Role of COX-1 and COX-2 in the release of prostanoids in murine lung and isolated lung fibroblasts

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Cyclooxygenase (COX) is the first enzyme in the conversion of arachidonic acid to prostanoids. There are two isoforms of COX; COX-1, which is constitutively expressed with a homeostatic role in most tissues, and COX-2, which while constitutively expressed in some discreet sites is generally inducible by growth factors and during inflammation. In the current study, we have used tissues and cells from knock-out mice to investigate the relative contributions of COX-1 and COX-2 to PGE_2 production by lung tissue *ex vivo* and by proliferating lung fibroblasts *in vitro*.

Lung tissues from WT (C57Bl6), COX-$1^{-/-}$ and COX-$2^{-/-}$ mice were immediately dissected (<15 min after death) and incubated (37 °C) for 30 min in DMEM containing 50 µM calcium ionophore (A23187). Release of PGE_2 was determined by competitive immunoassay. In parallel studies, murine lung fibroblasts from COX-$1^{-/-}$ and COX-$2^{-/-}$ mice were explanted and cultured before being seeded in 96-well plates at sub-confluence (5000-8000/well) and incubated for 24-48 hours in the presence of 10% FCS. Accumulated release of PGE_2 was then measured as above.

Over 30 min PGE_2 was released by lung pieces from wild type (1117 ± 55 pg/ml) and COX-$2^{-/-}$ (2013 ± 255 pg/ml) but not from COX-$1^{-/-}$ (<61pg/ml) mice (n=4). In contrast, proliferating lung fibroblasts from COX-$1^{-/-}$ (4978.9 ± 1392 pg/ml) mice released higher levels of PGE_2 than cells from COX-$2^{-/-}$ (1194 ± 617 ng/ml) mice (n=4 using cells from 2-3 separate mice for each genotype).

These results show that COX-1 activity underpins the stimulated release of PGE_2 in healthy mouse lung tissue. Conversely, COX-2 activity predominates in proliferating lung fibroblasts, which may be important as COX-derived PGE_2 mediates proliferation of lung fibroblasts (Trends Immunol.2004;25(1):40-6). Our results suggest a switch in COX isoform in lung cells during proliferation which could be relevant to our understanding of conditions such as idiopathic pulmonary fibrosis.