Hypertension Research (2010) 33, 114–115

www.nature.com/hr

COMMENTARY

Does therapeutic angiogenesis overcome CKD?

Yoshiaki Taniyama and Ryuichi Morishita

Hypertension Research (2010) **33,** 114–115; doi:10.1038/hr.2009.208; published online 11 December 2009

CKD AND CHRONIC HYPOXIA

Recent studies have emphasized the role of chronic hypoxia in the tubulointerstitium as a final common pathway in end-stage renal disease,[1] and showed that hypoxia in the kidney induces pro-fibrotic changes.[2] Hence, oxygenation in the kidney is likely to be a critical determinant of its life. In this context, renal protective effects of angiogenic factors, such as vascular endothelial growth factor (VEGF),[3] hepatocyte growth factor[4] and hypoxia-inducible factor,[5] are reported with some problems[6–8] (Figure 1).

This issue of *Hypertension Research* includes a paper by Noboru Fukuda and coworkers that addresses the effect of Sall1 on angiogenesis.[9] The *Sall1* gene is required for multiple developmental processes, and regulates morphogenesis and organogenesis especially in the kidney. On the other hand, VEGF has a critical role in renal development by promoting endothelial cell differentiation, capillary formation and proliferation of tubular epithelial cells, so the authors investigated the relationship between Sall1 and VEGF. *Sall1* gene transfer induces capillary neovascular formation in the rat cornea and mouse embryoid bodies, and increases VEGF-A promoter activity in HEK293T cells. This angiogenesis is inhibited by anti-VEGF neutralizing antibody. *Sall1*-deficient mice show severe renal dysplasia or complete renal agenesis, but normal vascular development.[10] It is unclear whether Sall1 affects vascular development, but Sall1 may induce renal organogenesis through angiogenic properties. *SALL1* expression is reduced in patients with[7] congenital dysplastic kidneys,[11] as well as in congenital obstructive nephropathy[12] (Figure 2), so therapeutic angiogenesis by *SALL1* gene transfer may rescue the kidney in patients with CKD.

Y Taniyama and R Morishita are at the Department of Clinical Gene Therapy, Osaka University Graduate School of Medicine, 2-2 Yamada-oka, Suita, Osaka 565-0871, Japan.
E-mail: taniyama@cgt.med.osaka-u.ac.jp

SALL1 IS A MEMBER OF *SPALT* FAMILY

The homeotic *spalt* gene of *Drosophila melanogaster* determines the identity of the anterior head and the posterior tail regions during early development.[13,14] At later stages, *spalt* is involved in the development of the wing disk, trachea and sensory organs.[15,16] Humans and mice have four functional *spalt*-related genes, *SALL1* to *SALL4* (*Sall1* to *Sall4* in mice). The human *SALL1* gene encodes transcription factors with a characteristic structure of evenly distributed zinc-finger domains. Human SALL1 has been described as a transcriptional repressor in a number of experimental settings, most of them involving the regulation of heterologous promoters fused to reporter genes.[10] *SALL1* gene expression is related to some human congenital diseases[11,12,15,17–19] (Figure 2). In particular, mutations in *SALL1* result in Townes–Brocks syndrome, a rare autosomal-dominant malformation syndrome characterized by dysplastic ears, pre-axial polydactyly and/or triphalangeal thumbs, imperforate anus, renal malformations and cardiac anomalies.[17] Confirming the role of *Sall1* in kidney formation, *SALL1* expression is reduced in patients with congenital dysplastic kidneys, a major cause of renal failure in infants,[11] as well as in congenital obstructive nephropathy, a common disease affecting the fetus and young children.[12]

In contrast, murine Sall1 was seen to function as a transcriptional repressor of the artificial promoter containing tandem GAL4-binding sites, when linked to the heterologous GAL4 DNA-binding domain, and also Sall1 was associated with HDAC and several components of the chromatin-remodeling complex.[20,21] Therefore, Sall1 could repress gene expression by recruiting the HDAC complex. On the other hand, Nishinakamura *et al.*[22] reported that the native form of Sall1 could function as a transcriptional activator in Wnt signaling, which is essential for many developmental processes, and that its activity correlated with its localization to heterochromatin. An increase in Sall1 proteins may squelch some transcriptional repressor complex, including HDAC, or be associated with chromatin-remodeling factors to alter the chromatin structure near the promoter region of Wnt target genes.

SALL1 AND RENAL STEM CELL

Moreover, Sall1 is necessary for the activation of some kidney mesenchymal markers, consistent with its role in ureteric bud invasion. Homozygous deletion in mice induces severe defects in the kidney, which indicates that Sall1 has an essential role in kidney development. Murine Sall1 has a role in maintaining cellular pluripotency and proliferation.[10] Thus, renal primordial cells in the ureteric bud epithelium and metanephric mesenchyme are able to produce nephrons and collecting ducts when induced from pluripotent embryonic stem cells. Only cells expressing high levels of *Sall1* can reconstitute a three-dimensional kidney structure in an organ culture setting, indicating that renal progenitors with multipotent capacity require Sall1.[23,24] In these cells, Sall1 is not required for the generation or differentiation of renal progenitors, but for their proliferation or survival.[23]

DOES *SALL1* GENE TRANSFER OVERCOME CKD?

Potentially, *SALL1* gene transfer may improve hypoxia through VEGF-induced angiogenesis and promote renal organogenesis to counteract CKD. VEGF is an essential molecule for glomerular structure, but recently deleterious effects of VEGF have been demonstrated in diabetic nephropathy.[6] Careful monitoring is therefore required in its use in CKD patients with diabetes.

Merit	Demerit
VEGF⇒ Angiogenesis, Anti-apoptosis	Diabetic nephropathy
HGF ⇒ Angiogenesis, TGF-beta inhibition	Cystic disease?
HIF ⇒ Angiogenesis,	EMT?
Sall1 ⇒ Angiogenesis, Renal stem cell?	Diabetic nephropathy?

Figure 1 Therapeutic angiogenesis for kidney disease were reported using VEGF, HGF and HIF. Each factor has a merit and demerit. The function of sall1 is not so clear, but sall1 may promote renal organogenesis. HGF; hepatocyte growth factor, HIF; hypoxia-inducible factor, EMT; epithelial–mesenchymal transformation.

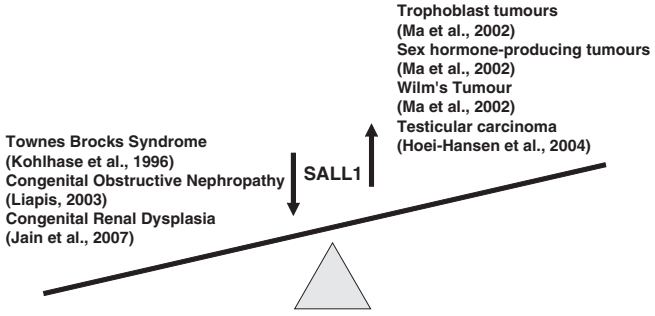

Figure 2 *SALL1* expression is reduced in patients with Townes–Brocks syndrome, congenital dysplastic kidneys and congenital obstructive nephropathy. On the other hand, *SALL1* expression is induced in patients with trophoblast tumors, sex hormone-producing tumors, Wilm's tumor and testicular carcinoma.

1 Eckardt KU, Bernhardt WM, Weidemann A, Warnecke C, Rosenberger C, Wiesener MS, Willam C. Role of hypoxia in the pathogenesis of renal disease. *Kidney Int Suppl* 2005; **99**: S46–S51.
2 Manotham K, Tanaka T, Matsumoto M, Ohse T, Inagi R, Miyata T, Kurokawa K, Fujita T, Ingelfinger JR, Nangaku M. Transdifferentiation of cultured tubular cells induced by hypoxia. *Kidney Int* 2004; **65**: 871–880.
3 Kim YG, Suga SI, Kang DH, Jefferson JA, Mazzali M, Gordon KL, Matsui K, Breiteneder-Geleff S, Shankland SJ, Hughes J, Kerjaschki D, Schreiner GF, Johnson RJ. Vascular endothelial growth factor accelerates renal recovery in experimental thrombotic microangiopathy. *Kidney Int* 2000; **58**: 2390–2399.
4 Yang J, Dai C, Liu Y. Systemic administration of naked plasmid encoding hepatocyte growth factor ameliorates chronic renal fibrosis in mice. *Gene Ther* 2001; **8**: 1470–1479.
5 Manotham K, Tanaka T, Ohse T, Kojima I, Miyata T, Inagi R, Tanaka H, Sassa R, Fujita T, Nangaku M. A biologic role of HIF-1 in the renal medulla. *Kidney Int* 2005; **67**: 1428–1439.
6 Doi K, Noiri E, Fujita T. Role of vascular endothelial growth factor in kidney disease. *Curr Vasc Pharmacol* (in press)
7 Takayama H, LaRochelle WJ, Sabnis SG, Otsuka T, Merlino G. Renal tubular hyperplasia, polycystic disease, and glomerulosclerosis in transgenic mice overexpressing hepatocyte growth factor/scatter factor. *Lab Invest* 1997; **77**: 131–138.
8 Higgins DF, Kimura K, Bernhardt WM, Shrimanker N, Akai Y, Hohenstein B, Saito Y, Johnson RS, Kretzler M, Cohen CD, Eckardt KU, Iwano M, Haase VH. Hypoxia promotes fibrogenesis *in vivo* via HIF-1 stimulation of epithelial-to-mesenchymal transition. *J Clin Invest* 2007; **117**: 3810–3820.
9 Yamamoto M, Fukuda N, Matsumoto T, Higuchi T, Ueno T, and Matsumoto K. Zinc-finger transcriptional factor Sall1 induces angiogenesis by activation of the gene for VEGF-A. *Hypertens Res* 2010; **33**: 143–148.
10 Nishinakamura R, Matsumoto Y, Nakao K, Nakamura K, Sato A, Copeland NG, Gilbert DJ, Jenkins NA, Scully S, Lacey DL, Katsuki M, Asashima M, Yokota T. Murine homolog of SALL1 is essential for ureteric bud invasion in kidney development. *Development* 2001; **128**: 3105–3115.
11 Jain S, Suarez AA, McGuire J, Liapis H. Expression profiles of congenital renal dysplasia reveal new insights into renal development and disease. *Pediatr Nephrol* 2007; **22**: 962–974.
12 Liapis H. Biology of congenital obstructive nephropathy. *Nephron Exp Nephrol* 2003; **93**: e87–e91.
13 Jurgens G. Head and tail development of the Drosophila embryo involves spalt, a novel homeotic gene. *EMBO J* 1988; **7**: 189–196.
14 Kuhnlein RP, Frommer G, Friedrich M, Gonzalez-Gaitan M, Weber A, Wagner-Bernholz JF, Gehring WJ, Jackle H, Schuh R. *spalt* encodes an evolutionarily conserved zinc finger protein of novel structure, which provides homeotic gene function in the head and tail region of the Drosophila embryo. *EMBO J* 1994; **13**: 168–179.
15 de Celis JF, Barrio R. Regulation and function of Spalt proteins during animal development. *Int J Dev Biol* 2009; **53**: 1385–1396.
16 Kuhnlein RP, Schuh R. Dual function of the region-specific homeotic gene *spalt* during Drosophila tracheal system development. *Development* 1996; **122**: 2215–2223.
17 Kohlhase J, Wischermann A, Reichenbach H, Froster U, Engel W. Mutations in the SALL1 putative transcription factor gene cause Townes-Brocks syndrome. *Nat Genet* 1998; **18**: 81–83.
18 Ma Y, Chai L, Cortez SC, Stopa EG, Steinhoff MM, Ford D, Morgan J, Maizel AL. SALL1 expression in the human pituitary-adrenal/gonadal axis. *J Endocrinol* 2002; **173**: 437–448.
19 Hoei-Hansen CE, Nielsen JE, Almstrup K, Hansen MA, Skakkebaek NE, Rajpert-DeMeyts E, Leffers H. Identification of genes differentially expressed in testes containing carcinoma *in situ*. *Mol Hum Reprod* 2004; **10**: 423–431.
20 Netzer C, Rieger L, Brero A, Zhang CD, Hinzke M, Kohlhase J, Bohlander SK. SALL1, the gene mutated in Townes-Brocks syndrome, encodes a transcriptional repressor which interacts with TRF1/PIN2 and localizes to pericentromeric heterochromatin. *Hum Mol Genet* 2001; **10**: 3017–3024.
21 Kiefer SM, Ohlemiller KK, Yang J, McDill BW, Kohlhase J, Rauchman M. Expression of a truncated Sall1 transcriptional repressor is responsible for Townes-Brocks syndrome birth defects. *Hum Mol Genet* 2003; **12**: 2221–2227.
22 Sato A, Kishida S, Tanaka T, Kikuchi A, Kodama T, Asashima M, Nishinakamura R. Sall1, a causative gene for Townes-Brocks syndrome, enhances the canonical Wnt signaling by localizing to heterochromatin. *Biochem Biophys Res Commun* 2004; **319**: 103–113.
23 Osafune K, Takasato M, Kispert A, Asashima M, Nishinakamura R. Identification of multipotent progenitors in the embryonic mouse kidney by a novel colony-forming assay. *Development* 2006; **133**: 151–161.
24 Yamamoto M, Cui L, Johkura K, Asanuma K, Okouchi Y, Ogiwara N, Sasaki K. Branching ducts similar to mesonephric ducts or ureteric buds in teratomas originating from mouse embryonic stem cells. *Am J Physiol Renal Physiol* 2006; **290**: F52–F60.