Dual inhibition of classical protein kinase c-alpha and beta isoforms reduces epithelial-to-mesenchymal transition of mesothelial cells and prevents peritoneal damage in a mouse model of chronic peritoneal exposure to high glucose dialysate

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Introduction

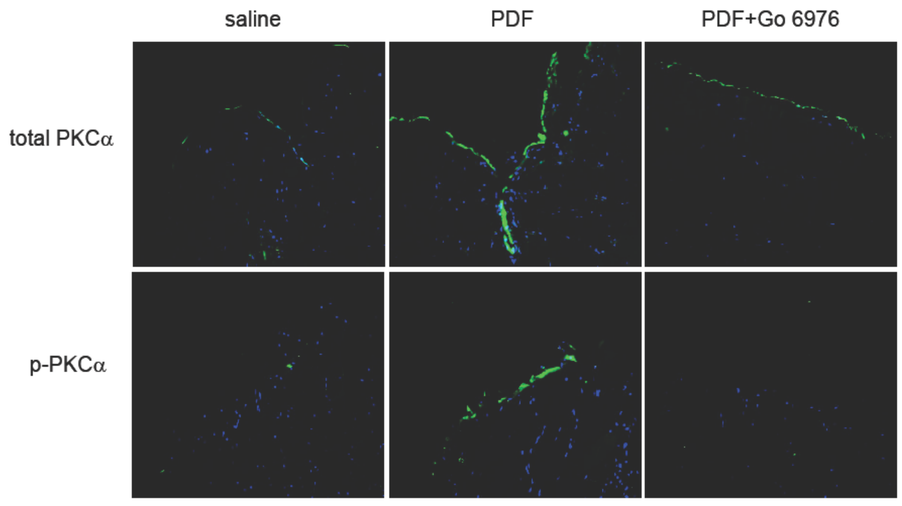
- During peritoneal dialysis (PD) peritoneal membrane (PM) damage occurs due to inflammation and epithelial-to-mesenchymal transition (EMT) of mesothelial cells.
- Classical protein kinase C isoforms alpha and beta (PKC α, PKC β) are involved in pro-inflammatory mediator release and TGF β signalling, both processes leading to fibrosis and ultrafiltration failure.
- We investigated the role of PKC α and PKC β in the effects of glucose-based peritoneal dialysis fluid (PDF) on PM using a mouse model of chronic peritoneal exposure to PDF.

Methods

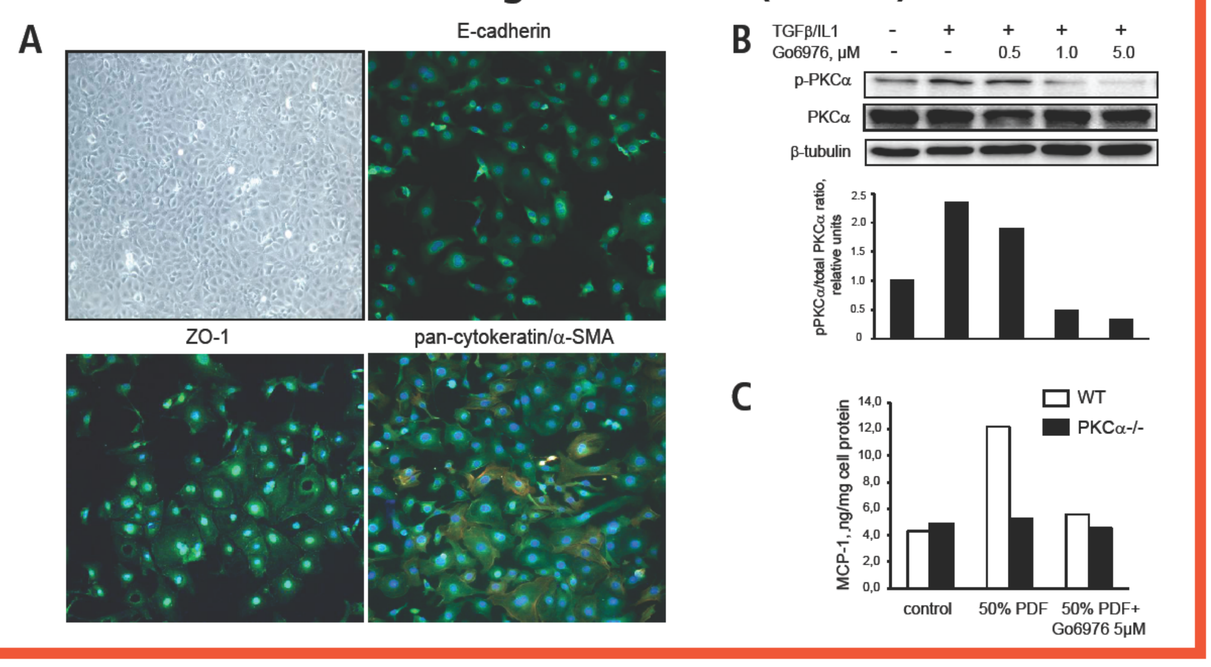
- Chronic PDF exposure for 5 weeks in C57BL6 wild type mice using a customized vascular access port. Controls received saline instead of PDF.
- Dual inhibition of PKC α and PKC β with Go6976, a cell-permeable, reversible, and ATP-competitive inhibitor of classical protein kinase C added at a 1µM concentration to saline or PDF.
- Ultrafiltration capacity of PM was evaluated using a modified ultrafiltration test. Histological and immunohistological analysis of peritoneum was performed. Pro-inflammatory mediator release was measured by specific ELISAs and cytometric bead array technology.

Results

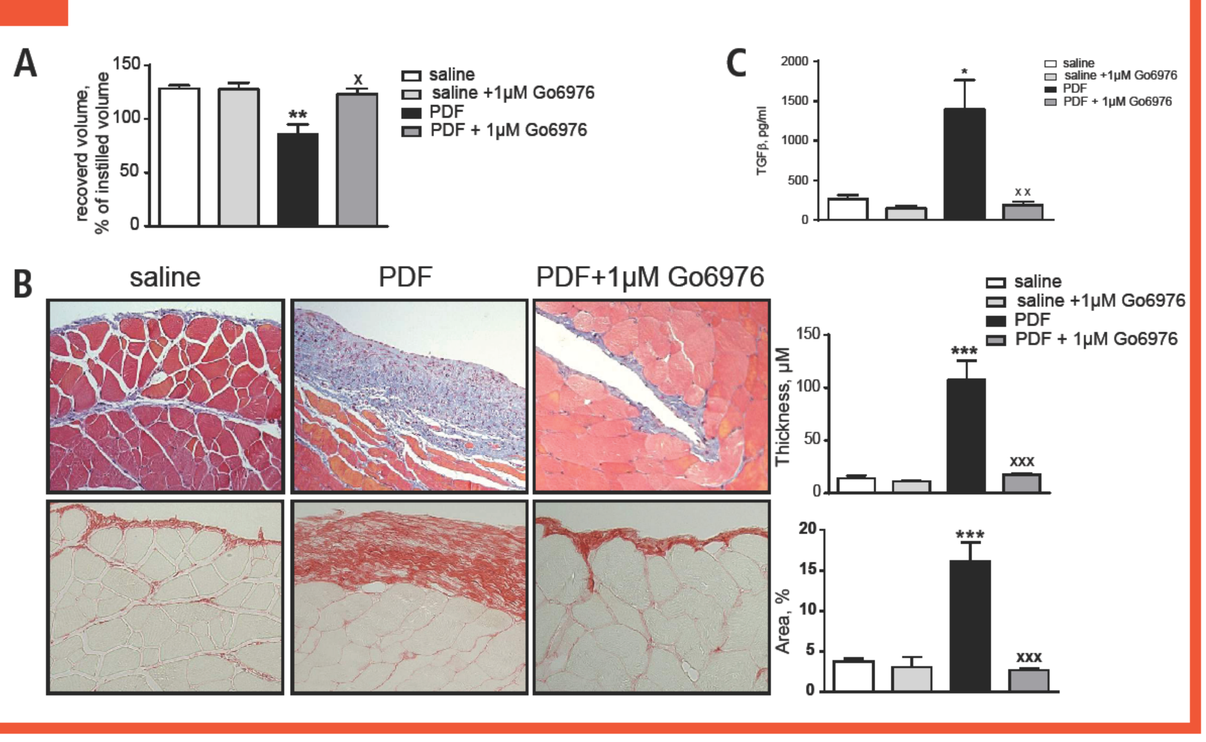
1 PKC α up-regulation during PD *in vivo* (C57BL6)



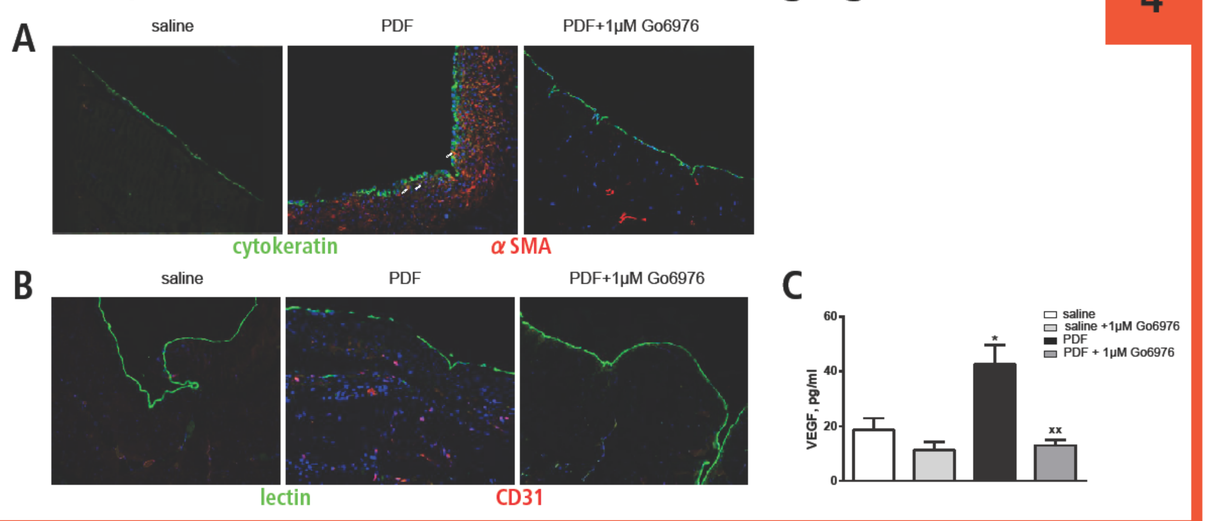
2 PKC α activation: physiological relevance under conditions simulating PD *in vitro* (MPMC)



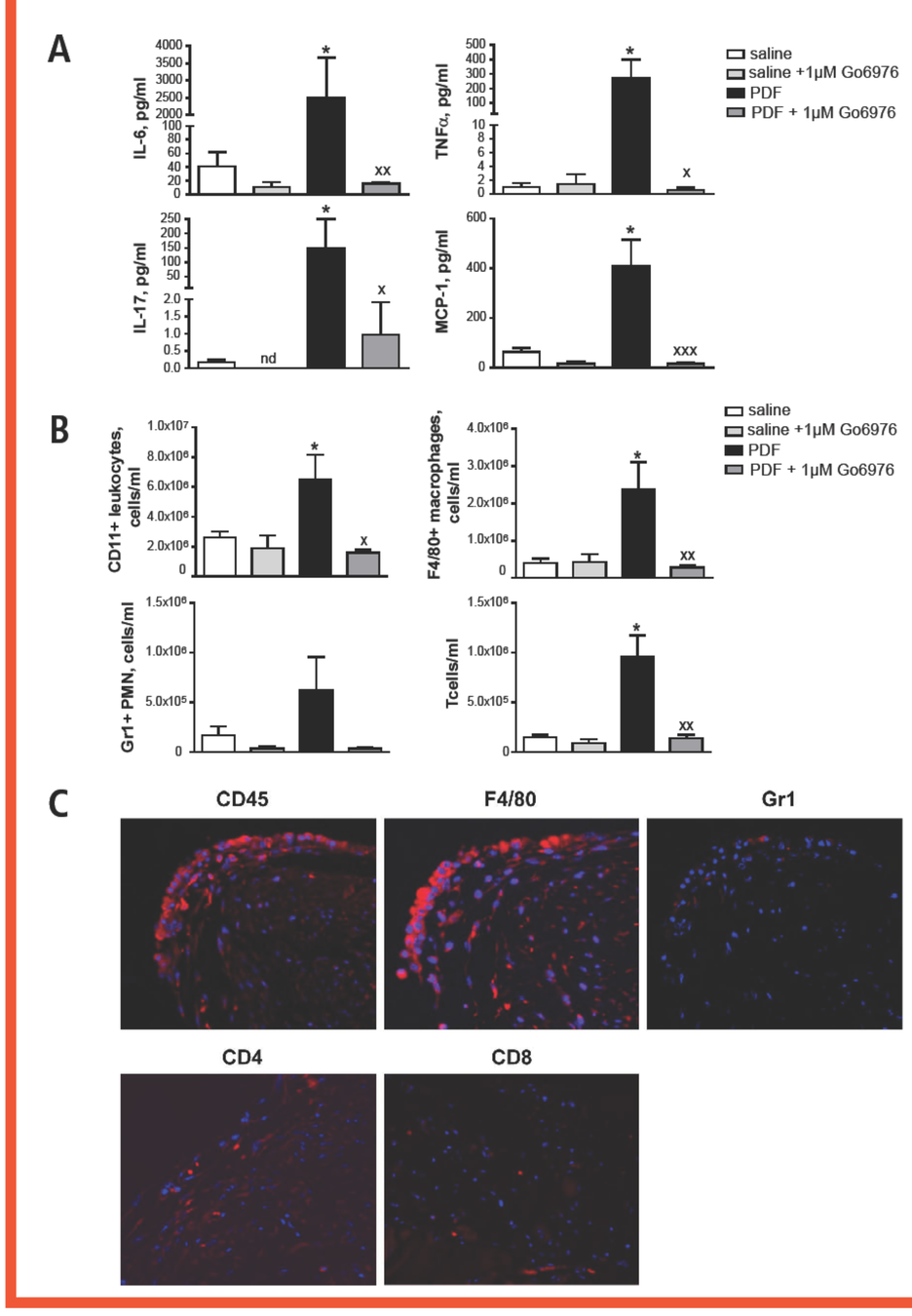
3 PKC α / β blockade *in vivo:* PM function & morphology



4 PKC α / β blockade *in vivo:* EMT & neoangiogenesis



5 PKC α / β blockade *in vivo:* inflammation



Conclusion

Dual inhibition of the classical PKC isoforms is a suitable therapeutic strategy in the prevention or amelioration of peritoneal damage during PD.

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L2) Dialysis. Peritoneal dialysis.
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