The third path of tubulointerstitial fibrosis: aberrant endothelial secretome

Mark Lipphardt[1,2], Jong W. Song[1,3], Kei Matsumoto[1,4], Sina Dadafarin[1], Hassan Dihazi[2], Gerhard Müller[2] and Michael S. Goligorsky[1]

[1]*Renal Research Institute, Departments of Medicine, Pharmacology and Physiology, New York Medical College at Touro University, Valhalla, New York, USA;* [2]*Department of Nephrology and Rheumatology, Göttingen University Medical Center, Georg August University, Göttingen, Germany;* [3]*Department of Anesthesiology and Pain Medicine, Yonsei University College of Medicine, Seoul, South Korea; and* [4]*Division of Nephrology, Department of Medicine, Showa University School of Medicine, Tokyo, Japan*

The secretome, defined as a portion of proteins secreted by specific cells to the extracellular space, secures a proper microenvironmental niche not only for the donor cells, but also for the neighboring cells, thus maintaining tissue homeostasis. Communication via secretory products exists between endothelial cells and fibroblasts, and this local mechanism maintains the viability and density of each compartment. Endothelial dysfunction, apart from obvious cell-autonomous defects, leads to the aberrant secretome, which predisposes fibroblasts to acquire a myofibroblastic fibrogenic phenotype. In our recent profiling of the secretome of such dysfunctional profibrogenic renal microvascular endothelial cells, we identified unique profibrogenic signatures, among which we detected ligands of Notch and Wnt-β-catenin pathways. Here, we stress the role of reprogramming cues in the immediate microenvironment of (myo)fibroblasts and the contribution of the endothelial secretome to the panoply of instructive signals in the vicinity of fibroblasts. We hope that this brief overview of endothelial-fibroblast communication in health and disease will lead to eventual unbiased proteomic mapping of individual secretomes of glomerular and tubular epithelial cells, pericytes, and podocytes through reductionist approaches to allow for the synthetic creation of a complex network of secretomic signals acting as reprogramming factors on individual cell types in the kidney. Knowledge of profibrogenic and antifibrogenic signatures in the secretome may garner future therapeutic efforts.

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Correspondence: *Michael S. Goligorsky, MD, PhD, NYMC, Basic Sciences Bldg, Room C23, 15 Dana Road, Valhalla, New York, USA, 10595. E-mail: michael_goligorsky@nymc.edu*

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General concept of the secretome

Communication is paramount for homeostasis in biological systems. Impaired communication is implicated in initiation and progression of the majority of chronic diseases, including genetic, neurologic, immune, cardiovascular, and metabolic conditions. Communication is universal wherever a community of individual species exists. The science of *allelopathy*, study of plant-released chemicals that influence growth and survival of neighboring organisms, is an example of plants communicating with each other, or the microbiome of the soil. Positive or negative allelopathy occurs according to whether released chemicals are supportive or harmful to the neighbors. Similar principles operate in the field of communication in the animal kingdom and between various cells. Hierarchical regulation by the central nervous and endocrine systems describes the control mechanisms governing local functions through the central regulators. In parallel with those, there is growing awareness that the local regulators *per se* determine or modulate local functions. More recently, it has been realized that secretory products of individual cells within an organ affect their own behavior, as well as that of neighboring cells and distant organs.

The cell secretome is defined as a portion of proteins secreted to the extracellular space, which in humans constitutes 13%–20% of the entire proteome.[1] More recently, proteins present in microvesicles (100 nm–1 μm in diameter) and exosomes (<100 nm in diameter), both organelles secreted by cells and containing up to 42% of the secretome[2] (see ExoCarta database of exosomal proteins at http://exocarta.ludwig.edu.au), have been incorporated into the original term. Obviously, the secretome is cell- and tissue-specific, and the secretomic signatures change in response to fluctuations in physiologic states or pathologic conditions. Notably, the multitude of nonprotein products released by the cells participate in cell-to-cell communication, but those are considered part of broader angiocrine signaling, a concept closely related to that of the endothelial secretome. Angiocrine signaling is defined as endothelium-produced instructive factors that influence adjacent cells "through secreted or membrane-bound inhibitory and stimulatory growth factors, trophogens, chemokines, cytokines, extracellular matrix components, exosome and other cellular products that are supplied by tissue-specific endothelial cells to help regulate

homeostatic and regenerative processes in a paracrine or juxtacrine manner."[3] Alas, the panoply of those signals is beyond the scope of this brief overview. Not surprisingly, studies of secretome/angiocrine signaling are considered of paramount importance in the discovery of diagnostic tools for cancer, infectious diseases, and senescence messaging and could serve as a guide toward therapeutic strategies or explanation for adaptive transfer of stem cells.[4] The field, however, remains immature.

Interstitial fibroblasts, interlocked between tubular epithelial cells and peritubular capillaries, receive secretory signals from both sources. This raises several questions. "Are instructive signals from those sources unidirectionally coherent or reciprocal?" "How are signals from both sources coordinated?" "How does a fibroblast make a decision as to which source to prefer in every case?" Very little information exists to address such a complexity of the four-cellular compartment (endothelial and epithelial cells, pericytes, and fibroblasts). Here, we shall take a reductionist approach and intentionally simplify the task to describe a role of the endothelial secretome in kidney maintenance, repair, or fibrogenesis[5] (Figure 1).

Ancestral uncertainty of myofibroblasts

True to the Virchow's theory of cell pathology, 2 main hypotheses currently ascribe progression of chronic kidney disease (CKD) to either the epithelial-mesenchymal transition and its more recent partial epithelial-mesenchymal transition variation,[6–8] or the pericyte-mesenchymal transition.[9] (Circulating fibrocytes, advocated by Asada *et al.*,[10] may represent yet another source of fibroblasts.) Although each of the proposed derivations has generated experimental evidence, at times conflicting, it is undisputed that fibrogenesis is a result of convergence of these pathways to generate myofibroblasts or to actuate the transition of quiescent fibroblasts to the matrix-synthesizing contractile myofibroblasts. Multiple reviews and explanatory comments[11,12] detail these pathways; thus they will be out of the scope of this review. Instead, we shall focus on fledgling data to suggest the existence of the third, endothelial, pathway of fibrogenesis.

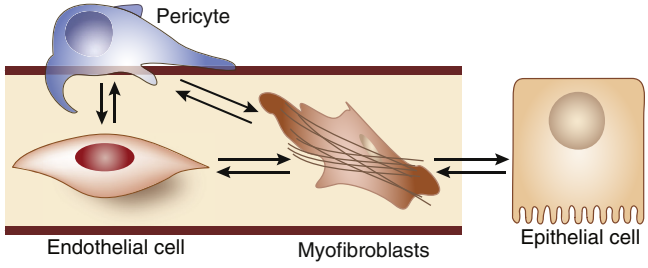

Figure 1 | Four-compartment model of (myo)fibroblast cross-talk with endothelial and epithelial cells. Pink background brackets the main subject of the present discussion. (Most recently, the fifth cell type, kidney-resident macrophage, closely associated with the peritubular capillary bed, has been identified).[5]

In general, vascular endothelium, apart from playing a supportive role in the maintenance of vascular structure and tissue architecture,[3] participates in acute kidney injury and in progression or regression of CKD,[13,14] in part through deployment of diverse secretory products. What is the proof that endothelial cells possess the capacity to affect the fibrogenic behavior of the neighboring cells, such as (myo)fibroblasts? In our studies of mice with the catalytically disabled silent information regulation homolog 2 (SIRT1) exclusively in endothelial cells, which are nearly indistinguishable from control mice under basal conditions, we found an exaggerated fibrogenesis after application of diverse noxious stimuli.[15] On the other hand, mice that are heterozygous for transforming growth factor (TGF) receptor 2 exclusively in endothelial cells, while indistinct from controls under basal conditions, are significantly protected against fibrogenic stressful stimuli.[16] Such opposing responses to fibrogenic stimuli in mice, distinguishable exclusively by their endothelial cell metabolic and signaling properties, can be attributed to context-dependent contrasting signals that emanate from the vascular endothelium and differentially instruct (myo)fibroblasts to attain a profibrogenic or antifibrogenic phenotype.

Here, we advance the thesis that the endothelial cell is an independent modifier of fibrogenesis. Modification is accomplished mainly by the action of the endothelial secretome on the (myo)fibroblast (paracrine regulation), as well as on endothelial cells (juxtacrine regulation). On the other hand, there may exist a counter-regulatory loop through a recently advocated putative (myo)fibroblast-to-endothelial cell transition supporting angiogenesis (see below) (Figure 2). In either case, however, this is accomplished by the secretome-induced changes in the cellular microenvironment. Notably, the juxtacrine endothelial signaling or paracrine signals from neighboring cells participate in pruning of renal microvasculature leading to its rarefaction, a critical driver of fibrogenesis. (The most recent analysis has confirmed this concept investigated by Bohle's group and Johnson's group.[17–19]) The existing dichotomy of the endothelial secretome is illustrated in Figure 2. While normally the secretome maintains the stem/progenitor cell niche and supports the neighboring epithelia, under pathologic conditions, the endothelial secretome provides instructions for regeneration and fibrosis: the balance between the two determines the outcome. Distinct mechanistic elements of such signaling are enumerated in the lower part of the Figure 2.

Myofibroblasts and tissue rigidity

Every researcher who has ever cultured primary epithelial or endothelial cells knows first-hand that, after several passages, these cells acquire a fibroblastic phenotype. Fibroblasts, not surprisingly, comprise a heterogeneous population. Indeed, they derive from distinct embryologic roots (For instance, dermal fibroblasts, depending on the site, derive from the dermomyotome or neural crest.[20–24]) Fetal fibroblasts derive from the undifferentiated mesenchyme and critically differ from their adult progeny in the ability to achieve scar-free

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