Recent development of antiangiogenic therapy for renal cell carcinoma (RCC) has significantly improved the treatment of these often refractory tumors. However, not all patients respond to therapy and assays for predicting outcome are needed. As a first step, we analyzed a retrospective cohort of tumors and assessed the ability of VEGF and VEGF receptors (VEGF-R1, -R2 and -R3) to classify tumors. We analyzed tissue microarrays containing 330 RCCs using a novel method of automated quantitative analysis of VEGF and VEGF-R expression by fluorescent immunohistochemistry. Expression of markers was separately quantified within three tissue components: tumor cells, endothelial cells and adjacent normal epithelium. VEGF and VEGF receptors were tightly coexpressed both within tumors and within adjacent normal cells (all P-values <0.001). Tumor cell expression of VEGF-R1 and -R2 was strongly and inversely correlated with vessel area (P<0.0001). Unsupervised hierarchical clustering classified tumors by coordinated expression of VEGF and VEGF-Rs. The distribution of clear cell and papillary tumors was not significantly different between clusters. Clusters with high expression of VEGF and VEGF-Rs in the tumor cells exhibited poor survival when compared with the other clusters on uni- and multivariable analysis. VEGF and VEGF receptors exhibit a complex pattern of coordinated expression in RCC. Clustering tumors by VEGF and VEGF-R in tissue components demonstrates distinct tumor phenotypes with different outcomes, and may provide a means for determining which tumors will respond to what antiangiogenic therapies.

Editorial Comment: Renal cell carcinoma was first categorized pathologically and then on a molecular basis. The identification of hypoxia regulated genes, including vascular endothelial growth factor (VEGF) pathways, has been well delineated. Subsequently there have been new medications that target specific inhibitors of the VEGF pathway, including sorafenib and sunitinib. In this study tissue was assessed with the expression of VEGF and VEGF receptors (VEGF-R1, VEGF-R2 and VEGF-R3) in 3 tissue components—renal cell carcinoma cells, endothelial cells and normal adjacent renal tissue. On multivariate analysis it turned out that clustering of high VEGF/VEGF-R was an independent predictor of poor survival. These findings suggest that there may be a way of determining which tumors will respond to antiangiogenic therapy, so that molecular markers may start to dictate which treatment is indicated in a specific patient.

Fray F. Marshall, M.D.
Mitochondrial DNA Content: Its Genetic Heritability and Association With Renal Cell Carcinoma


Department of Epidemiology, University of Texas M. D. Anderson Cancer Center, Houston, Texas


Background: The extent to which mitochondrial DNA (mtDNA) content (also termed mtDNA copy number) in normal human cells is influenced by genetic factors has yet to be established. In addition, whether inherited variation of mtDNA content in normal cells contributes to cancer susceptibility remains unclear. Renal cell carcinoma accounts for 85% of all renal cancers. No studies have investigated the association between mtDNA content and the risk of renal cell carcinoma. Methods: We first used a classic twin study design to estimate the genetic contribution to the determination of mtDNA content. mtDNA content was measured by quantitative real-time polymerase chain reaction in peripheral blood lymphocytes from 250 monozygotic twins, 92 dizygotic twins, and 33 siblings (ie, individual siblings of a pair of twins). We used biometric genetic modeling to estimate heritability of mtDNA content. We then used a case-control study with 260 case patients with renal cell carcinoma and 281 matched control subjects and multivariable logistic regression analysis to examine the association between mtDNA content in peripheral blood lymphocytes and the risk of renal cell carcinoma. All statistical tests were two-sided. Results: The heritability (ie, proportion of phenotypic variation in a population that is attributable to genetic variation among individuals) of mtDNA content was 65% (95% confidence interval [CI] = 50% to 72%; P < .001). Case patients with renal cell carcinoma had a statistically significantly lower mtDNA content (1.18 copies) than control subjects (1.29 copies) (difference = 0.11, 95% CI = 0.03 to 0.17; P = .006). Low mtDNA content (ie, less than the median in control subjects) was associated with a statistically significantly increased risk of renal cell carcinoma, compared with high content (odds ratio = 1.53, 95% CI = 1.07 to 2.19). In a trend analysis, a statistically significant dose-response relationship was detected between lower mtDNA content and increasing risk of renal cell carcinoma (P for trend <.001). Conclusions: mtDNA content appears to have high heritability. Low mtDNA content appears to be associated with increased risk of renal cell carcinoma.

Editorial Comment: Changes in mitochondrial respiratory function in cancer have been recognized for many years. Only recently has mtDNA been studied in more detail in cancers. Depletion of mtDNA alters mitochondrial gene expression, and can change oxidative phosphorylation and enhance reactive oxygen species in aerobic metabolism. These changes can be mitogenic, mutagenic and associated with malignancy. Certainly some of this risk can be inherited.1 A decrease in mitochondrial copy number, which is sometimes called mitochondrial depletion, has been reported in many cancers, including hepatocellular, breast and ovarian. In this study reduced mtDNA content was associated with a 1.56-fold increased risk of renal cell carcinoma, strongly suggesting that mitochondrial DNA depletion may be an important factor in the evolution of renal cell carcinoma.

Fray F. Marshall, M.D.