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Euro Nephrology 2020: New insights into Cardio-Renal interactions – Role of NGAL - Yacov Shacham - Tel-Aviv University

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Introduction:
Since dialysis is joined by bad quality of life and life expectancy, kidney transplantation is the option of choice for many patients. However, the transplantation of a kidney is necessarily accompanied by injury. The consequences include delayed allograft function, acute tubular necrosis, and acute kidney injury. End stage renal infection (ESRD) is the last period of ongoing kidney sickness. Hemo-or peritoneal dialysis is life-saving in patients who progress to constant renal disappointment. In any case, since dialysis is joined by inferior quality of life and future, kidney transplantation, as a type of renal substitution treatment, is the choice of decision for some patients. In North America, roughly 75% of all strong organ transfers performed are kidney transfers. The transplantation of a kidney or some other organ starting with one individual then onto the next is essentially joined by injury, regardless of whether at the hour of obtainment, the conservation time. Injury may happen during those times of either warm or cold ischemia. The results incorporate deferred allograft work (DGF), intense cylindrical rot, and intense kidney injury (AKI). Minute injury can likewise add to localized necrosis and to an expanded rate of intense dismissal. In this examination, we zeroed in on the progressions saw in the proteome of kidney exposed to ischemia during machine cold perfusion. The oxidative stress of the graft during ischemia and reperfusion leads to an increased activity of matrix metalloproteinase (MMPs), and MMPs, in turn, are able to degrade intra- and extracellular proteins(causing the progressions of protein content in kidneys) prompting organ injury and brokenness. Consequently, the principle point of the current examination was to more readily portray the nephroprotective movement of doxycycline (MMPs inhibitor) during ex vivo kidney cold perfusion in a rodent model. The distinguishing proof of the potential components whereby doxycycline secures the transfer kidney could yield different targets and thus other pharmacologic ways to deal with shielding the transfer kidney from protection injury.

Objectives: A pharma co-proteomics approach was used to identify potential molecular targets associated with kidney preservation injury. The principle point was to all the more likely portray the nephroprotective movement of doxycycline (Doxy) during ex vivo kidney cold perfusion in a rodent model. Rat kidneys were cold perfused with or without Doxy for 22 hours. Perfusates were dissected for the presence of injury markers. Proteins extracted from kidneys were analyzed by 2-dimensional gel electrophoresis. The kidney was perfused for 22 h; this time was longer than the typical clinically utilized protection time to expand the shots at noticing huge injury of Proteins of interest were identified by MS. Toward the finish of the perfusion, the kidney was put away at − 80 °C. The action of LDH in perfusates was estimated with the LDH Activity Assay unit (Sigma-Aldrich, Billerica, MA, US, Reference number: MAK 066) as per the producer's guidance. The LDH action was estimated as the measure of NADH created inside a moment from the change of lactate into pyruvate by LDH, which was distinguished by colorimetric examine. The LDH action was communicated as milliunits per milliliter of perfusate (mU/ml which is nmol of NADH/min per milliliter of perfusate). All samples (n = 4/group) were analyzed in duplicate.

Results: A two-fold increases in LDH activity and 10-fold in NGAL was seen in perfusates from ischemic kidneys compared to the controls ($p<0.05$). Levels of all analyzed markers were normalized by 100 µM Doxy. Perfusion with 100 µM Doxy protected mitochondria and inhibited formation of dense bodies, observed by the electron microscopy. Mass spectrometry analysis identified that N(G), N(G)-dimethylarginine, dimethylaminohydrolase and Phosphoglycerate kinase 1 were decreased after cold perfusion, perfusion with Doxy led to an increase in their levels. LDH, NGAL and total protein levels were measured in perfusates as markers of injury. A two-fold increase in LDH activity and total protein level were observed in perfusates from ischemic kidneys perfused without Doxy compared to that seen in control kidneys. An almost 10-fold increase in NGAL levels was seen in perfusates from ischemic kidneys compared to the controls. Levels of all analyzed markers were normalized by 100 µM Doxy. Protein level changes observed from 2DE for some proteins, was verified by immunoblotting (according to commercial availability of antibodies). In 2DE triosephosphate isomerase (protein #1), aminoacylase 1 were not changed in 22 h perfusates. Phosphoglycerate kinase (protein #8) was identified as significantly decreased in the perfusate at 22 h. In perfusates from kidneys protected with Doxy levels of these 3 proteins were significantly increased in comparison to control levels. The results of immunoblot analysis were in accordance with the changes in protein levels observed in 2DE for protein #6 (aminoacylase-1) and protein #8 (phosphoglycerate kinase). For protein #1 (triosephosphate isomerase) a significant decrease in its level after 22 h of perfusion compared to control group was observed in WB analysis, whereas there was no difference between those groups in 2DE.

This work is partly presented at Joint Event European Nephrology Conference at October 12-13, 2020 Zurich, Switzerland

Conclusions: Machine cold perfusion led to significant kidney injury. However doxycycline, an inhibitor of MMPs, decreased kidney injury, may be as a result of mitochondrial protection and hence the maintenance of mitochondrial structure.

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