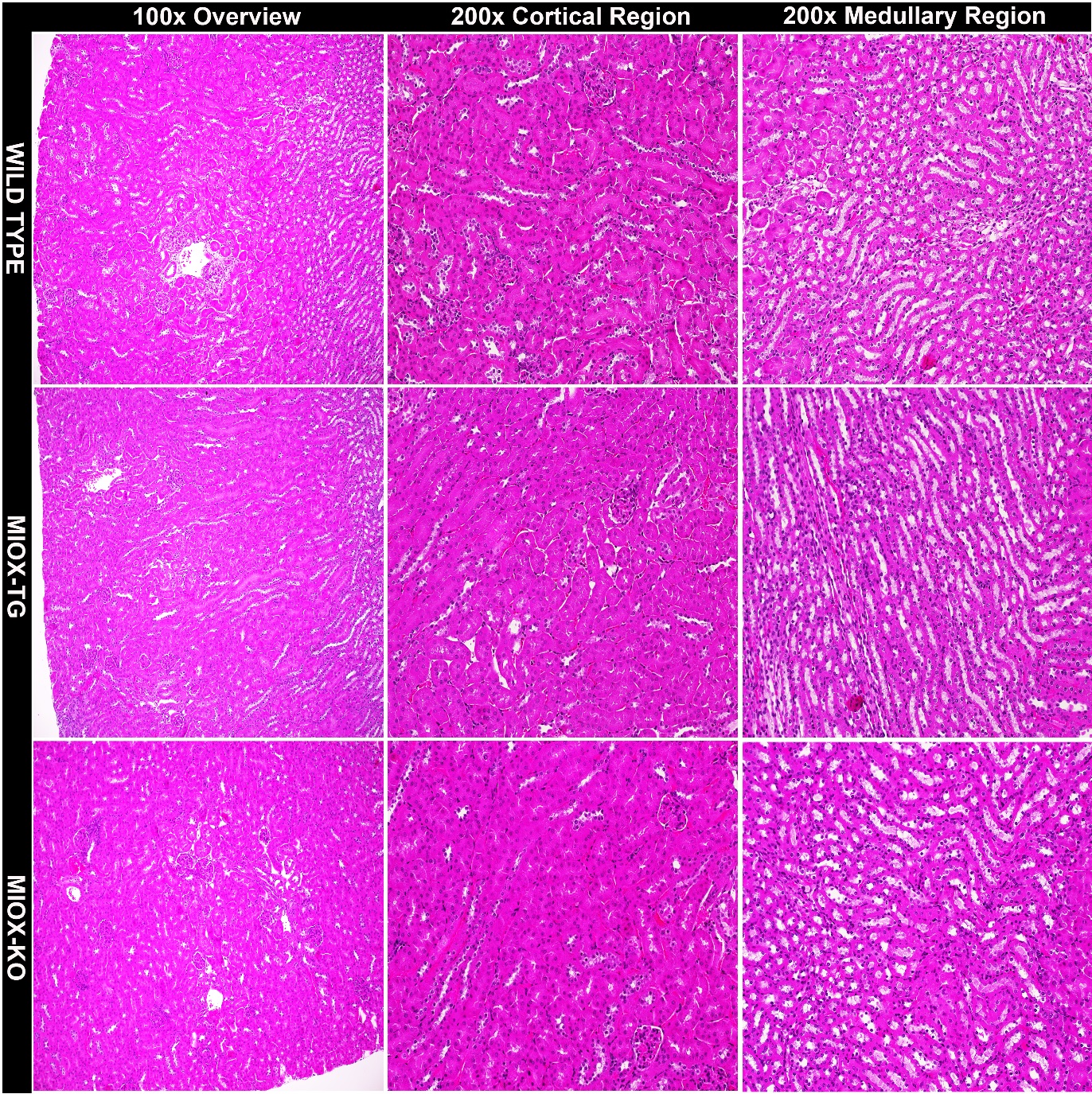
****.

**Supplemental figure 1.** **Schema highlighting the similarities between the polyol and glucuronate-xylulose (G-X) pathway**. During the polyol pathway (**panel A**) there are perturbations in the NADPH:NADP+ and NAD+:NADH ratios with consequential altered redox, *i.e.*, oxidant stress. Akin to polyol pathway is G-X pathway (**panel B**) where *myo*-inositol is catabolized by *myo*-inositol oxygenase (MIOX), and in various subsequent steps there are perturbations in the NADPH:NADP+ and NAD+:NADH ratios with anticipated altered redox (adapted from Ref. 25 with permission).



**Supplemental figure 2.** **Bar** **graph depicting serum levels of cystatin C in various strains of mice.** Diabetic WT, MIOX-TG and Akita mice had elevated levels of cystatin C, suggesting renal injury in the setting of type 1 diabetes induced by the administration of streptozotocin (STZ). MIOX-KO mice had low levels of cystatin C. Interestingly, *Ins2*Akita mice showed relatively high levels of cystatin C which decreased significantly in *Ins2*Akita/KO mice.

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**Supplemental figure 3. Light photomicrographs of kidneys harvested from various strains of mice (Wild type, MIOX-TG & MIOX-KO).** No discernible morphological differences are observed in both medullary and cortical regions of the kidney at 100X or 200X magnifications among various strains of mice. (Hematoxylin & Eosin stain).



**Supplemental figure 4.** **Western blot analyses depicting renal MIOX expression in different strains of mice (WT, MIOX-TG & MIOX-KO) in settings of diabetes**. MIOX-TG mice had a remarkably increased MIOX expression following streptozotocin (STZ) administration. *Ins2*Akita mice also had a relatively high expression of MIOX. Interestingly, MIOX-KO and *Ins2*Akita/KO mice had no detectable expression of MIOX.

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**Supplemental figure 5.** **Schema depicting the plausible events initiated by hyperglycemia leading to accentuation of tubulo-interstitial injury with MIOX overexpression.** Conceivably, XBP1:MIOX and ORE:MIOX interactions under high glucose ambience accentuate cyclical ER and oxidant stress. This combined cellular stress leads to perturbations in mitochondrial homeostasis and activation of TGF-/Smad signaling, resulting ultimately in tubular epithelial injury and tubulo-interstitial fibrosis.

**Supplementary TABLE I**

|  |  |  |
| --- | --- | --- |
| **Reagents** | **Catalogue Number** | **Vendor** |
| HK-2 cells, proximal tubular cell line | CRL-2190 | ATCC |
| pcDNA3.1 | V79020 | Invitrogen Corporation |
| Anti-XBP1 antibody | ab37152 | Abcam |
| Anti-GRP78/BiP antibody | ab21685 | Abcam |
| Anti -TGF-β antibody | ab66073 | Abcam |
| Anti -NOX4 antibody | ab133303 | Abcam |
| NAD/NADH assay kit | ab65348 | Abcam |
| Glutathione assay kit | 703002 | Cayman Chemical |
| Anti-phospho-PDK1 antibody | 3061S | Cell Signaling Technology |
| Anti-phosphoserine-PKC substrate | 2261S | Cell Signaling Technology |
| Anti-Smad3 antibody | 9523S | Cell Signaling Technology |
| Anti-Smad4 antibody | 46535S | Cell Signaling Technology |
| Anti-p-samd2/3 antibody | 8828S | Cell Signaling Technology |
| Anti-Histone H3 antibody | 9715S | Cell Signaling Technology |
| Anti-Bcl2 antibody | 2876S | Cell Signaling Technology |
| Anti-cleaved caspase-3 antibody | 9661S | Cell Signaling Technology |
| Anti-Bax antibody | SC-526 | Santa Cruz Biotechnology |
| Anti-NOX4 antibody | SC-21860 | Santa Cruz Biotechnology |
| XBP1 siRNA | SC-38627 | Santa Cruz Biotechnology |
| siRNA universal control | SICOO1 | Origene Technologies |
| TO-PRO-3-iodide | T3605 | Life Technologies |
| Fast SYBR Green Mix | 4367659 | Life Technologies |
| Dulbecco’s Modified Eagle’s Medium | D5523 | Sigma |
| 2’-7’-dichlorofluroescein diacetate | D6883 | Sigma |
| Dihydroethidium | D7008 | Sigma |
| N-acetyl cysteine | A7250 | Sigma |
| Anti-β-actin antibody | A5441 | Sigma |
| Collagen1 antibody | C2456 | Sigma |
| Fibronectin antibody | F3648 | Sigma |
| ChIP assay kit | 17-295 | Millipore |
| LipofectamineTM 2000 | 11668027 | Thermo Fischer Scientific |
| QuantiChrom™ Creatinine Assay Kit | DICT-500 | Bio-assay System |
| Mouse KIM1 ELISA Kit | ab119596 | Abcam |
| Mouse/Rat Cystatin C Quantikine ELISA Kit | MSCTC0 | R & D Systems |
| Albuwell M Test Kit | 1011 | Exocell |
| Creatinine Companion | 1012 | Exocell |
| QuantiChrom™ Urea Assay Kit | DIUR-100 | Bio-assay System |
| *myo*-Inositol assay kit | K-INOSL | Megazyme |
| Accu-Check Glucometer | 06988580001 | Aviva Plus |
| Anti-rabbit IgG-HRP antibody | A0545 | Sigma |
| Anti -Mouse IgG-HRP antibody | A9917 | Sigma |
| Anti -Rabbit IgG-FITC antibody | F9887 | Sigma |
| Anti -Mouse IgG-FITC antibody | F0257 | Sigma |
| Anti-MIOX antibody | - | Ref. # 26 of the manuscript |