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Abstract: Activation of hypoxia-inducible factor (HIF) is due to loss of von Hippel-Lindau protein (pVHL) function in most clear cell renal cell carcinomas (ccRCCs). Here we describe a novel pVHL-independent mechanism of HIF regulation and identify nuclear factor (NF)-κB essential modulator (NEMO) as a hitherto unknown oncogenic factor influencing human ccRCC progression. Over 60% of human ccRCCs (n=157) have negative or weak NEMO protein expression by immunohistochemistry. Moderate/strong NEMO protein expression is more frequent in VHL wild-type ccRCCs. We show that NEMO stabilizes HIF? via direct interaction and independently of NF-κB signaling in vitro. NEMO prolongs tumor cell survival via regulation of apoptosis and activation of epithelial-to-mesenchymal transition, facilitating tumor metastasis. Our findings suggest that NEMO-driven HIF activation is involved in progression of ccRCC. Therefore, NEMO may represent a clinically relevant link between NF-κB and the VHL/HIF pathways. Targeting NEMO with specific inhibitors in patients with metastatic ccRCC could be a novel treatment approach in patients with ccRCC expressing functional pVHL.

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