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Title: Importin-7 knockdown reduces corticosteroid induced glucocorticoid receptor nuclear localisation and suppression of IL-1β induced CXCL8

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Body: Background: Corticosteroids (CS) are highly recommended in the treatment of asthma and COPD. CS act via binding to the glucocorticoid receptor (GR). Upon activation, GR translocates into the nucleus, an essential prerequisite for CS function. Two groups of nuclear receptors, importin and exportin mediate RanGTPases-dependent transport across the nuclear membrane. In an in vitro nuclear import assay, importin-7 resulted in the nuclear import of the nuclear localisation signal fragment of GR. We therefore hypothesised, Importin-7 is crucial for corticosteroid-induced GR nuclear translocation. Method: We initially investigated whether GR binds to Importin-7 in U937 monocytes, followed by the effects of Importin-7 siRNA knockdown on fluticasone propionate (FP) induced GR nuclear localisation and suppression of IL-1β induced CXCL8. siRNA Importin-7 knockdown was achieved via electroporation and results were compared to a negative siRNA control. Statistical analysis was performed using non-parametric analysis. Results: Cytoplasmic and nuclear levels of Importin-7 protein expression were significantly decreased by 38.4%±19.9 and 42.7%±28.6, respectively, post 36h siRNA Importin-7 transfection. Additionally, 36hr post siRNA Importin-7 transfection, FP (10^{-9}M) increase in nuclear GR levels at 2h and suppression of IL-1β induced CXCL8 secretion at 16h were significantly decreased by 39.3%±12.3 and 32.4%, respectively. Conclusions: Importin 7 knockdown reduced FP induction of GR nuclear localisation and FP suppression of IL-1β induced CXCL8. Importin-7 is a potential therapeutic target that maybe manipulated to improve CS function and activity.