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Protective Roles of Peroxisome Proliferator-activated Receptor-gamma (PPAR- γ) against Peritoneal Membrane Injury

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Continuous exposure of the peritoneal membrane to unphysiologic PD solutions during short- and long-term dialysis results in injury of the mesothelium. The protective roles of PPAR- γ agonist on mesothelium injury were investigated in both in vitro and in vivo. Methods: 24 Male Sprague-Dawley rats were subjected to twice daily injections (10 mL/100gm) with 4.25% PD solution \pm 0.1 μ M pioglitazone (PGZ), a PPAR- γ agonist. After 12-week injections, morphologies of peritoneal membrane, imprints of mesothelial monolayer, and transforming growth factor (TGF)- β mRNA were determined. To investigate the protective mechanism, omental derived primary human mesothelial cells (HPMC) were characterized by positive staining for cytokeratin and sudan III and were incubated with 1.5% PD solution \pm 0.1 μ M PGZ for 16 hours. The mesothelium injury were determined by calculating a ratio of LDH supernatant/attached and the mesothelial death were assessed by morphological changes and by positive TUNEL staining. Results: In-vivo studied, submesothelial thickness and fibrosis in omental and diaphragmatic peritoneum were increased significantly while mesothelial cells were injured and disappeared in rats exposed to the PD solution. All the above abnormalities were significantly ameliorated when rats were co-injected with PGZ. At baseline of in-vitro studies, PPAR- γ was strongly nuclear expression in the HPMC which was down-regulated after exposure to PD solution. HPMC cultured with 1.5% PD solution showed time-dependent morphological changes, which were accompanied by cell injury and apoptosis. Activation of PPAR- γ using 0.1 μ M PGZ significantly abrogated HPMC injury, loss of mesothelial markers, and apoptosis in response to the PD solution. Beneficial effects on HPMC injury were further confirmed by using another PPAR- γ agonist, rosiglitazone. TGF- β was activated both in-vivo and in-vitro studies by PD solution and was attenuated by PGZ. Conclusion: PPAR- γ is normally expressed in HPMC, and its activation is protective against PD solution-induced mesothelial injury which may be mediated partly by manipulating TGF- β expression.