

Indoxyl Sulfate Induces Renal Fibrosis by Enhancing p53-TGF- β 1-Smad3 Pathway in Proximal Tubular Cells

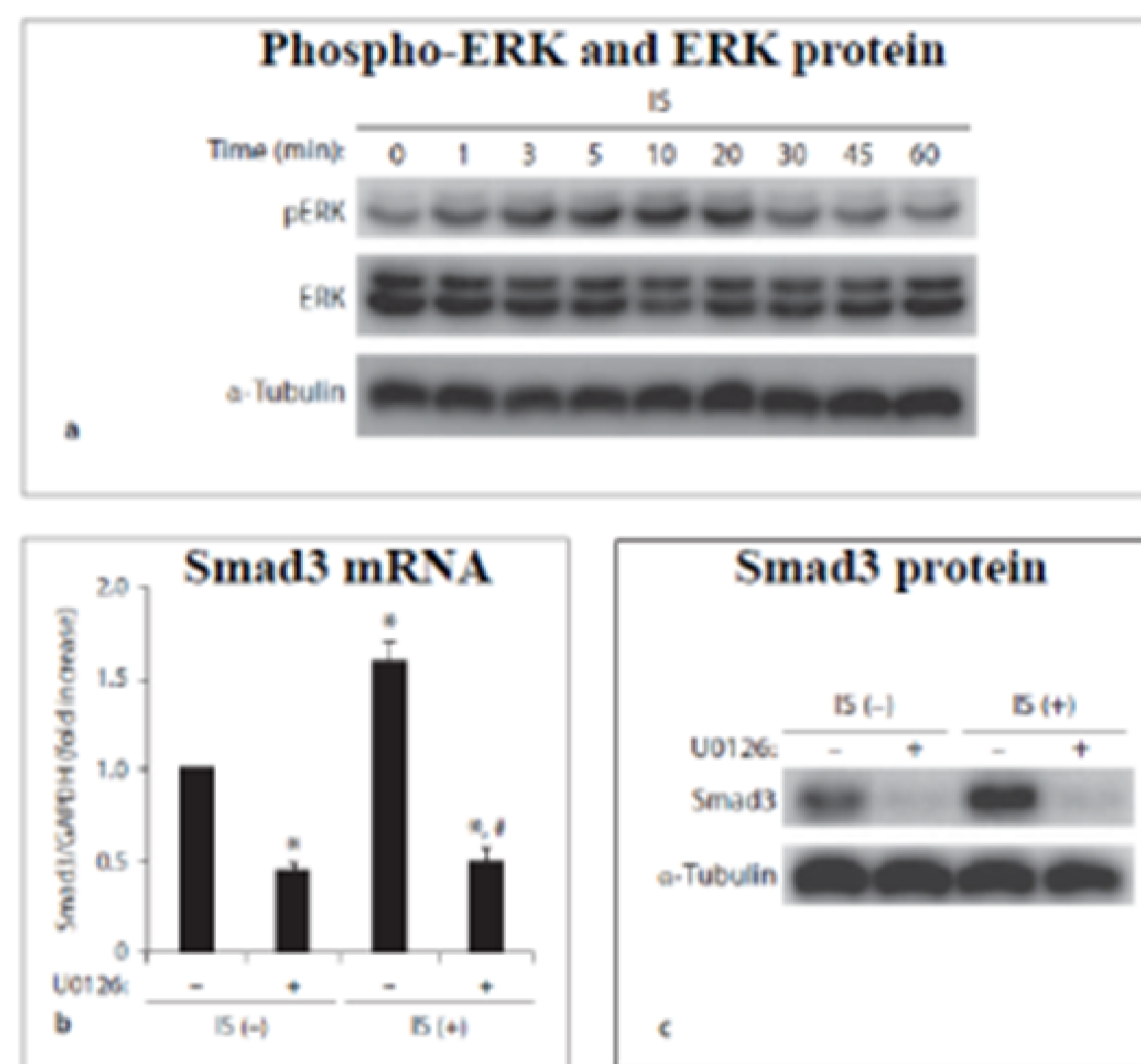
Toshimitsu Niwa, Hidehisa Shimizu, Maimaiti Yisireyili, Fuyuhiko Nishijima*
Nagoya University Graduate School of Medicine, Nagoya, *Biomedical Research laboratories, Kureha, Tokyo, Japan.

Aim

Indoxyl sulfate-induced activation of nuclear factor (NF)- κ B promotes transforming growth factor (TGF)- β 1 in human proximal tubular cells (HK-2 cells).

The present study aimed to elucidate the crosstalk among indoxyl sulfate, p53 and TGF- β 1-Smad3 signaling in proximal tubular cells.

Indoxyl sulfate induces Smad3 expression through ERK activation in HK-2 cells



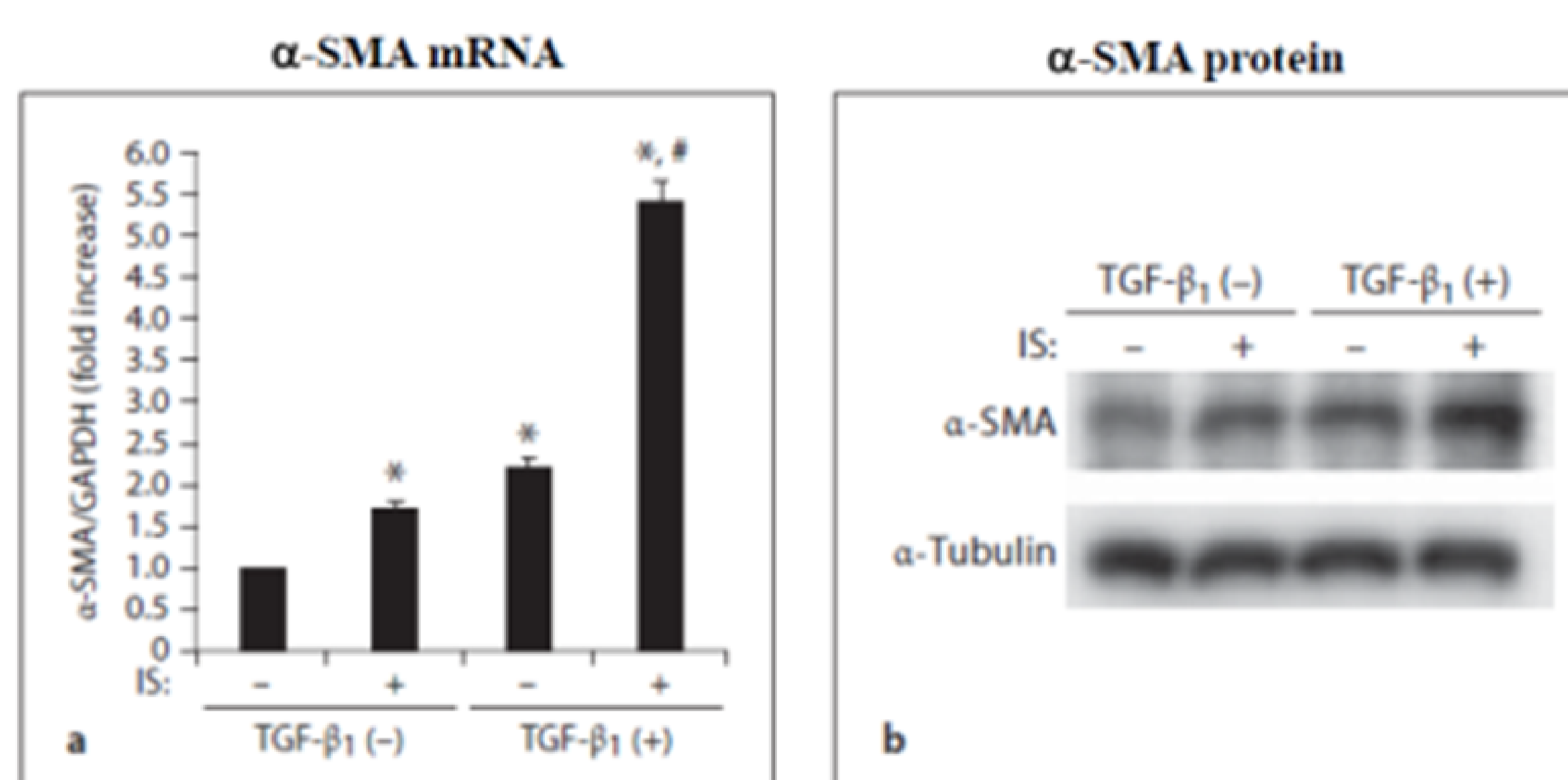
Methods

The effects of indoxyl sulfate on the expression of TGF- β 1, Smad3, and α -smooth muscle actin (α -SMA) were determined using HK-2 cells.

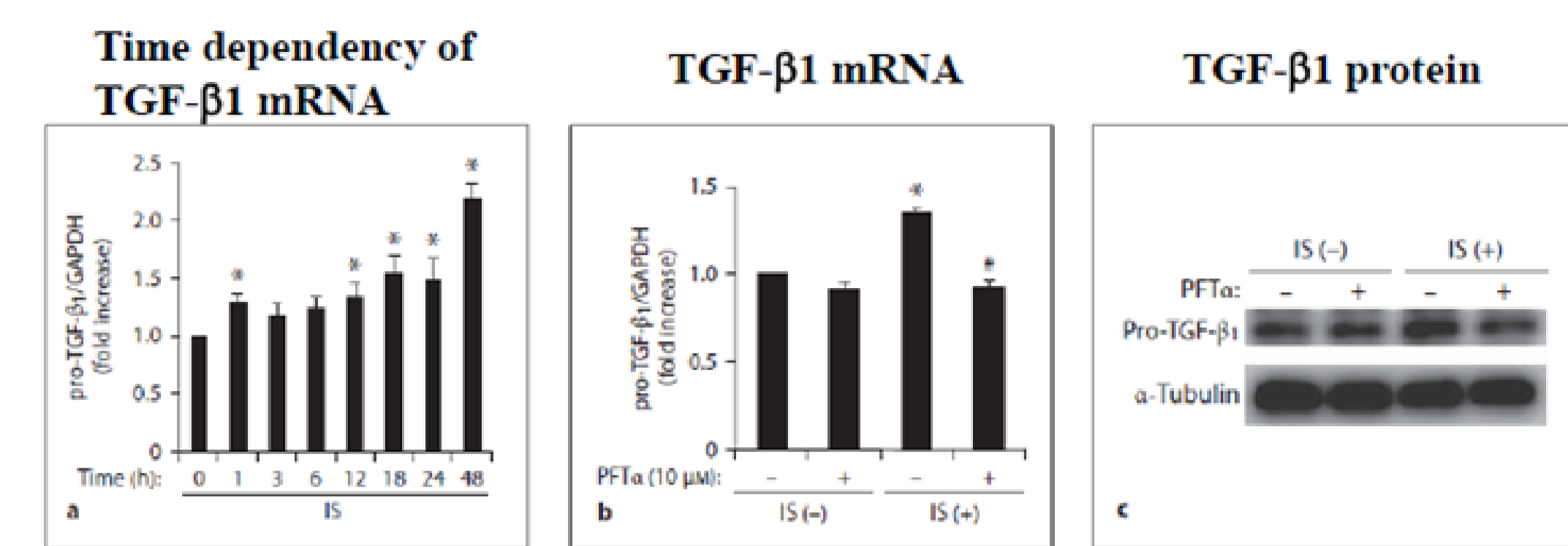
As for *in vivo* experiments, following animals were used:

- (1) Dahl salt-resistant normotensive rats (DN), and
- (2) indoxyl sulfate-administered Dahl salt-resistant normotensive rats (DN+IS).

Indoxyl sulfate promotes TGF- β 1-induced α -SMA expression in HK-2 cells

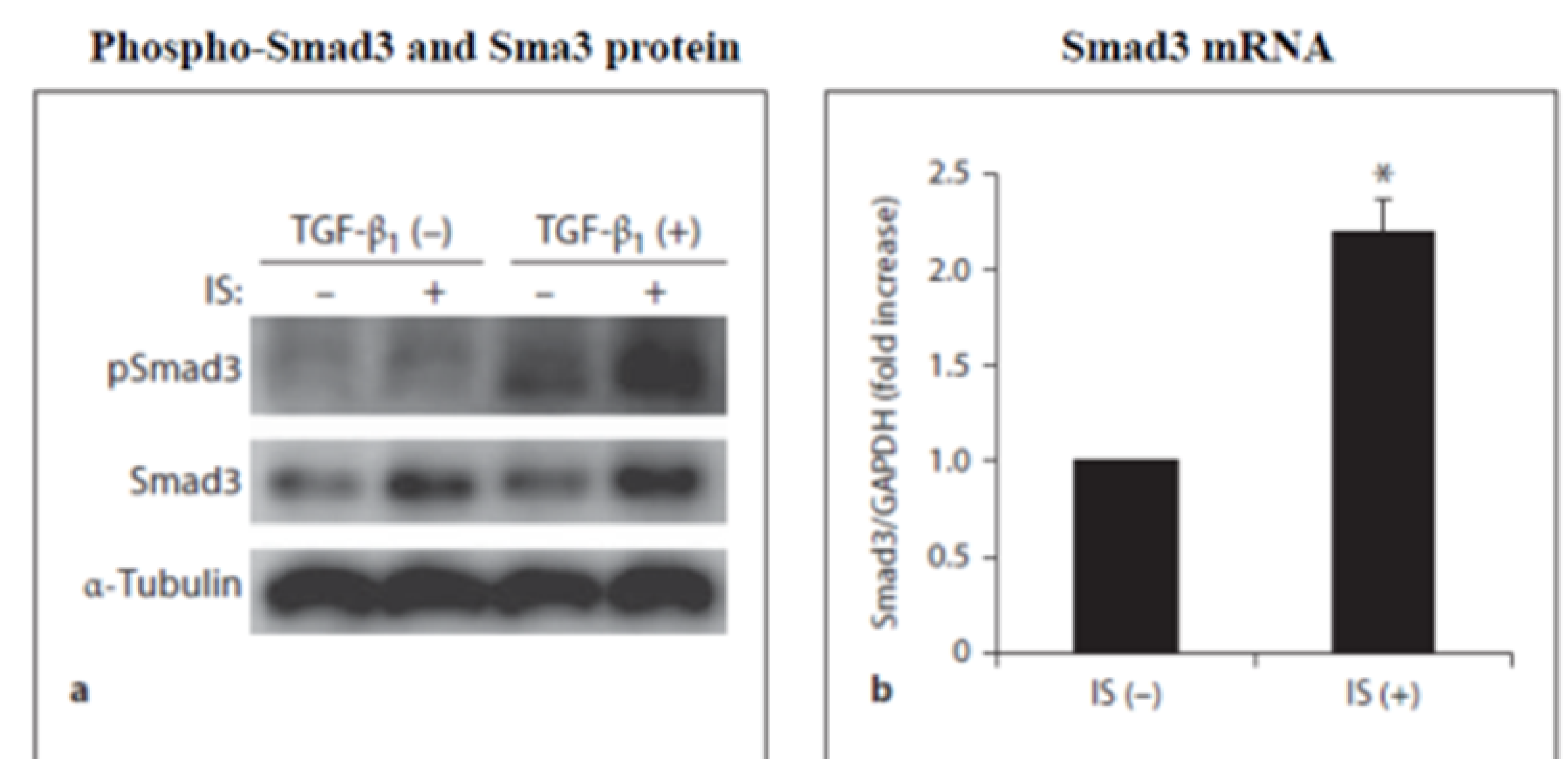


Indoxyl sulfate induces TGF- β 1 expression, which is suppressed by PFT α in HK-2 cells

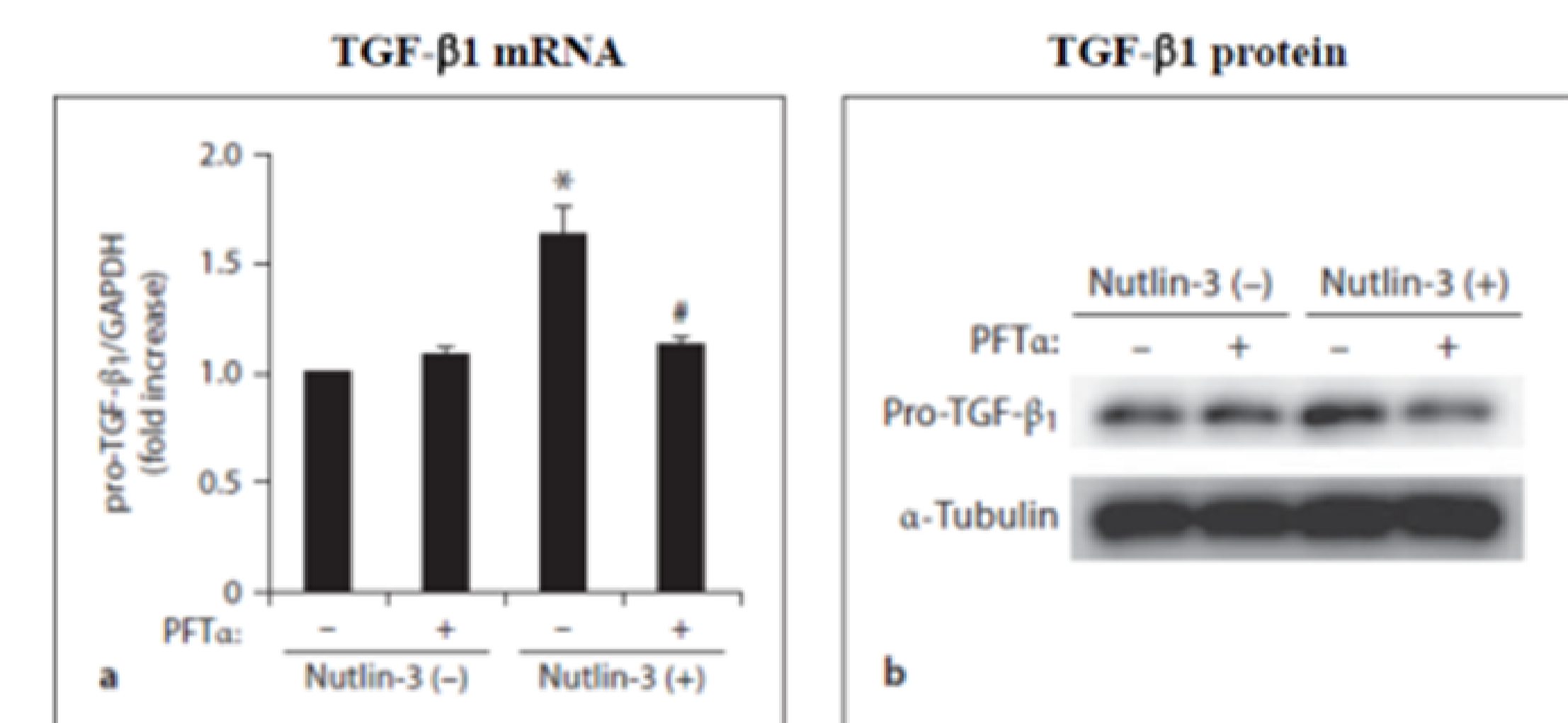


IS: indoxyl sulfate (250 μ M)
PFT α : a specific p53 inhibitor

Indoxyl sulfate enhances TGF- β 1-induced phosphorylation and expression of Smad3 in HK-2 cells

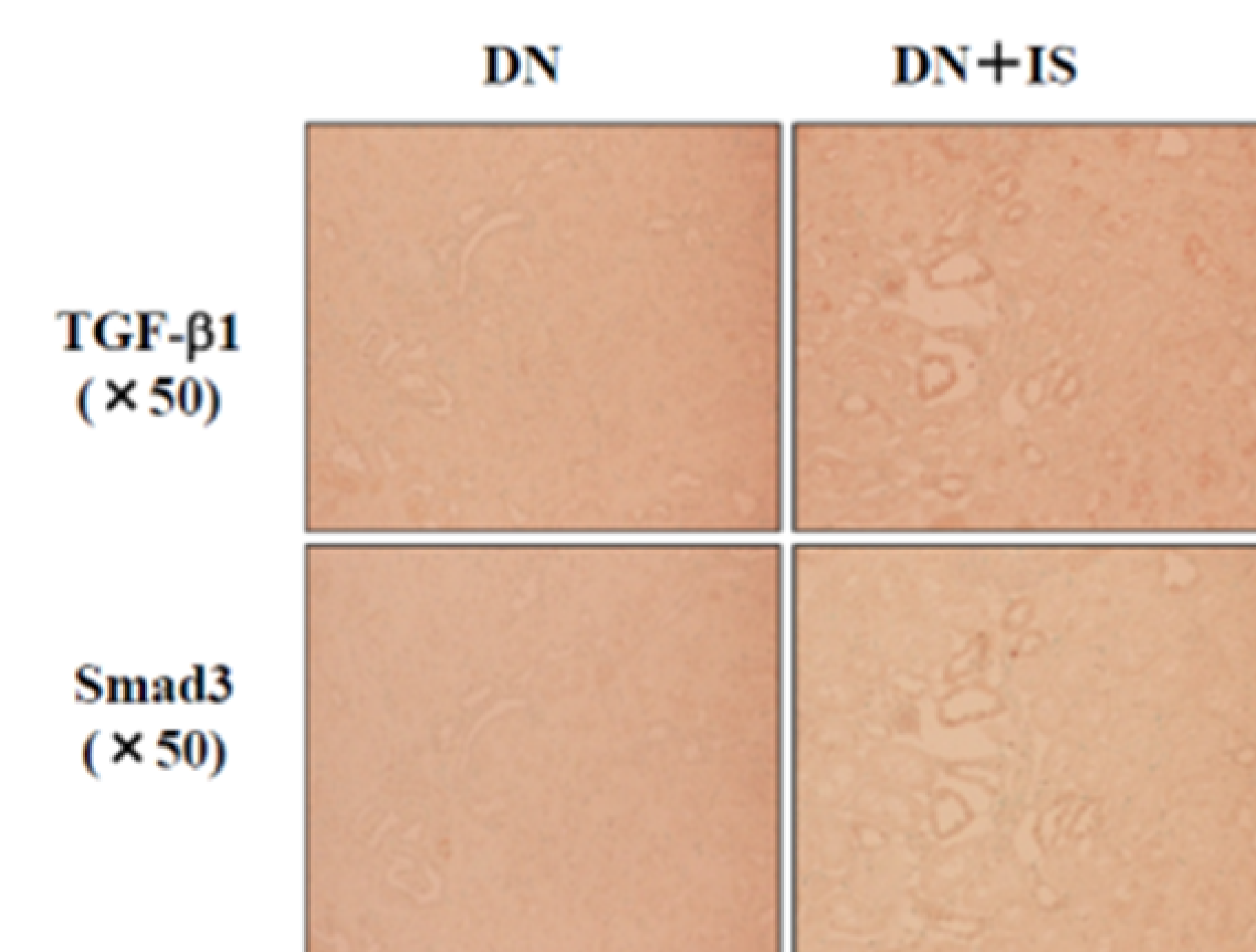


Nutlin-3 induces TGF- β 1 expression, which is suppressed by PFT α in HK-2 cells



Nutlin-3: a specific p53 inducer
PFT α : a specific p53 inhibitor

Indoxyl sulfate increased TGF- β 1- and Smad3-positive area in the kidneys



Conclusion

Indoxyl sulfate stimulates p53-induced TGF- β 1 expression and TGF- β 1-induced α -SMA expression in proximal tubular cells.

Indoxyl sulfate-induced Smad3 accelerates TGF- β 1-induced α -SMA expression through ERK activation.

Thus, indoxyl sulfate enhances p53-TGF- β 1-Smad3 pathway in proximal tubular cells.

