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Editorial

An Update on von Hippel-Lindau Disease and Related Translational Research

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von Hippel-Lindau (VHL) disease is an autosomal dominant hereditary multicancer syndrome manifesting as central nervous system (CNS) hemangioblastoma, retinal hemangioma, renal cell cancer, pheochromocytoma or pancreatic neuroendocrine tumor [1]. Through progress in the diagnosis and therapy of these tumors and identification of the causative gene (von Hippel-Lindau tumor suppressor gene) [2], most patients with this disorder have been accurately diagnosed and satisfactorily treated, but the pathogenesis of these tumors is not yet fully clear. CNS hemangioblastoma is suggested to originate from embryonic hemangioblasts, and it develops exclusively in the cerebellum, spinal cord, and brain stem [3]. The treatment for CNS hemangioblastoma is basically by surgery, but occasionally by radiation, mainly stereotaxic irradiation. The degree of difficulty of treatment for this CNS tumor depends on its location [4-6]. However, most of them are resectable without neurological deficits [4-6]. In VHL disease, a clear cell type of renal cell carcinoma (RCC) multiplies and develops bilaterally [7]. Recently, treatment of RCC associated with *VHL* disease is by laparoscopic enucleation [8] or radiofrequency ablation [9]; and new anti-cancer drugs have elongated the overall survival of RCC patients [10]. Retinal hemangiomas are usually treated by cryotherapy or laser photocoagulation [11], but recently new approaches have been tried [12]. Pheochromocytoma associated with *VHL* disease is a manifestation of VHL type 2 [13]. Measurement of catecholamines and their metabolic products in blood and urine is necessary for the diagnosis. Partial adrenalectomy to preserve glandular function is recommended as the operation for pheochromocytoma associated with VHL [14]. Pancreatic neuroendocrine tumors (P-NETs) are occasionally associated with VHL disease. These tumors are of low malignancy, but frequently metastasize to the liver. Resectable lesions of P-NET are candidates for function-reserving surgery, with or without metastasis [15]. Identification of the causative gene, von Hippel-Lindau tumor suppressor gene (*VHL* gene), has enabled genetic testing for von Hippel-Lindau disease [16]. The mutation sites (genotypes) are related to the types of developing tumors (phenotypes), and genetic testing affords identification of carriers of mutated *VHL* genes. Hot spots of germline mutations, identified in exon 3 of the *VHL* gene, are correlated with type-2 *VHL* with pheochromocytoma [17]. At present, treatment guidelines for tumors associated with *VHL* disease are available in various countries. Functions of *VHL* protein include inhibition of mRNA elongation [18], inhibition of hypoxia inducible factor-α1 under normoxia [19], and induction of neuronal differentiation by neuronal stem cells [20]. The basic function of *VHL* protein is considered to depend on a multi-protein VHL complex containing elongin B, elongin C, cul-2, and Rbx1, with the *VHL* complex functioning as an E3 ubiquitin ligase. Then, it was reported that VHL proteins harboring mutations that disrupt elongin BC binding are unstable and rapidly degraded by proteasomes and that wild-type VHL proteins are directly stabilized by associating

with both elongins B and C [21]. In addition, it has been suggested that VHL protein plays an important role not only in neuronal differentiation of neural stem cells, but also in transcription in cancer stem cells via inhibition of Stat 3 [22]. Therefore, as translational research related to *VHL*, neuronal regenerative therapy with transplantation of VHL-peptide-treated stem cells appears to be promising [23-26], and the use of *VHL* protein for the regulation of cancer might also be useful [22].

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