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## «TGF-BETA EN LA PROGRESIÓN DE LA LESIÓN RENAL»

# *Angiotensin II and TGF-β in Progression of Fibrotic Renal Disease: Beyond Hemodynamics*

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Better understanding of the hemodynamic-independent actions of the renin-angiotensin system (RAS) may lead to improved therapies for renal fibrosis. The conventional view of the RAS is that its role is solely hemodynamic. The RAS maintains systemic blood pressure, modulates glomerular pressure and flow and regulates sodium and potassium transport in the renal tubule. Pharmacologic blockade of the RAS is beneficial in treating hypertension, as well as primary renal and cardiac diseases. The therapeutic benefits are attributed to blocking the hemodynamic effects of RAS e.g., lowering blood pressure or intraglomerular pressure. Of course this is all true, but it appears to be only part of the explanation of the therapeutic effects. Recent findings from several laboratories using different experimental approaches have revealed a whole new dimension to the RAS that is beyond the realm of hemodynamics. This new understanding of the RAS has important clinical implications. It predicts and explains why blockade of the RAS, with angiotensin converting enzyme (ACE) inhibitors, the newer receptor antagonists or both together will significantly slow the progression of renal disease but not stop it i.e., renal protection, but not prevention. However, it further suggests that a combination of angiotensin II blockade with another agent(s) may truly halt progressive fibrosis.

The new picture of the biological role of the RAS that is emerging is that it is best viewed as part of a system of interconnected emergency «911» molecules designed to be activated following tissue injury. The purpose of the «911» molecules is to preserve biological integrity and function by maintaining blood flow, stopping hemorrhage, and initiating the complex task of tissue repair. A paradigm for «911» molecules is the recent discovery that angiotensin II stimulates and enhances the production of both plasminogen activator inhibitor-type I (PAI-I) and transforming growth factor-β (TGF-β). Why this interconnection? The vital role of the RAS in maintaining blood pressure and organ perfusion in response to volume depletion or blood loss is well understood. PAI-I is key to stabilizing a fibrin clot, that stops hemorrhage and which also acts as a provisional matrix at the initiation of tissue repair. PAI-I also facilitates the deposition of new extracellular matrix by preventing its degradation by newly generated plasmin. TGF-β's role is to deposit new extracellular matrix by simultaneously stimulating its synthesis, inhibiting its degradation by also stimulating PAI-I production and by modulating the expression of new cell matrix receptors that facilitate extracellular matrix deposition. TGF-β also regulates the actions of other cytokines that induce cell proliferation and angiogenesis.

Thus activation of the RAS leads, not only to protective hemodynamic changes, but also to a comprehensive «911» response to repair injured tissue via induction of PAI-I and TGF-β. But herein lies two problems with important clinical implications: 1) If the overexpression of PAI-I and TGF-β is not terminated, it will lead to pathological accumulation of extracellular matrix which is fibrosis. 2) Although angiotensin II can activate and sustain a «911» response, blockade of angiotensin II with drugs, even at super doses only partially turns the response off. Thus these drugs slow the progression of fibrosis, but do not stop it. There are several possible reasons for this that are not mutually exclusive. For example, the «911» response may be biologically too important to be easily turned off by blocking only one arm or the

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underlying active disease process may continue to activate the system through pathways other than RAS. This suggests that a combination of angiotensin II blockade with an agent targeted at other factor(s) might normalize TGF-β expression and thus halt progressive renal fibrosis.