible for the expression of colligin/HSP47.





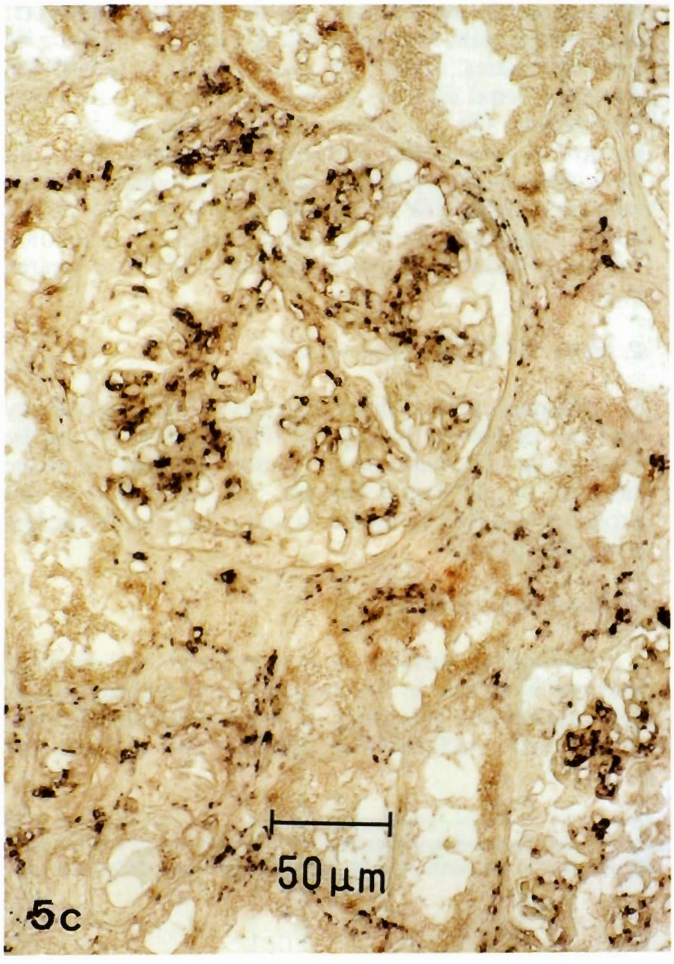


Fig. 5. Immunohistochemistry for colligin/HSP47 in control kidney **(a)**, IgA nephropathy **(b)** and diabetic nephropathy **(c)**. Note that in contrast to the control kidney (a), the expression of colligin/HSP47 is significantly increased in the glomeruli of IgA nephropathy **(d)** and diabetic nephropathy (c).

2. Pulmonary fibrosis

Human pulmonary fibrotic diseases are histologically characterized by proliferation of interstitial cells with deposition of extracellular matrix, predominantly collagens, which subsequently lead to a gradual deterioration of pulmonary function. Autopsy examination of cases with various human pulmonary fibrotic diseases, including organizing pneumonia, interstitial pneumonia, diffuse alveolar damage and pulmonary fibrosis, showed increased deposition of collagen in areas of pulmonary fibrosis, which was associated with overexpression of colligin/HSP47 (Fig. 6a). Double staining showed that colligin/HSP47-expressing cells were mostly myofibroblasts (Fig. 6b) and fibroblasts (Fig. 6c) (Razzaque et al., 1998c). In addition, increased expression of HSP47 was found to colocalize with increased deposition of type III collagen (Fig. 6d). Our results in the human lung were similar to those observed in bleomycin-induced pulmonary fibrosis in rats (Razzaque et al., 1998a).

Modulating colligin/HSP47 and modifying fibrosis

1. In vitro studies

Using in vitro studies, Sauk et al. (1994) demonstrated that phosphorothioate antisense oligodeoxynucleotides to colligin/HSP47 could inhibit the production of colligin/HSP47 and consequently diminish the production of type I procollagen α (1) chains.

2. In vivo models

1. Life-long caloric restriction

We have recently shown that the expression of colligin/HSP47 and collagens in various organs is substantially increased during the sclerotic/fibrotic process, including the aging kidney of F 344 rats (Razzaque et al., 1998e). Since increased expression of colligin/HSP47 was closely associated with age-related fibrotic process in F 344 rats, we speculated that factors altering the fibrotic process in aging kidney should modulate the expression of colligin/HSP47. Earlier studies have shown that life-long dietary restriction can modulate this age-related fibrotic process (Maeda et al., 1985, Razzaque et al., 1999). We postulated that improvement in the renal fibrotic process in rats on dietary-restriction correlated with modulation of colligin/HSP47 expression. In experiments using diet-restricted F 344 rats, we have recently demonstrated that life-long calorie-restriction is associated with a reduced expression of colligin/HSP47 in the kidney, relative to that in aged-matched normally-fed control rats, and that such reduction was closely associated with diminished collagen deposition and improvement in renal histology (Razzaque et al., 1999). These results strongly indicate the involvement of colligin/HSP47 in the age-related fibrotic process and that changes in its expression could subsequently modulate the fibrotic process.

2. Antisense therapy

As mentioned above, the expression of colligin/HSP47 is substantially increased in parallel with glomerular deposition of collagens in experimental glomerulonephritis (Razzaque and Taguchi, 1997). In a recent in vivo study by Sunamoto et al. (1998b), it was demonstrated that inhibition of colligin/HSP47 by antisense oligodeoxynucleotides markedly suppressed the production of collagens and subsequently attenuated the histological manifestations of Thy-1 nephritis. These results suggest a pivotal role for colligin/HSP47 in the glomerulosclerotic process.

Future directions

1. Marker of phenotypically altered cells

α-smooth muscle actin is widely used to identify phenotypically altered renal interstitial cells, glomerular mesangial cells and interstitial cells of the lung in various injuries, while vimentin is used for identifying damaged renal tubular epithelial cells and pulmonary fibroblasts. On the other hand, desmin is used as a marker of glomerular epithelial cell injury. Since all these phenotypically altered cells in the kidney and lung are also colligin/HSP47-expressing cells, colligin/HSP47 could, therefore, be potentially useful as a common marker of various phenotypically altered and/or injured cells.

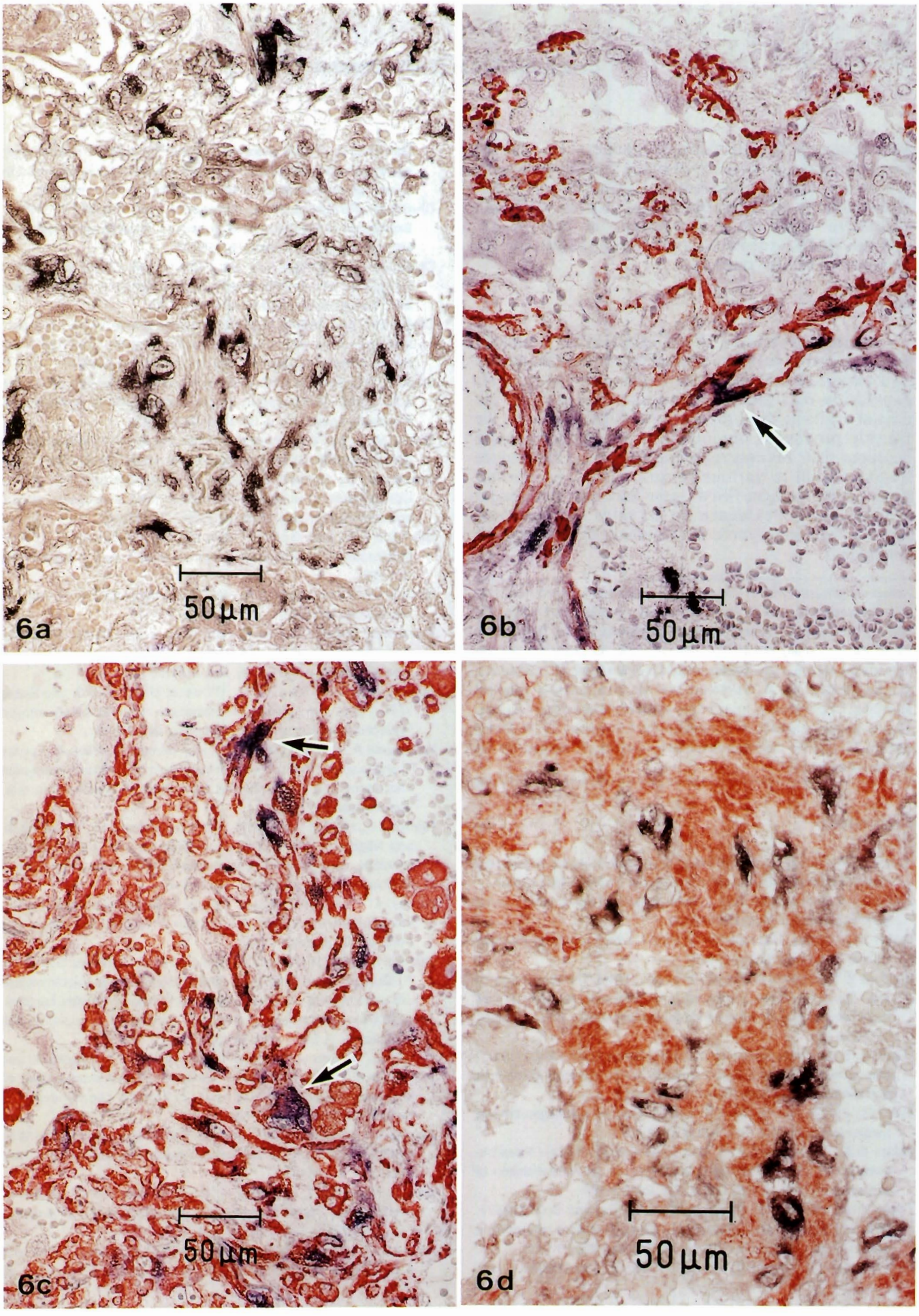
2. Marker of fibrosis and/or healing

Although more work has yet to be done, it is likely that the pattern of colligin/HSP47 expression can be used as an important marker and/or predictor of tissue fibrosis. In addition to fibrosis, the expression of this protein could also be used to monitor the state of healing in various injuries.

3. Therapeutic potentials

Beyond supportive care, no effective or specific therapy is available for the treatment of progressive sclerotic/fibrotic processes in various chronic diseases. Since colligin/HSP47 is actively involved in the

Fig. 6. Immunohistochemistry for colligin/HSP47 in a case of idiopathic pulmonary fibrosis **(a)**, showing overexpression of colligin/HSP47 in and around areas of fibrosis. Double-staining shows that colligin/HSP47 expressing cells are mostly α-smooth muscle actin-positive myofibroblasts **(b)** and vimentin-positive fibroblasts **(c)** and colocalized type III collagen **(d)**.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subsequent sclerotic/fibrotic process in various experimental and human sclerotic/fibrotic diseases, lowering of high levels of colligin/HSP47 might alter/halt/slow the sclerotic/fibrotic process. Although extensive work is still needed, at this stage, colligin/HSP47 seems be a promising target for the treatment of fibrotic diseases.

Conclusions

Induced expression of colligin/HSP47 is closely related to subsequent sclerosis/fibrosis in both human and experimental diseases and modulation of its expression may alter the fibrotic process. With the current available data, the role of colligin/HSP47 in the fibrotic process is obvious, but we still have more questions than answers regarding the factors that induce its expression in various fibrotic disorders. Further studies using colligin/HSP47 gene knockout mice might provide a direct evidence for its roles and functions ranging from embryonic development to pathological conditions.

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