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Otgonchimeg Rentsendorj, J Nephrol Ther 2016, 6:5(Suppl)
http://dx.doi.org/10.4172/2161-0959.C1.030

Altered epigenetic regulation of renal antioxidant enzyme systems in guinea pigs infused with polymerized cell-free hemoglobin

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Polymerized cell-free hemoglobins are being developed as oxygen and plasma volume-expanding therapeutics though their potential to promote oxidative tissue injury has raised safety concerns. Using a guinea pig exchange transfusion model, we explored oxidant mechanisms of polymerized bovine hemoglobin (HbG) in renal injury. Several renal injury markers including oxidative stress and inflammation markers were targeted. HbG infusion increased tubular injury markers including neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury marker-1 and reduced the transcription of glomerular filtration barrier components including podocin, and nephrin. Increased renal heme oxygensase-1 (HO-1) and decreased enzymatic antioxidants including SOD isoforms 1-3, GPx1, GPx3, GPx4, and CAT were also detected at the mRNA, protein, and activity levels. Furthermore, DNA methylation analyses identified CpG hypermethylation in the gene promoters for all enzymatic antioxidants that we studied suggested an epigenetic-based mechanism underlying the observed gene repression. HbG also induced oxidative stress as evidenced by increased renal lipid peroxidation end-products and 4-HNE immunostaining, which could be the result of the depleted antioxidant defenses and/or serve as a trigger for increased DNA methylation. Together, these findings provide evidence that the renal exposure to HbG suppresses the function of major antioxidant defense systems which may have relevant implications for understanding the safety of hemoglobin-based products and may serve as sensitive and specific biomarkers in kidney injury.

Biography

Oti Rentsendorj has over 15 years research-based experience in endothelial molecular biology, biomarkers, blood products, renal and lung injuries, toxicology, and virology. She received her PhD (Molecular biology) at the Hungarian Academy of Sciences in Szeged in 2006. She was a visiting scholar, postdoc, and a research associate at the Johns Hopkins University in between 2004-2014. In January 2015, she joined the Laboratory of Biochemistry and Vascular Biology, Division of Hematology Research and Review at CBER, FDA. Her current research focuses on "Animal models and tissue injuries induced by hemoglobin-mediated oxidative stress". She has authored 50+ abstracts and papers.

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