Use of Molecular Pathology to Predict Outcomes in RCC

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Variability in Clinical Behavior

- As many as 20-30% of surgically treated patients (T1/T2) with clear cell renal cell carcinoma (ccRCC) develop local or distant recurrence , and nearly 50% will eventually develop stage IV (metastatic) disease.
  - Can we predict which tumors are going to recur?
- One of the key dilemmas in the management of metastatic ccRCC is the manifestation of innate or acquired resistance to anti-angiogenic therapy.
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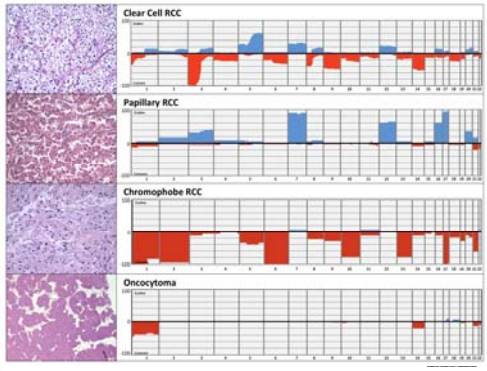
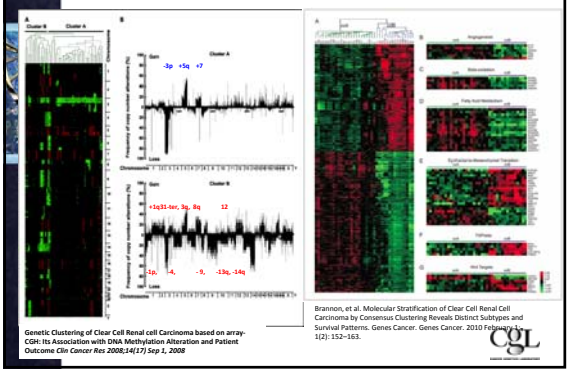
Summary Profiles of Renal Tumors



Molecular Subtypes of ccRCC



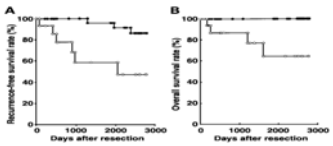
Genetic Clustering of Clear Cell Renal cell Carcinoma based on array-CGH: Its Association with DNA Methylation Alteration and Patient Outcome *Clin Cancer Res 2008;14(17) Sep 1, 2008*

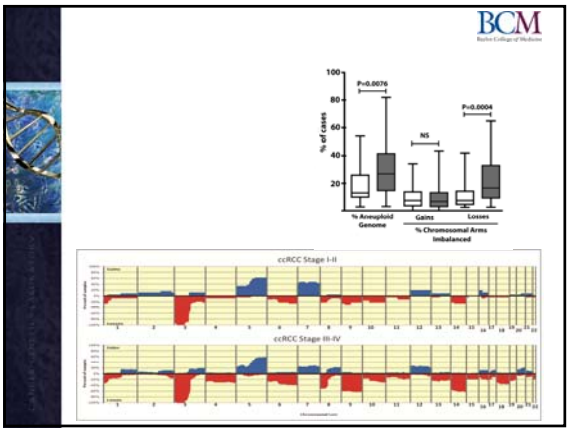
Brannon, et al. Molecular Stratification of Clear Cell Renal Cell Carcinoma by Consensus Clustering Reveals Distinct Subtypes and Survival Patterns. Genes Cancer. Genes Cancer. 2010 February; 1(2): 152–163.

Recurrence Prognosis – Additional Evidence

Other studies have confirmed the role of chromosomal imbalances as prognostic markers in clear cell and papillary RCC.

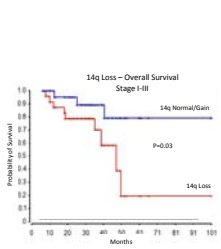
- ccRCC, 9p loss – bad prognostic factor (Brunelli M, et al. Pathol. 2008, 21(1):1-6).
- ccRCC, 9p loss – adverse predictor (Klatte T, et al. J Clin Oncol. 2009, 27(5):746-53).
- pRCC, 1q gain – adverse predictor (Szponar A, et al. Int J Cancer. 2009, 124(9):2071-6).
- ccRCC, Genomic profiles predict recurrence (Arai E, et al. Clin Cancer Res 2008;14(17) Sep 1, 2008)

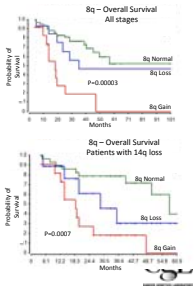




Renal Tumors: Prognosis

- 14q loss is associated with poor outcome in non-metastatic ccRCC patients
- 8q gain is prognostic for decreased OS in ccRCC patients and appears to further decrease survival in patients with 14q loss.





Monzon FA et al. Chromosome 14q loss defines a molecular subtype of clear cell renal cell carcinoma that is associated with poor prognosis. Mod Pathol 2011

- Differential expression of HIF1α is associated with 14q loss

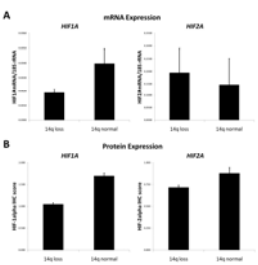
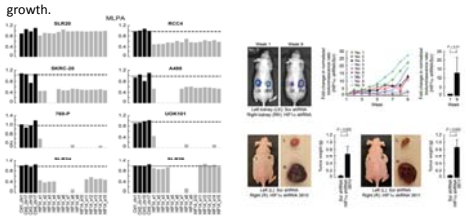


Image from Powis Lab website, MD Anderson Cancer Center

Kaelin and collborators identified focal, homozygous, deletions of the HIF1α locus on 14q in clear cell renal carcinoma cell lines. Wild-type HIF1α, but not the products of these altered loci, suppress renal carcinoma growth. Conversely, downregulation of HIF1α in HIF1α-proficient lines promote tumor growth.



Shen et al. Cancer Discov. 2011 Aug;1(3):222-235.

Research article

Open access

Downregulation of SAV1 plays a role in pathogenesis of high-grade clear cell renal cell carcinoma

Keiko Matsuura, Chisato Nakada, Mizuho Mashio, Takahiro Narimatsu, Taichiro Yoshimoto, Masato Tanigawa, Yoshiyuki Tsukamoto, Naoki Hijiya, Ichiro Takeuchi, Takeo Nomura, Fuminori Sato, Hiromitsu Mimata, Masao Seto and Masatsugu Moriyama

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BMC Cancer 2011, **11**:523 doi:10.1186/1471-2407-11-523
Published: 20 December 2011

Ann Surg Oncol
DOI 10.1245/s10434-011-2206-3

Annals of SURGICAL ONCOLOGY

ORIGINAL ARTICLE – TRANSLATIONAL RESEARCH AND BIOMARKERS

***NDRG2* Is Involved in the Oncogenic Properties of Renal Cell Carcinoma and Its Loss Is a Novel Independent Poor Prognostic Factor After Nephrectomy**

Zhe Long Liang, MD[1], Kyeongah Kang, PhD[2], Sukjoon Yoon, PhD[2], Song Mei Huang, MD[3], Jae Sung Lim, MD[3], Jin Man Kim, MD[1], Jong-Seok Lim, PhD[2], and Hyo Jin Lee, MD[4]

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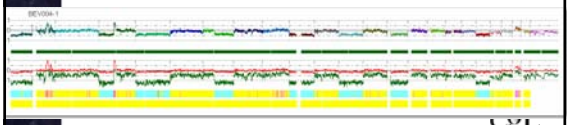
Studies on Response to Therapy

- **MDACC Sorafenib Study**
  - Sorafenib alone vs. sorafenib-IFN (post nephrectomy)
  - Tumor response, progression-free survival (PFS) and overall survival (OS) were analyzed with regard to marker levels in 26 tumor samples.
- **MDACC Bevacizumab Study**
- 50 patient study pretreated newly diagnosed mRCC patients with four cycles of bevacizumab 10mg/kg IV every two weeks prior to nephrectomy, and continued therapy in patients who demonstrated stable disease or response.

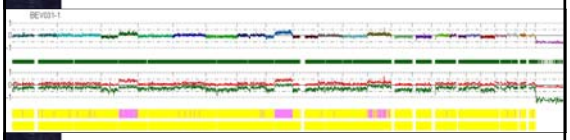
Sorafenib Cohort

- **Multivariate Cox Proportional Hazards Regression for Progression Free Survival (PFS)**
- **Longer PFS**
  - **5q gain** – HR = 0.25, 95% CI 0.08 to 0.81, P = 0.021
- **Shorter PFS**
  - **1q gain** - HR = 0.067 CI 0.006-0.76, P = 0.0292 (univariate model for sorafenib alone arm)
  - **9p loss** - HR = 0.29, 95% CI 0.08 to 1.09, P = 0.0673



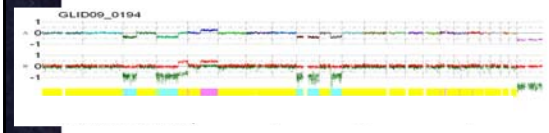
Sorafenib Cohort

- **Multivariate model to predict time to progression**
  - **14q loss** - HR = 20.478, CI 1.300- 322.601, P = 0.0318 (Interaction with treatment arm);
  - **14q loss** - HR = 5.146, CI 0.971 - 27.267, P = 0.0541 (Sorafenib only arm)
  - **18p loss** – HR (for normal 18p) = 0.045, CI 0.002-0.826, P = 0.0368



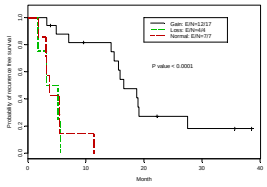
Bevacizumab Cohort

- **Significant association with response, Fisher's exact test**
  - **14q loss**, CRPR/SDPD, P = 0.0473
  - **5p / q gain**, CRPRSD / PD, P = 0.02
  - **8q gain**, CRPRSD / PD, P = 0.04



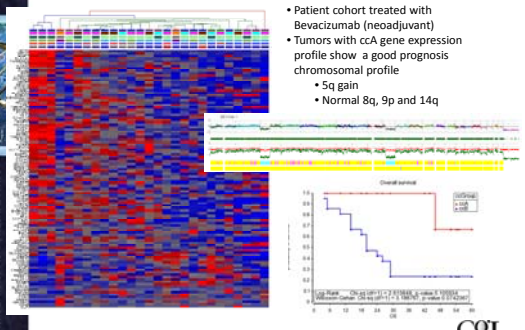
Bevacizumab Cohort

- **Significant association with overal survival (OS), log rank**
  - **5q gain, HR = 0.59**, 95% CI (0.36 , 0.96), P = 0.002
- **Significant association with recurrence free survival (RFS), multivariate Cox**
  - **5q gain, HR = 0.06**, 95% CI (0.01, 0.31), P = 0.00083
  - **15q loss, HR = 0.23**, 95% CI (0.07, 0.82), P = 0.024



Gene Expression and Chromosomal Profiles

- Patient cohort treated with Bevacizumab (neoadjuvant)
- Tumors with ccA gene expression profile show a good prognosis chromosomal profile
  - 5q gain
  - Normal 8q, 9p and 14q



What's next

- Confirm association of chromosomal loss with therapeutic response to antiangiogenic agents.
  - Bevacizumab, Erlotinib, Sunitinib
- Insights into biology and/or marker discovery
  - Loss of chromosomal regions associated with outcome could reflect:
    - Loss of additional tumor suppressor genes
    - Selection of mutated (constitutively active) oncogenes
  - Study correlations of VHL-HIF-VEGF proteins with outcome/genomic patterns
  - Search for TSGs in areas of association or genes that interact with treatment pathways
- Role of endothelial cells
  - Phenotype and Genotype

Conclusions

- SNP arrays are a powerful tool for whole-genome analysis of chromosomal lesions (virtual karyotyping) in renal tumors.
- Chromosomal imbalances are associated with recurrence and outcome measures and could be used as prognostic markers
  - 5q gain is associated with better PFS in both Sorafenib and Bevacizumab cohorts and with better response in Bevacizumab treated patients .
  - 14q loss is associated with recurrence, shorter time to progression in Sorafenib cohort and associated with worse response in Bevacizumab treated patients .
  - Unclear if effect is related to prognosis (aggressive tumors) or therapeutic response prediction (tumors less sensitive to therapy), or both.
- Need to identify candidate genes to establish molecular mechanisms for recurrence and/or resistance to therapy

Acknowledgements

Methodist The Methodist Hospital

Martin Powers MD, Karla Alvarez BSc, Benita Mathai, Hyun-Jung Kim MD

GU Pathology
Luan Truong M.D., Alberto Ayala, M.D. Steven Shen M.D., Ph.D. & Rae Jo M.D., M.S., Ph.D.

UT Physicians

Eric Jonasch MD

Bob Amato DO

More Collaborators:

- Jill Hagenkord MD, Zoran Gatalica MD & Shera Kash, PhD – Creighton
- Pheroze Tamboli MD, Kanishka Sircar MD – MD Anderson Cancer Center
- Clinical Genomics Facility, UPMC – Maureen Lyons-Weiler Msc and Christin Sciulli Bsc
- Julia Bridge MD - U of Nebraska,

Questions?