Klotho, HMGB-1 and Kynurenine Mediates Injury in Renal Transplantation

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Brain death is associated with immune activation and tissue injuries, counterregulated by activation of the tryptophan pathway producing kynurenine (Kyn). High mobility group box 1 (HMGB1) is a nuclear factor released as an early mediator of repair, inflammation and destruction. Klotho (K) is a putative aging-suppressor and deficiency is involved in acute kidney injury and chronic kidney disease. Kyn suppresses T-cell reactivity upregulated by the proinflammatory cytokines IFN-γ and TNF-α. In a retrospective study, we compared results of HMGB1, Kyn and K in renal transplantation to estimate their impact on immediate and long-term graft-function.

Patients and Methods
A consecutive group of patients after renal transplantation (n=123) were included (mean age 42±11 y., duration of dialysis 41±23 months). Furthermore sera from 97 organ donors (mean age 38.4±12 y.) could be evaluated.

Results
HMGB-1 was significant elevated in donors with delayed renal function (DGF). HMGB1 was positive correlated (r²=0.718) to the days until creatinine felt < 200μmol/l (9.66±10 (PF) vs. 25.8±14 (DGF);p<.001). Klotho was negative correlated to HMGB1 and significant lower in patients with a graft survival <60 months (p<0.001).
In 36 % of the donors Kyn was elevated (+3s) in contrast to IL-6 and CRP. If Kyn values were <3s in the postoperative period between week 3 and 7, long-term function (10years) was significantly better (71% vs. 31%).
ATG-induction treatment decreased HMGB-1 significantly (p<.001) by - 87% (+11) compared to TDT with an increase of + 24% (+9).

Conclusion
Kyn is indicating a functional counter-regulation of the activated innate immune response (donor) and showed an excellent correlation to rejection and long term-function. Elevated HMGB-1 indicates the grade of injury.
Treatment is of benefit concerning DGF and long-term function. HMGB-1 and Klotho are predictive marker of graft injury.