HO-1 OVEREXPRESSION REDUCES PROTEINURIA IN EARLY GLOMERULAR IMMUNE INJURY.

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HO-1, the rate-limiting heme degradation enzyme, has emerged as a renoprotective protein in various models of kidney injury. However, we demonstrated that, compared to tubules, glomeruli are refractory to HO-1 upregulation in response to injury. We, therefore, generated transgenic mice with overexpression of HO-1 targeted to glomerular epithelial cells (GEC) using a nephrin (Neph) promoter to drive expression of FLAG-tagged human (h)HO-1. In these mice we explored: 1) whether integrity of glomerular permeability to protein is altered, and 2) whether this overexpression reduces proteinuria following onset of glomerulonephritis induced by antibody against the GBM (anti-GBM GN). In transgenic mice, there was a 16-fold higher transgene expression in kidney compared to other organs (liver). Dual immunostaining for (FLAG-tagged HO-1) transprotein and the GEC marker WT-1 overlaid on GEC. The transgenic mice were no different from wild-type littermates with respect to motility, fur color, body weight, breeding capability and urinary protein excretion rate, indicating that GEC-targeted HO-1 overexpression had no effect on glomerular protein permeability. There was a significant reduction in urine protein excretion (Up/Uc) in transgenic compared to wild-type mice following onset of anti-GBM GN. Specifically, Up/Uc in transgenic mice (n=8) was 0.97 ± 0.43 on day - 4, 2.62 ± 0.43 on day 3, and 3.43 ± 1.94 on day 6. Up/Uc in wild type mice (n=7) was 1.03 ± 0.51 on day -4, 5.48 ± 2.56 on day 3, and 8.34 ± 4.76 on day 6. This salutary effect was abolished by day 9 at which point Up/Uc in transgenic mice (n=8) was 41.5 ± 68.7 while Up/Uc in wild type (n=7) was 41.6 ± 58.2. These observations indicate that GEC-targeted HO-1 expression reduces proteinuria at early stages of anti-GBM GN. The transient nature of this effect could be due to the pronounced increase in synthesis/release of potent HO-1 inducers, including reactive oxygen and nitrogen species and cytokines, known to occur in glomeruli at these stages. Increased HO-1 activity promotes degradation of heme, resulting in the generation of bilirubin, ferritin and CO, offering powerful local antioxidant and cytoprotective functions to the kidney.