

Letter to the Editor

A default renal regeneration in chronic kidney disease

Narisa Futrakul^a and Monnipha Sila-asna^b

^a *Physiology Department, King Chulalongkorn Memorial Hospital, Bangkok 10330, Thailand*

^b *Institute for Research and Development of Technological Science, Salaya, Mahidol University, Nakornpathom 73170, Thailand*

As it is well established, the normal balance between renal microvascular injury and renal microvascular regeneration maintains the normal vascular integrity. In previous papers [1–3], we showed that: (1) in the normal balanced stage, renal microvascular injury may be induced by the enhancement of circulating toxins such as oxidative stress, associated with altered immunocirculatory balance between pro-inflammatory and anti-inflammatory cytokines; (2) increased circulating toxin activity may induce renal microvascular endothelial injury expressed as enhanced circulating endothelial cell loss and enhanced *in vitro* endothelial cell cytotoxicity; (3) glomerular endothelial cell dysfunction may be associated with elevation of renal arteriolar resistance and reductions in renal plasma flow and peritubular capillary flow. In this letter, we like to report that such renal microvascular injury may be well compensated in general population by minimized circulating toxins through enhanced antioxidant activity such as glutathione, vitamins C and E, and anti-inflammatory cytokine interleukin-10.

The figure shows our hypothesized mechanism responsible for the renal regeneration in chronic kidney diseases. The response is initiated with recruitment of endothelial progenitor cells to the site of vascular injury. Endothelial progenitor cell is triggered by increment of vascular endothelial growth factor (VEGF). The enhanced VEGF activates eNOS activity through Flt-1 receptor or VEGF receptor-1, by which it enhances NO production. In addition, such repair triggers angiopoietin-1 which acts through tie-2 receptor and results in inducing normal strength and maturation of endothelium. All these preceding factors would encompass in the regenerative process of normal vascular repair.

It must be mentioned here that multiple complex factors may induce defective state of the renal microvascular regeneration in chronic kidney disease. There are a number of evidences indicating a defective VEGF by which it activates the alternative path through KDR receptor and induces uncoupling of eNOS and eventually decreases the NO production [4,5]. In addition, reduction in NO production is complicated by deficiencies in its substrate arginine and cofactor tetrahydrobiopterin (BH₄) due to enhanced oxidative stress [6]. Endothelial progenitor cell is encountered to be depleted in chronic kidney disease by uremic environment as well as by depletion of erythropoietin. A depleted state of bioavailable NO in conjunction with a deficient VEGF would impair regeneration and proliferation of endothelial cell. Instead, the enhanced angiopoietin-2 encountered in chronic kidney disease would alternatively

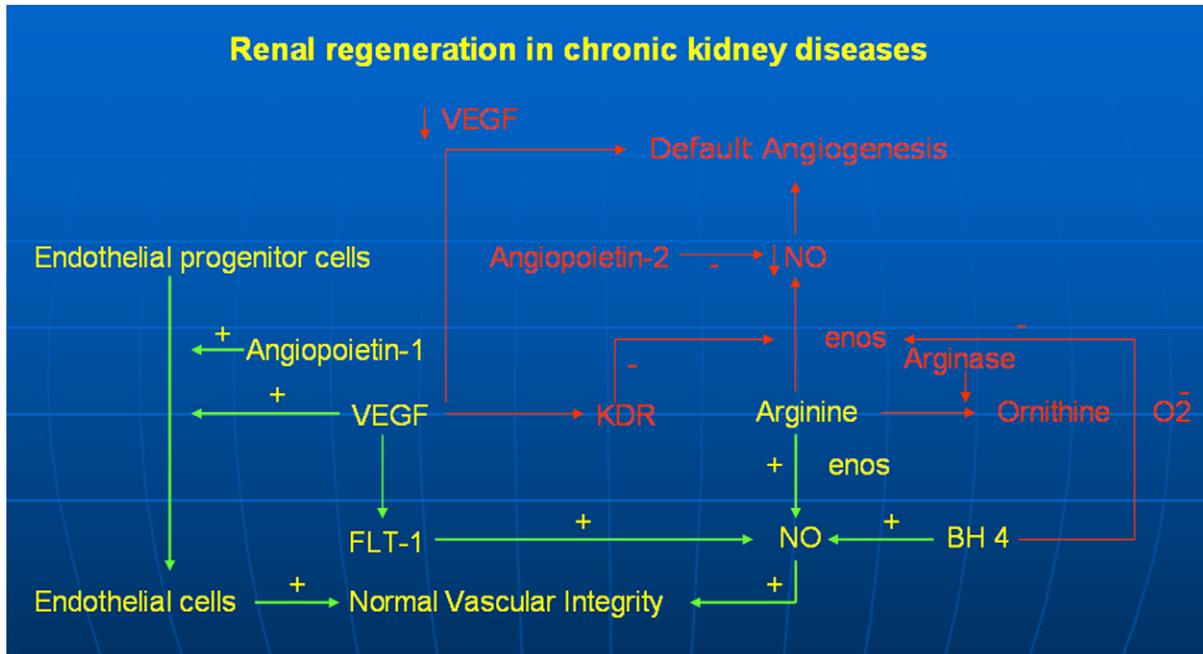


Fig. 1. Mechanism of renal regeneration. Thick arrow indicates normal endothelial regeneration, while thin arrow indicates default angiogenesis in chronic disease.

activate the proliferation of smooth muscle cell and induce a default angiogenesis and renal microvascular rarefaction which would continuously produce an ischemic injury to the tubulointerstitial structure [7].

This study is supported by Thailand Research Fund and National Research Council Fund.

References

- [1] N. Futrakul, M. Boonyen, S. Patumraj, P. Siriviriyakul, P. Tosukhowong and P. Futrakul, Treatment of glomerular endothelial dysfunction in steroid-resistant nephrosis with *Ganoderma lucidum*, vitamins C, E and vasodilators, *Clin. Hemorheol. Microcirc.* **29** (2003), 205–210.
- [2] N. Futrakul, T. Panichakul, S. Sirisinha, P. Futrakul and P. Siriviriyakul, Glomerular endothelial dysfunction in chronic kidney disease, *Ren. Fail.* **26** (2004), 259–264.
- [3] N. Futrakul, P. Butthep, V. Vongthavarawat, P. Futrakul, S. Sirisalipoch, T. Chaivatnarat and S. Suwanwalaikorn, Early detection of endothelial injury and dysfunction in conjunction with correction of hemodynamic maladjustment can effectively restore renal function in type 2 diabetic nephropathy, *Clin. Hemorheol. Microcirc.* **34** (2006), 373–381.
- [4] N. Futrakul, P. Butthep, S. Patumrak, P. Siriviriyakul and P. Futrakul, Microvascular disease and endothelial dysfunction in chronic kidney diseases: therapeutic implication, *Clin. Hemorheol. Microcirc.* **34** (2006), 265–271.
- [5] U. Forstermann and T. Munzel, Endothelial nitric oxide synthase in vascular disease from marvel to menace, *Circulation* **113** (2006), 1708–1714.
- [6] U. Fiedler, Y. Reiss, M. Scharfenecker, V. Grunow, S. Koidl, G. Thurston, N.W. Gale, M. Witznath, S. Rosseau, N. Suttorp, A. Sobke, M. Herrmann, K.T. Preisoner, P. Vajkoezy and H.G. Augustin, Angiopoietin-2 sensitizes endothelial cells to TNF- α and has a crucial role in the induction of inflammation, *Nat. Med.* **12** (2006), 235–239.
- [7] A.I. Nykanen, R. Krebs, A. Saaristo, P. Turunen, K. Alitalo, S. Yla-Herttuala, P.K. Koskinen and K.B. Lemstrom, Angiopoietin-1 protects against the development of cardiac allograft arteriosclerosis, *Circulation* **107** (2003), 1308–1314.