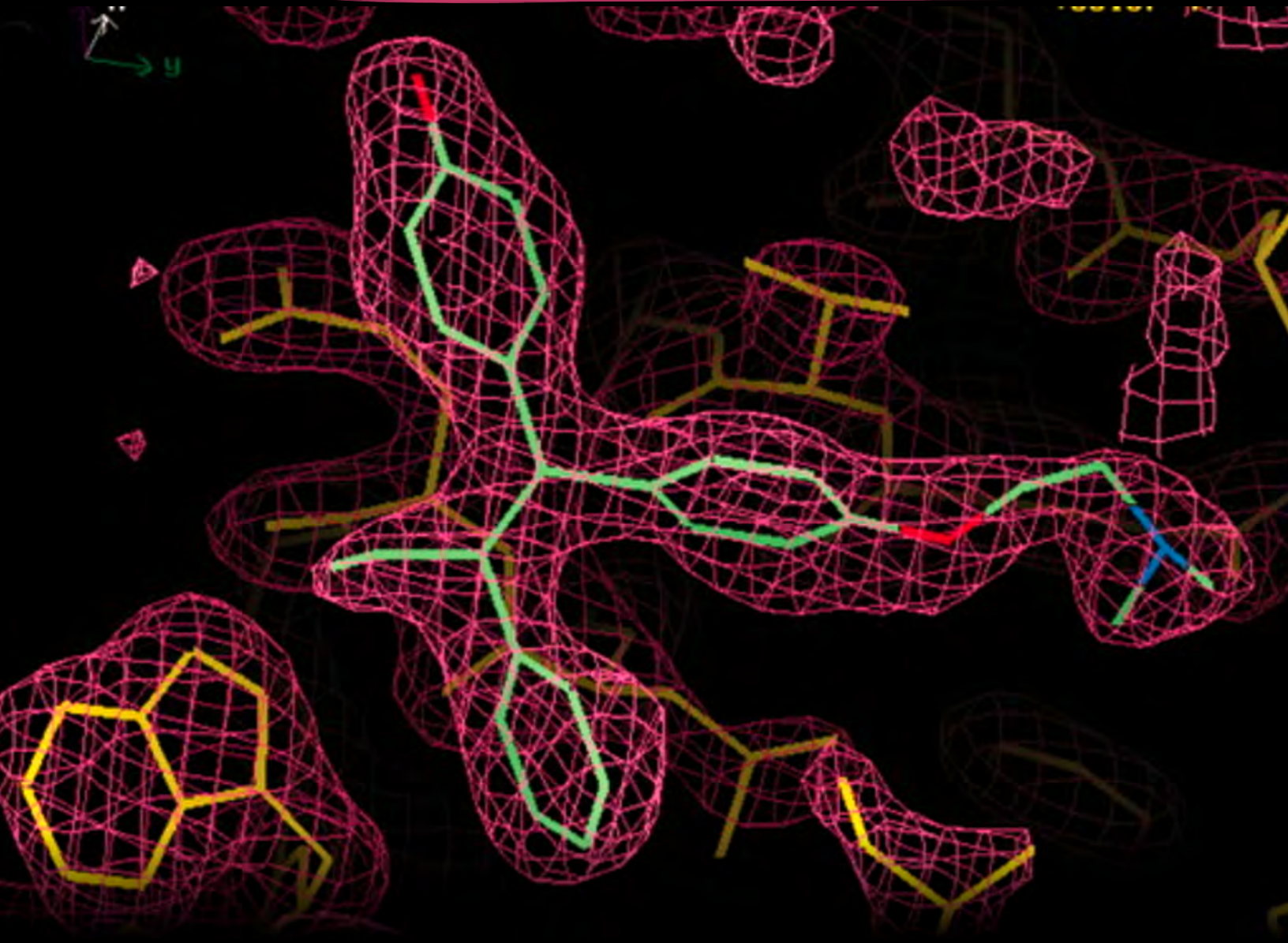
Cincinnati Cancer Symposium Series



Jensen Symposium on Nuclear Receptors

2009 ABSTRACT BOOK

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Sponsored by:
Department of Cancer and Cell Biology
Cincinnati Cancer Consortium

UNIVERSITY OF Cincinnati

MicroRNA Function in Kidney Cancer

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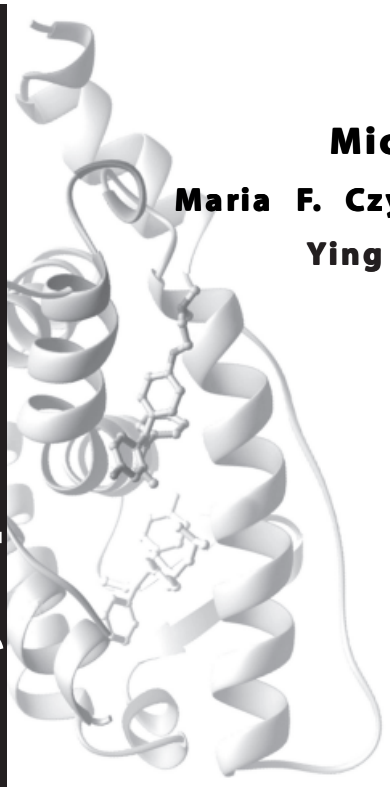
Renal cancer accounts for 3% of adult malignancies in the US and is the 6th leading cause of cancer mortality. MicroRNAs (miRs) participate in cancer initiation and progression. In human tumors, distinct miR expression profiles are specific to particular diagnoses and progression patterns, and are predictive of response to treatment .Thus, the analysis of miR target genes may point to novel regulatory pathways with potential as therapeutic targets.

We examined gene expression in tumors with the goal of identifying miR genes involved in oncogenesis of the most frequent and malignant form of kidney cancer, renal clear cell carcinoma (RCCC). Analysis of miR expression in 109 human RCCC using TaqMan MicroRNA assays demonstrated a significant and nearly universal decrease in mir204 expression in tumor tissue as compared to normal kidney, with the level of mir204 reduction correlating with tumor grade. In human RCCC cell lines, expression of mir204 positively correlated with the presence of the von Hippel-Lindau (VHL) tumor suppressor, which is lost in 40% to 80% of human RCCC. Stable transfection of mir204 into VHL(-) cells led to no surviving proliferating cells, indicating that mir204 can inhibit cell growth. The mir204 gene is located in intron 6 of a large gene (exons 1-25) encoding a transient receptor potential Ca^{2+} channel, TRPM3. We have validated several mir204 targets involved in membrane function and intracellular trafficking, such as CAV1 (caveolin1), RAB22A and 14, CDH2, and MAPRE2. Of these, CAV1, with a conserved mir204 binding site in its proximal 3'untranslated region (UTR), is of particular interest because CAV1 is a well established regulator of many signaling pathways in cancer and its membrane-associated fraction is upregulated in human RCCC tumors in a manner correlating with tumor grade. In tumors and cells, CAV1 levels correlate inversely with levels of mir204. CAV1 knockdown in VHL(-) cells inhibits cell proliferation and BrdU incorporation under serum-starvation conditions, and inhibits formation of tumors by VHL(-) cells in nude mice. Surprisingly, CAV1 knockdown inhibits expression of TRPM3. We have also discovered a previously unreported, conserved mir204 site in the 3'UTR of TRPM3 mRNA. In addition, we showed that the TRPM3 channel is repressed by endogenous mir204 in VHL(+) cells.

We propose that mir204 orchestrates the coordinated repression of an interconnected network of targets that regulate intracellular trafficking (CAV1) and intracellular calcium concentration (TRPM3). This tumor-suppressing activity is connected to the VHL tumor-suppressing pathway. Clearly, this is a novel regulatory pathway with many investigative opportunities. The significance of this research is the potential identification of novel targets for treatment of RCCC, in particular mir204 and a membrane channel protein, TRPM3. For example, delivery of mir204 to human RCCC or inhibition of TRPM3 channel activity by small molecules might become feasible and significant methods of treatment.

Supported by: NCI CA122346, DoD W81XWH-07-02-0026.



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