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The role of transforming growth factor-β signaling and hypoxia-inducible factors in renal cell carcinoma

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Abstract
Renal cell carcinoma (RCC) is the cancer of the kidneys; about 1000 cases of RCCs are diagnosed in Sweden each year. RCC can be classified into several subtypes, clear cell renal cell carcinoma (ccRCC) is most common accounting to about 70% of all RCCs, and also the most lethal; papillary renal cell carcinoma (pRCC) accounts to about 10%-15%, while chromophobe renal cell carcinoma (chRCC) accounts to about 5% of all RCCs. There is a need to study the distinguishing features of RCC subtypes to design treatment. Von Hippel-Lindau tumor suppressor gene (VHL) is often inactivated in ccRCC, unlike in pRCC or chRCC. Transforming growth factor-β (TGF-β) is a cytokine involved in various biological processes such as differentiation, proliferation, apoptosis, migration, and epithelial-mesenchymal transition. TGF-β exerts its functions through canonical (Smad-dependent) and non-canonical (Smad-independent) signaling pathways. In the first study, we have shown that both canonical and non-canonical TGF-β signaling pathways are associated with ccRCC tumor progression. VHL is known to have a dampening effect on TGF-β signaling in RCC. However, the effects of pVHL status on the TGF-β signaling pathway in ccRCC and non-ccRCC has not yet been studied in detail. In the second study, we have attempted to study the effects of the TGF-β signaling pathway in the presence or absence of pVHL in ccRCC and non-ccRCC. We show that, in ccRCC, VHL has an inhibiting effect exclusively on canonical TGF-β signaling, and has no effect on non-canonical TGF-β signaling via ALK5-ICD. In non-ccRCC, TGF-β signaling did not have an effect on tumor progression. Further, we demonstrate that VHL, through its ubiquitin ligases activity ubiquitinates ALK5 in a K48 dependent manner and subjects it to proteasomal degradation. During the normoxic conditions, VHL is implicated in ubiquitination and proteasomal degradation of Hypoxia-inducible factors (HIFs). In hypoxic conditions or when loss of VHL occurs, HIFs accumulates in the cytoplasm, and enters the nucleus to initiate angiogenesis, cell proliferation, and tumor progression. In the third study, we have explored a potential synergistic cross-talk between TGF-β signaling and hypoxia in ccRCC. We demonstrate a correlation between TGF-β signaling components and HIF-1α/2α in ccRCC. We also show that TGF-β signaling enhances the expression of HIF-1α/2α and their target genes even under normoxic conditions, dependent on the kinase activity of ALK5 and dictated by the status of VHL. We present novel data that the synergistic crosstalk between hypoxia and TGF-β is orchestrated through interactions between ALK5 and HIF-1α/2α. HIF-3α remains less studied when compared with HIF-1α and HIF-2α; in the fourth study, we have analyzed the roles of HIF-3α in ccRCC and pRCC. We show that HIF-3α is associated with advanced stage and metastasized tumors. We also show that HIF-3α is associated with TRAF6, a crucial component of TGF-β signaling.

Keywords
Renal cell carcinoma, ccRCC, non-ccRCC, transforming growth factor-β, hypoxia, ALK5, pVHL, HIF-α, SNAIL1

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