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Title: Inhaled corticosteroids (ICS) attenuates epithelial mesenchymal transition (EMT) in COPD: A key to understanding long term benefits?

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Body: Introduction: We recently published that EMT is an active process in COPD airways. Our knowledge about the effects of ICS on this process in COPD is very limited. Objective: To assess the effects of ICS on EMT in endobronchial biopsies (ebb) from COPD patients. Methods: A double-blinded, randomized, placebo-controlled study assessed the effects of inhaled fluticasone propionate (FP; 500µg twice daily) on EMT in 34 COPD patients. Ebb were assessed for EMT related reticular basement membrane (Rbm) fragmentation and immunostained for the EMT signatures S100A4 (a fibroblast epitope), matrix-metalloproteinase-9 (MMP-9) and epithelial activation marker, epidermal growth factor receptor (EGFR). Results:

Comparison at baseline and after treatment (FP, n=23 and placebo, n=11)

Markers	Before (FP)	After (FP)	Before (Placebo)	After (Placebo)
% Rbm fragmentation	19.1 (0.2-42.8)*	2.6 (0-88.6)†	24.0 (6.6-100)	26.9 (2.5-48.5)
S100A4 positive cells in BE per mm of Rbm	25.8 (2.4-55.3)*	12.3 (0.6-24.9)†	19.8 (2.9-31.6)	17.4 (10.3-35.5)
S100A4 positive cells in Rbm per mm of Rbm	44.4 (15.3-92.6)*	20.8 (2.6-60.7)†	23.1 (14-82.9)	29.3 (3.6-48.1)
	0.6 (0-22.4)*	0 (0-10.6)†	1.1 (0-4.1)	1.3 (0-2.7)

MMP-9 positive cells in Rbm clefts per mm of Rbm				
EGFR % epithelium	34 (14.6-59.5)*	5.8 (2.6-43.8)†	14.4 (3.6-38.2)	10.3 (1.3-39.1)

Data expressed as medians and ranges. * No significant difference at baseline. † Significant difference after treatment with FP ($p<0.03$).

Conclusions: This is the first study to report that ICS have potent anti-EMT effects in COPD. This may be a mechanistic link between ICS treatment and long term reduction in smoking-related lung cancer seen in COPD.