Brief Communication

Link between dysregulated hypoxia signaling and aberrant methylation in clear cell renal cell carcinoma?

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Dysregulated pseudo-hypoxia (through its effects on cell survival, angiogenesis, metabolism, invasion) and epigenetic dysregulation [through widespread suppression of tumor suppressor genes involved in cell cycle, apoptosis, adhesion, immune evasion, etc. (1)] are considered to be the two central driving pathogenic features in the progression of clear cell Renal Cell Carcinoma (ccRCC) (2,3). These two features also play a significant role in mediating the chemoresistance of radioresistance of ccRCC. The finding of increased DNA methyltransferase 1 (DNMT1) expression in ccRCC by Li *et al*. (4) provides one mechanistic reason for the previously reported genome wide aberrant methylation seen in ccRCC, leading to the suppression of various important tumor suppressor genes (3,5). Strikingly, this finding may also establish a link between the driver hypoxia inducible factor (HIF) pathway and aberrant methylation seen in von Hippel-Lindau (*VHL*) defective ccRCC.

Biallelic *VHL* gene defects are seen in up to 75% of patients with sporadic ccRCC (6). pVHL, product of the *VHL* tumor suppressor gene, plays a key role in oxygen sensing by targeting HIF-α for ubiquitination and proteasomal degradation. In the absence of *VHL* activity, HIF-α is stabilized, translocates to the nucleus, where it combines with the constitutionally expressed HIF-1β to form heterodimers that bind to hypoxia response elements (HREs) in a wide range of gene promoters, leading to a pseudo-hypoxic state (7,8). Interestingly, HIF-1α has been shown to enhance the expression of DNMT1 and DNMT3b in cardiac fibroblasts. The promoter region of DNMT1 and DNMT3a was seen to have well defined HREs (9). Therefore, it is possible that the finding of enhanced expression of DNMT1 in ccRCC is due to the enhanced HIF-α stabilization seen in ccRCC.

This potential link between dysregulated hypoxia signaling and aberrant methylation in ccRCC needs to be further studied with correlative studies on HIF-1α/HIF-2α expression and DNMT1 expression in ccRCC and with HIF-α knockdown impact on DNMT1 expression and genome wide methylation in ccRCC. Establishing a link between the driver HIF pathway and the genome-wide aberrant methylation in ccRCC could have a significant translational impact, as we could then expect HIF modifying treatment strategies to also have a restorative effect on the aberrant epigenetics in ccRCC.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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