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Title: Defective A20 signalling in CF: Anti-inflammatory action of gibberellins

Dr. Catriona 14131 Kelly c.kelly@keele.ac.uk [1], Dr. James 33165 Reihill j.reihill@qub.ac.uk [2], Ms. Beth 33169 Malconsom b.malconsom@qub.ac.uk [2], Ms. Agnieszka 33177 Czerwiec a.czerwiec@qub.ac.uk [2], Prof. Burkhard 33175 Hirsch burkhard.hirsch@charite.de [3], Prof. Stuart 33167 Elborn s.elborn@qub.ac.uk [2], Prof. Madeleine 33168 Ennis m.ennis@qub.ac.uk [2] and Dr. Bettina 33166 Schock b.schock@qub.ac.uk [2]. [1] Institute for Science and Technology in Medicine, Keele University, Keele, United Kingdom, ST5 5BG ; [2] Centre for Infection and Immunity, Queen's University of Belfast, Belfast, United Kingdom and [3] Institute of Pathology, Charité-University Medicine, Berlin, Germany .

Body: Introduction: A20 negatively regulates NF-κB signalling and is induced in response to bacteria or viruses. Recently, we reported significant reductions in the expression/function of A20 in the CF airway epithelium (Kelly et al. ERJ 2012). The plant diterpene Gibberellin (GA) induces A20-like zinc fingers in plants and has anti-inflammatory properties in mammals. However the anti-inflammatory mechanism has not been described. We hypothesized that GA works via an A20-dependent mechanism and examined the effects on airways inflammation in CF. Methods: Human bronchial epithelial cell lines (16HBE14o- and CFBE41o-) and Primary Nasal Epithelial cells (NECs) from healthy volunteers were used. Cells were pre-incubated with GA, (30μM, 1h) and stimulated with P. aeruginosa LPS (10μg/ml). Effects of GA on cytotoxicity (MTT) and proliferation (CellTiter 96 Proliferation Assay) were examined. IL-8 was measured by ELISA. A20 and p65 mRNA and protein expression was measured by qPCR and Western Blot. A20 was silenced in 16HBE14o- cells using siRNA. Results: 30μM GA did not increase cytotoxicity or cellular proliferation in any cell type. Pre-incubation with GA significantly induced A20 mRNA and protein expression in LPS-stimulated cells (16HBE14o-, CFBE41o- and NECs). A20 induction was accompanied by a reduction in IL-8 release and p65 expression. The anti-inflammatory effect (IL-8 release) of GA was lost in 16HBE14o- cells treated with A20 siRNA. Conclusions: GA exerts anti-inflammatory effects in airway epithelial cells. Work is on-going in CF NECs. Initial investigations suggest that the anti-inflammatory effect of GA is A20-dependent. GA may therefore overcome defective A20 signalling in CF airways disease.