PDGF PATHWAY GENE EXPRESSION HETEROGENEITY IN RENAL CELL CARCINOMAS

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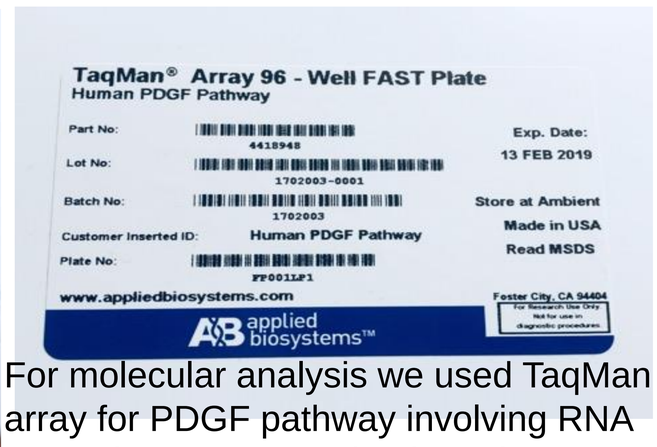
Introduction

Several targeted therapies are already approved and applied in patients with clear cell renal cell carcinoma (CCRCC), most of them targeting PDGF pathway. Patients response is highly heterogeneous and resistance to therapy appeared early during treatment. Thus, we aim to study PDGF pathway expression profile correlated with tumor vessels type, grade and invasion.

Methods and Materials

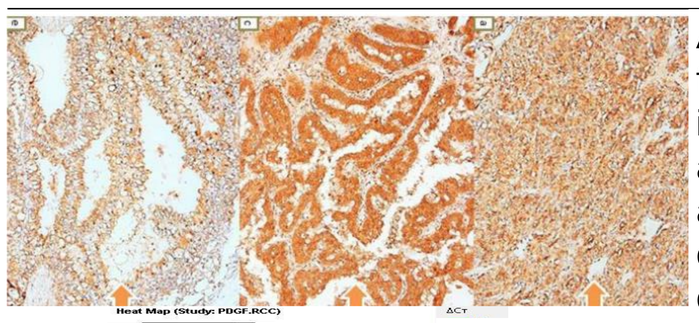
Fifty cases of CCRCC were preliminary evaluated by histopathology and we selected cases for immunohistochemistry and molecular analysis. Cases evaluation included histopathology for type and grade, assessement of PDGF by immunohistochemistry and RNAscope technique and tumor grouping with emphasis to tumor vessels types previously described by our team. Results were evaluated by DATA ASSIST software and gene expression profile was correlated with grade, invasion, tumor vessels types, VEGF, VEGF165b



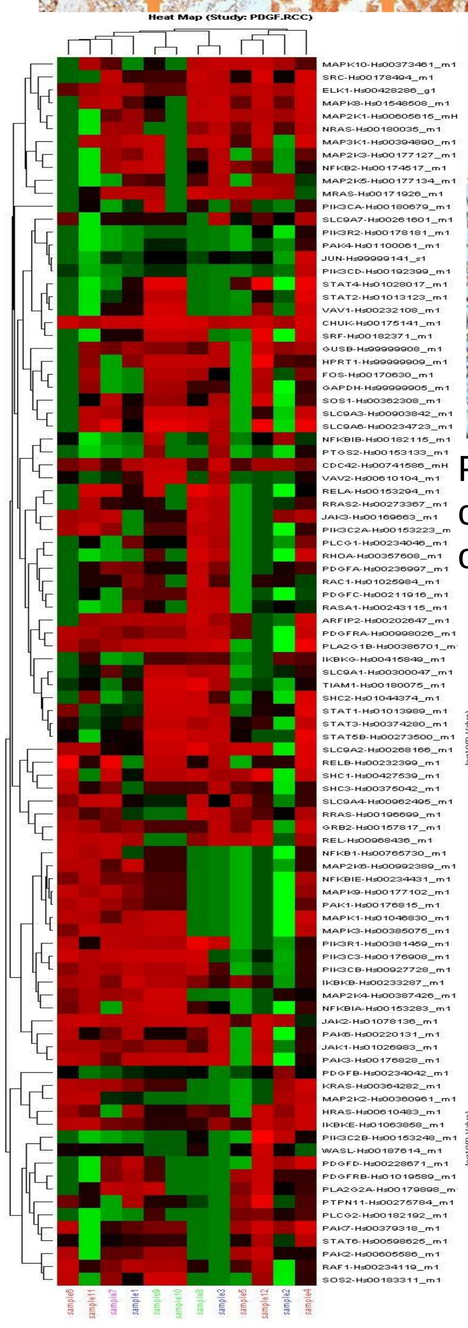
For molecular analysis we used TaqMan array for PDGF pathway involving RNA extraction, cDNA synthesis and RT PCR technique applied to PDGF Pathway 96-well plates containing 92 genes and 4 control genes.

Results

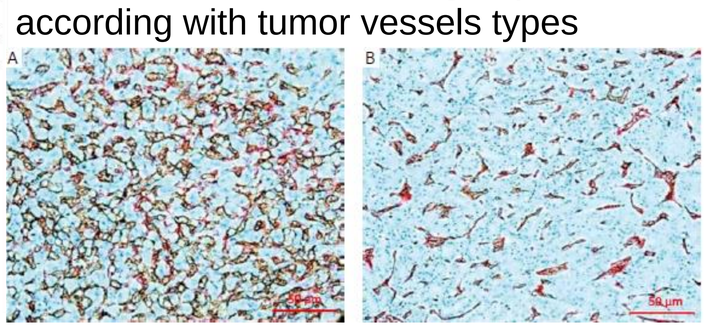
	Reticular Both CD34+/SMA+ CD34+/SMA– Small intercapillary distance	Diffuse CD34+/SMA+ exclusively Large intercapillary distance	Fasciculate CD34+/SMA+ exclusively	Trabecular CD34+/SMA+ exclusively Large intercapillary distance
Clear cell	predominant	rare	–	–
Papillary	–	rare	predominant	–
Cromophobe	–	predominant	–	rare
Unclassified	–	predominant presence of particular structures as glomeruloid bodies	–	rare



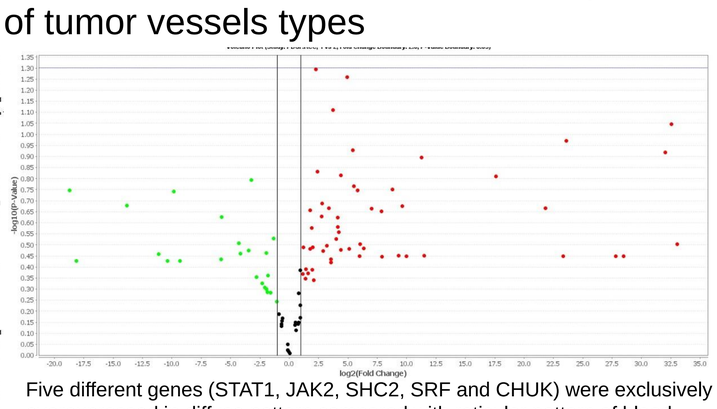
All CCRCC were positive for PDGF BB by immunohistochemistry and RNAscope technique and 91,6% out of these cases confirmed this expression by RT PCR.



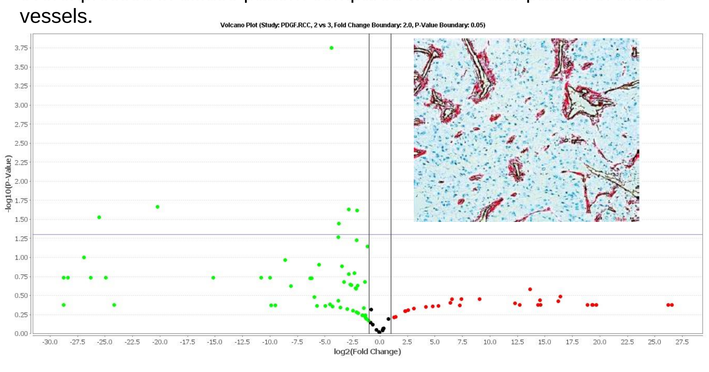
Difference in gene expression profile were observed when we grouped cases according with tumor vessels types



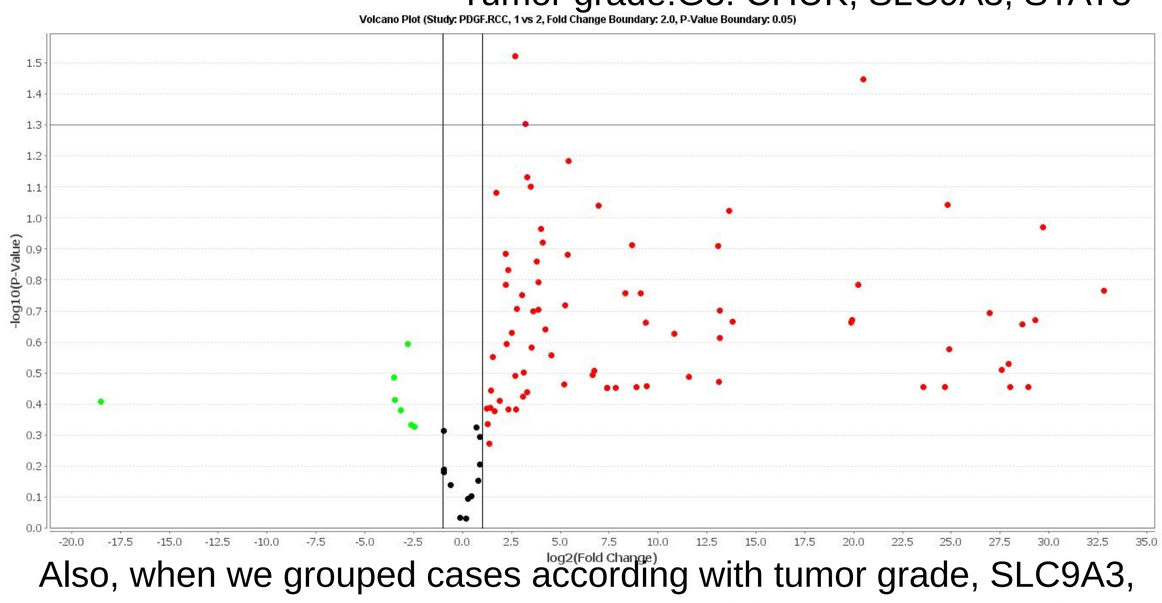
PIK3C3 and SLC9A3 were significantly correlated with reticular and diffuse pattern of tumor vessels types



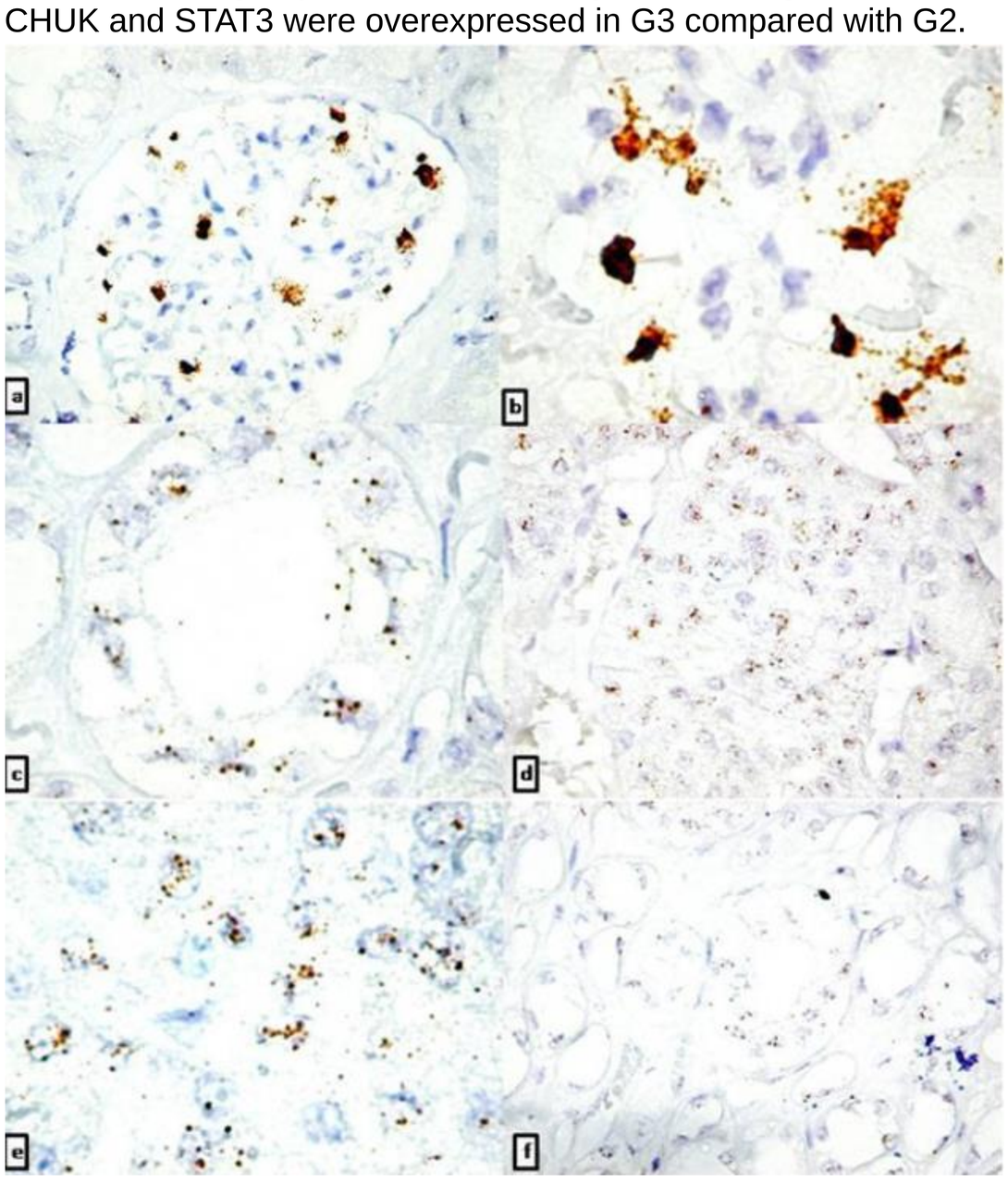
Five different genes (STAT1, JAK2, SHC2, SRF and CHUK) were exclusively overexpressed in diffuse pattern compared with reticular pattern of blood vessels.

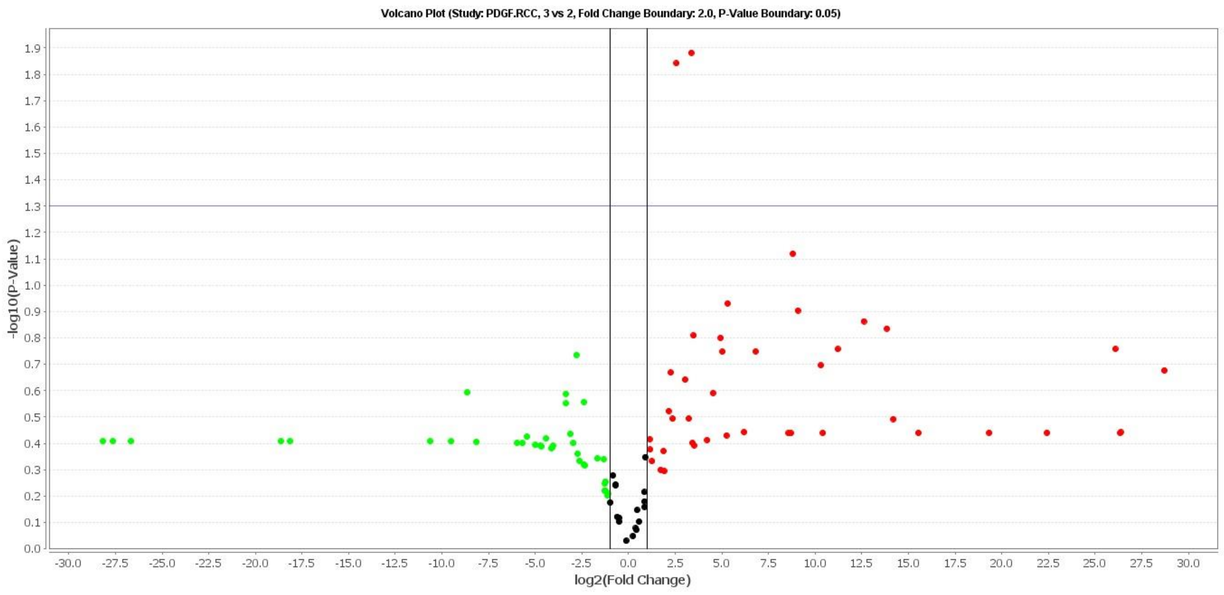


Tumor grade:G3: CHUK, SLC9A3, STAT3



Also, when we grouped cases according with tumor grade, SLC9A3, CHUK and STAT3 were overexpressed in G3 compared with G2.





PIK3C3 and SLC9A3 were differentially overexpressed according with intensity of VEGF.

No significant correlation has been found between PDGF gene expression and invasion.

Conclusions

We may conclude that CCRCC showed a high molecular heterogeneity of PDGF pathway gene expression profile with an impact on early maturation of tumor vessels previously observed. Also, this heterogeneous gene expression profile may explain the different response to targeted therapies and in part resistance to therapy differently developed among patients.

References

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