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Title: RNA-seq analysis of transforming growth factor-β-induced glucocorticoid resistance in human bronchial epithelial cells

Ms. Christine 26618 Keenan crkeenan@student.unimelb.edu.au [1], Dr. Guillermo 26619 Lopez-Campos guillermo.lopez@unimelb.edu.au [2], Dr. Saad 26620 Salem ssalem@student.unimelb.edu.au [1], Ms. Trudi 26621 Harris tharris@unimelb.edu.au [1], Dr. Michael 26622 Schuliga schuliga@unimelb.edu.au [1], Dr. Cameron 26623 Johnstone Cameron.Johnstone@petermac.org [3] and Prof. Alastair 26624 Stewart astew@unimelb.edu.au [1]. [1] Department of Pharmacology, The University of Melbourne, Parkville, Victoria, Australia, 3010 ; [2] Health and Biomedical Informatics Unit, The University of Melbourne, Parkville, Victoria, Australia, 3010 and [3] Cancer Cell Biology Program, Peter MacCallum Cancer Centre, East Melbourne, Victoria, Australia, 3002 .

Body: Introduction: Glucocorticoid (GC) resistance limits the successful treatment of chronic inflammatory diseases. We have identified Transforming Growth Factor-β (TGF-β) as a novel inducer of GC insensitivity in the epithelial cell lines A549 and BEAS-2B. This resistance is not prevented by inhibiting known non-canonical TGF-β signalling pathways, but may be partially due to decreased GRα nuclear localisation in A549 cells, but not in BEAS-2B cells. Aim: To use RNA-seq to facilitate efforts to reveal the mechanism of TGF-β-induced GC resistance. Methods: BEAS-2B cells pre-treated for 24h with 40pM TGF-β were treated with 30nM dexamethasone (Dex) for 4h then total RNA was extracted. RNA-seq was performed using an Illumina HiSeq™ 2000 sequencer. Changes from control of more than 2.5 fold were analysed as significant changes and a subset of the observed expression changes were confirmed by RT-qPCR. Results: RNA-seq analysis detected 108 genes with expression up-regulated by Dex. Six of these that were up-regulated by TGF-β alone were removed to prevent confounding analyses. Sixty-six genes were only up-regulated by Dex in the absence of TGF-β, and 36 genes were still up-regulated by Dex in the presence of TGF-β. Conclusions: TGF-β impairs a subset of GC gene regulatory effects in BEAS-2B cells. RNA-seq analysis identified 2 sets of genes up-regulated by GCs, one of which remains inducible and the other which is rendered insensitive to GC activation in the presence of TGF-β. Understanding the differences in regulation of these two groups of GC-sensitive genes may lead to therapeutic strategies to reactivate their expression in chronic inflammatory and fibrotic disease.