INHIBITION OF MATRIX METALLOPROTEINASE-2 & -9 ACTIVITIES BY FARNESOID X RECEPTOR IN VASCULAR SMOOTH MUSCLE CELLS

Yoyo T.Y. Li, Karen E. Swales, [§]Gareth J. Thomas, Timothy D. Warner and David Bishop-Bailey. William Harvey Research Institute and [§]Tumour Biology, Institute of Cancer, Barts & the London, Queen Mary University of London, London, EC1M 6BQ.

The farnesoid X receptor (FXR; NR1H4) is a ligand-activated transcription factor that regulates bile acid and lipid homeostasis, and is expressed in the vasculature (Bishop-Bailey *et al*., 2004). The matrix metalloproteinases (MMP) are a family of Zn^{+}-dependent endopeptidases that digest extracellular matrix. The gelatinases (MMP-2 and -9) regulate tissue remodelling, and are considered to be important in atherosclerotic plaque stability. We have therefore investigated whether FXR regulates the activities of MMP-2 and -9 in rat aortic smooth muscle cells (RASMC).

RASMC culture and RT-PCR were as previously described (Bishop-Bailey *et al*., 2004). The FXR ligand, 6α-ethyl-chenodeoxycholic acid (6ECDCA; 30μM) or vehicle was added to confluent monolayers of RASMC 1h prior to 24h incubation with IL-1β (10ng/ml) or vehicle under serum-free conditions. The conditioned media were then removed for zymography (Singh *et al*., 2000) and quantification of the gelatinolytic activities by densitometry (Image J). Expression of mRNA for MMP-2 and -9 were assessed by RT-PCR (Burbridge *et al*., 2002).

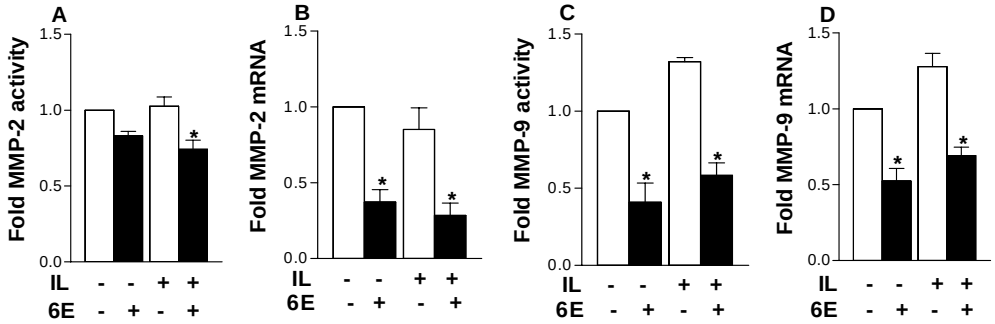

*Figure 1: 6ECDCA (6E) inhibits (A) MMP-2 activity & (B) MMP-2 mRNA, and (C) MMP-9 activity and (D) MMP-9 mRNA, determined by zymography and RT-PCR, respectively. All data represents mean ± S.E.M n=3-5 from 3-5 experiments. * indicates p<0.05 by one-way ANOVA (Bonferroni's post-test).*

MMP-2 activity and mRNA (Figure 1A & B) were not changed by IL-1β, but the activity and expression of inducible MMP-9 (Figure 1C & D) were increased. 6ECDCA reduced both MMP-2 and -9 activities and gene expression in the presence or absence of IL-1β (Figure 1).

FXR ligands down-regulate MMP-2 and -9 activities. FXR may therefore be a novel regulator of vascular remodelling and plaque stability.

Bishop-Bailey *et al*. (2004). *Proc. Natl. Acad. Sci. USA.* **101**, 3668-73.
Burbridge *et al*. (2002). *Angiogenesis*. **5**, 215-26.
Singh *et al*. (2000). *Arch. Oral. Biol*. **45**, 431-40.

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