EXPRESSION OF CD40, TH1/TH2 CYTOKINES AND HISTOPATHOLOGY IN A NEW MODEL OF RENAL ACUTE REJECTION.

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To have an available model of kidney transplant over-expressing the co-stimulatory molecule CD40, we characterized a new model of acute rat renal rejection based on survival, renal function, histology, cytokines and CD40 expression, among other mediators of the inmuno-inflammatory response.

Renal transplant with/without cold ischemia (CI) was performed between syngeneic (NoAR & CINoAR) and allogeneic (AR & CIAR) rats. Allogeneic rats were followed until clinical aspect and creatinine recommended their sacrifice. Syngeneic rats were sacrificed the 7th day. Banff criteria; C4d, C3, IgG as markers of antibody-mediated acute rejection (AbAR); collagen-IV in basal membrane; QRT-PCR for CD40, TNFα, INFγ, TGFβ and IL12; CD40 protein (WB and immunohistochemistry); and plasmatic TH1/TH2 cytokines were evaluated.

Renal insufficiency appeared from the 5th post-transplant day in both acute rejection groups but not in NoAR group. CI in rejecting animals increased mortality due to renal insufficiency. While syngeneic kidneys had a well conserved renal architecture, AR group displayed tubular necrosis, scarce cellular infiltration, interstitial haemorrhage, vascular fibrinoid necrosis and cariorexis. The combination of alloreactivity plus CI resulted in the exacerbation of the humoral component of the acute rejection with alterations in renal function and histology, and complement deposition in peritubular capillary. Acute rejection induced by alloreactivity is related with the increase of CD40, both TH1 and TH2 cytokines, and capillary COL-IV. The addition of CI over-activates the acute rejection process via a humoral component, with complement deposition in PTC, and highly deteriorated histology and renal function. In rejecting groups, the TH1/TH2 ratio was decreased, probably as a self-protection mechanism to confront an over-expressed immune-inflammatory response.

We have characterized a new renal acute rejection model that over-expresses CD40

group	MST (days)	%Surv day 7	sCr 7 µmol/L	Banff	COL IV confocal	TNF-α mRNA	INF-γ mRNA	TGFβ mRNA	TH1/TH2 plasma	CD40 Prot WB	CD40 mRNA
AR	8.6 ±0.9 [ab]	85 [a]	440±44 [ab]	31% AR (IA,III) [ab]	248±69	173±39 [ab]	454±84 [ab]	11.1±2.6 [ab]	1.2±0.2 [a]	1.6±0.3 [a]	19.4±2.2 [ab]
CIAR	5.8 ±1.3 [abc]	50 [ab]	456±79 [ab]	67% AbAR [abc]	308±31 [a]	120±22	618±249 [ab]	14.4±3.4 [ab]	1.3±0.3 [a]	2.0±0.3 [a]	20.4±6.4 [ab]
NoAR	>180	100	57±3	100% Normal	158±43	31±17	30±17	0.8±0.3	4.3±1.8	0.7±0.1	2.8±0.8
CINoAR	>180	83	71±6	83% Normal	302±42 [a]	57±31	54±40	0.5±0.1	1.7±0.3	1.0±0.0	5.6±0.8

$p<0.05$ ANOVA, Fisher's test; Kaplan-Meier; χ^2; ***a***: vs NoAR; ***b***: vs CINoAR ***c***: vs AR