Macrophage Inflammatory Protein-3 is Downregulated in Clear Cell Renal Cell Carcinomas and Correlates with Stage and Grade

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Background: Macrophage inflammatory protein-3 (MIP-3, aka CCL20) is an inflammatory and homeostatic chemokine that interacts with the CCR6 receptor to attract immature dendritic cells and lymphocytes. Studies have shown upregulation of MIP-3 in pancreatic, breast, cervical, hepatocellular, and hematopoietic malignancies. Increased expression of MIP-3 has also been demonstrated in renal transplant specimens with rejection, but the expression of MIP-3 has not been studied in clear cell renal cell carcinoma (CCRCC).

Design: Immunohistochemistry for MIP-3 was performed on microarrays that contained matched primary CCRCC and normal kidney specimens (n=133) spotted in triplicate, as well as unmatched metastatic CCRCC specimens (n=40). Each spot was assigned an H-score (percentage of cells expressing MIP-3 by intensity of expression) by a pathologist. Statistical analysis was performed using STATA to calculate Kruskal-Wallis equality-of-populations rank test results.

Results: MIP-3 expression was downregulated in both primary and metastatic CCRCCs as compared to normal kidney (P=0.0001) by both H-score and percentage of cells expressing MIP-3 independent of intensity. Expression did not differ between primary and metastatic CCRCCs (P=0.525). The H-score showed positive correlation with tumor stage (P=0.0173) and Fuhrman grade (P=0.0009) of primary CCRCCs, but did not correlate with overall survival, disease-specific survival, or disease progression. Percentage of cells expressing MIP-3 showed positive correlation with Fuhrman grade (P=0.0337), but not tumor stage, overall survival, or disease-specific survival. In metastatic CCRCCs, the H-score inversely correlated with disease-specific survival (P=0.0349).

Conclusion: In primary and metastatic CCRCCs expression of MIP-3 is downregulated as compared to normal kidney, suggesting a possible difference in the role of dendritic and inflammatory cells in CCRCCs as compared to other malignancies where MIP-3 has been found to be upregulated. In primary tumors, increased expression of MIP-3 is correlated with tumor stage and Fuhrman grade. Our finding of inverse correlation of MIP-3 expression in metastatic tumors with survival merits further investigation.