Dysfunctional interaction of C/EBPalpha and the glucocorticoid receptor in asthmatic bronchial smooth-muscle cells

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BACKGROUND
Increased proliferation of bronchial smooth-muscle cells may lead to increased muscle mass in the airways of patients with asthma. The antiproliferative effect of glucocorticoids in bronchial smooth-muscle cells in subjects without asthma is mediated by a complex of the glucocorticoid receptor and the CCAAT/enhancer binding protein alpha (C/EBPalpha). We examined the signaling pathway controlling the inhibitory effect of glucocorticoids on cell proliferation and interleukin-6 synthesis in bronchial smooth-muscle cells of subjects with asthma and those without asthma.

METHODS
Lines of bronchial smooth-muscle cells were established from cells from 20 subjects with asthma, 8 subjects with emphysema, and 26 control subjects. Cell proliferation was determined by means of cell counts and [3H]thymidine incorporation. Signal transduction was studied by means of an electrophoretic DNA mobility-shift assay, a supershift electrophoretic-mobility assay, immunoblotting, use of C/EBPalpha antisense oligonucleotides, and use of a human C/EBPalpha expression vector. Interleukin-6 release was determined by means of an enzyme-linked immunosorbent assay.

RESULTS
Glucocorticoids activated the glucocorticoid receptor and inhibited serum-induced secretion of interleukin-6 in bronchial smooth-muscle cells from both subjects with asthma and those without asthma; however, glucocorticoids inhibited proliferation only in bronchial smooth-muscle cells from subjects without asthma. C/EBPalpha protein was detected by immunoblotting in all bronchial smooth-muscle cells from subjects without asthma but not in those with asthma, whereas the protein was expressed in lymphocytes from both groups of subjects. C/EBPalpha antisense oligonucleotides or the glucocorticoid-receptor inhibitor mifepristone reversed the antiproliferative effect of glucocorticoids in bronchial smooth-muscle cells from subjects without asthma. When bronchial smooth-muscle cells from subjects with asthma were transiently transfected with an expression vector for human C/EBPalpha, two
forms of the protein were expressed, and subsequent administration of glucocorticoids inhibited cell proliferation.

CONCLUSIONS
We hypothesize that a cell-type-specific absence of C/EBPα is responsible for the enhanced proliferation of bronchial smooth-muscle cells derived from subjects with asthma and that it explains the failure of glucocorticoids to inhibit proliferation in vitro.

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