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A.C.Camargo Cancer Center
Especializado em Vida

PATIENT-DERIVED RENAL CELL CARCINOMA XENOGRAFTS CAPTURE TUMOR GENETIC PROFILES AND AGGRESSIVE BEHAVIORS

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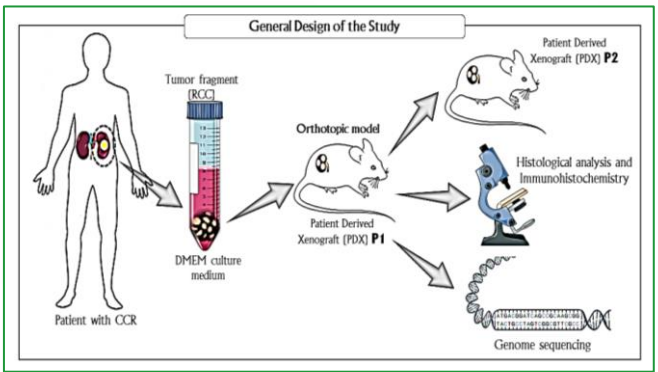
INTRODUCTION

- Patient-derived xenografts (PDX) have emerged as one of the most promising model systems to study cancer biology and to develop new antineoplastic drugs. Renal cell carcinoma (RCC) represents up to 90% of all kidney tumors, exhibits aggressive behavior, and has a propensity for metastasis.
- At diagnosis, 30% of patients with RCC have metastases, while up to 50% of those with localized disease treated with curative protocols experience recurrence.
- Therefore, the central objective of the present study was to establish a platform of studies based on morphological and genetic characterization of renal tumors in immunodeficient animals.

MATERIALS AND METHODS



RESULTS

Table 1: Clinical characteristics of patients and tumor implantation route influencing PDX take rate.

	PDX engraftment	Orthotopic Yes N = 19	Orthotopic Total N = 70	*P*	Ectopic Total N = 17
Gender	Male	12	48	0.76	10
	Female	7	22		7
Age	Mean	59.5	56.9		63
Time to growth (months)	Mean	6	–		–
	Minimum	1	–		
	Maximum	13	–		
Subtype	Clear cell	15	55	1.00	13
	Papillary	3	10		3
	MiT family translocation	0	2		0
	Unclassifiable	1	3		1
Staging	pT1a	5	24	0.09	11
	pT1b	4	21		3
	pT2a	0	2		0
	pT3a	7	19		3
	pT3b	3	3		0
	pT4	0	1		0
Histologic grade	1	0	3	0.49	0
	2	6	24		6
	3	7	29		8
	4	6	14		3
Sarcomatoid	Yes	5	9	0.05	0
	No	14	61		17
Rhabdoid	Yes	6	11	0.05	0
	No	13	59		17
Necrosis	Yes	8	23	0.393	5
	No	11	47		12

Figure 1: Standardization of the Orthotopic Implant Model. (A) Left lumbotomy; (B) Isolation of the kidney; (C) Transversal incision in renal capsule; (D) 4 subcapsular tumor fragments.

RESULTS

Table 2: Genetic characterization

Histology	Pathological staging	Gene	Mutation type	Primary tumor frequency	PDX frequency
Clear Cells	pT1b	BAP1	Missense	10,0%	99,0%
		CDKN2A	Missense	2,9%	0,0%
		TP53	Missense	10,9%	82,0%
		TP53	LoF	6,7%	4,4%
Papillary	pT3a N1	ARID1A	LoF	42,0%	49,2%
		ARID1A	LoF	42,8%	46,0%
Clear Cells	pT3a	VHL	LoF	28,5%	79,3%
		PBRM1	LoF	31,8%	98,0%
		KDM5C	LoF	47,0%	99,0%
Clear Cells	pT1a	VHL	Missense	17,3%	0,0%
		PBRM1	LoF	19,9%	0,0%
Clear Cells	pT1a	VHL	LoF	46,1%	86,1%
		PBRM1	LoF	50,5%	88,5%
		AR	Missense	7,1%	2,4%
Clear Cells	pT3a	VHL	LoF	53,3%	78,1%
		SETD2	LoF	54,2%	71,9%
		PBRM1	LoF	50,3%	69,0%
Clear Cells	pT3b	SETD2	LoF	31,1%	68,1%
		KDM5C	Missense	26,9%	57,1%
Papillary	pT1a	MET	Missense	51,5%	67,0%
		SMARCA4	Missense	37,8%	51,6%
Clear Cells	pT3a	VHL	LoF	44,0%	99,1%
		PBRM1	LoF	2,8%	0,0%
		SETD2	LoF	1,7%	0,0%
		PBRM1	LoF	42,0%	100,0%
Clear Cells	pT3b	TP53	Missense	32,8%	99,7%

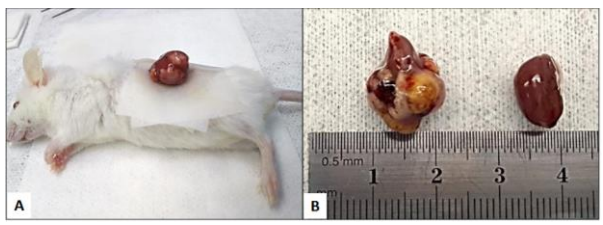


Figure 2: Evidence of tumor growth (A) Tumor growth. (B) Comparison between the kidneys

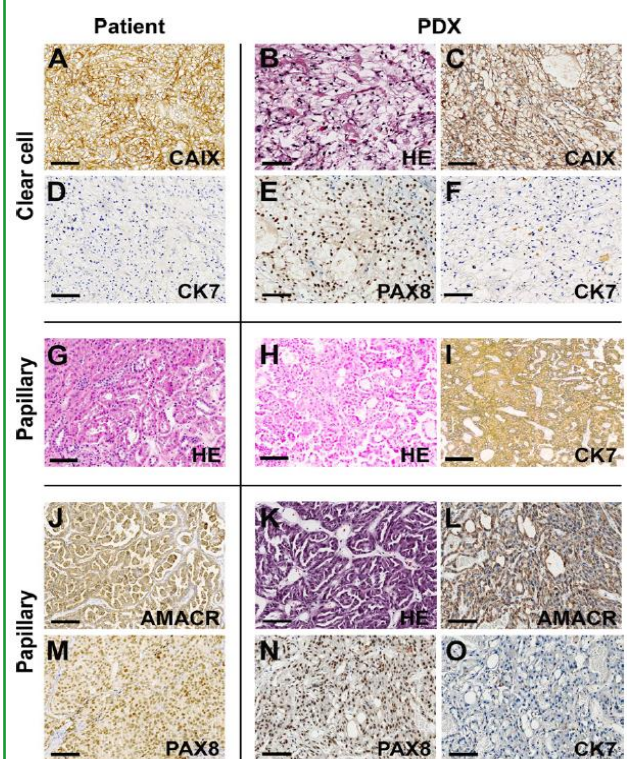


Figure 3: Patient-derived xenografts preserve the major morphologic characteristics of RCC. Calibration bars = 100um.

CONCLUSION

Taken together, these results suggest that the orthotopic xenograft model of RCC represents a suitable tool to study RCC biology, identify biomarkers, and to test therapeutic candidates.

CONTACT

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