Tobacco Smoke-induced Lung Cell Proliferation Mediated by Tumor Necrosis Factor α-converting Enzyme and Amphiregulin*

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Cells dividing at the time of carcinogen exposure are at particular risk for neoplasia. Tobacco smoke contains numerous carcinogens, and we find that smoke, in the absence of exogenous growth factors, is capable of stimulating cell proliferation. The smoke-triggered mechanism includes the generation of oxygen radicals, which in turn stimulate tumor necrosis factor α-converting enzyme (a disintegrin and metalloproteinase (ADAM) 17) to cleave transmembrane amphiregulin, a ligand for the epidermal growth factor receptor (EGFR). The binding of amphiregulin to EGFR then stimulates proliferation of lung epithelial cells. These results shed light on the pathogenesis of lung cancer, suggest novel drug targets for the reduction of cancer risk in smokers, and provide insight into how EGFR integrates responses to diverse noxious stimuli.

Eighty-seven percent of lung malignancies, the leading cause of cancer deaths in both men and women, are caused by smoking (American Lung Association Website, 2002). Although this has been known for some time, the molecular pathogenesis of lung cancer remains obscure. Perhaps the most significant advances have been in the identification of smoke carcinogens. Benzo[α]pyrene is converted in the lung to benzopyrenediol epoxide, which forms adducts on guanine residues, most notably those in the tumor suppressor gene p53 (1). Because of its role in the mitotic arrest of cells with damaged DNA, key mutations in p53 provoke the accumulation of other mutations eventually leading to lung cancer.

However, conversion of adducts to mutations can only occur in proliferating cells (2, 3) suggesting that tobacco smoke must also promote cell division before carcinogens such as benzopyrenediol epoxide can effectively mutate DNA. Indeed, hyperproliferation occurs in response to smoke exposure (4, 5) and very likely increases cancer risk in the presence of tobacco carcinogens.

The mechanism by which tobacco smoke stimulates lung cell proliferation is unknown. Based on the involvement of the epidermal growth factor receptor (EGFR) in response to noxious stimuli (6, 7), we tested and confirmed the involvement of EGFR in the response of the host cell to tobacco smoke (8). In the experiments reported here, we identify mechanisms triggered by smoke that result in both phosphorylation (activation) of EGFR and cell proliferation.

MATERIALS AND METHODS

Reagents—All tissue culture media and antibiotics were obtained from Invitrogen or the University of California, San Francisco, cell culture facility. Chemical inhibitors were purchased from Calbiochem except N-acetyl-l-cysteine and N,N-dimethylthioureas and diphenyliodonium chloride, which were purchased from Sigma. Blocking EGFR antibody AB-1 was purchased from Calbiochem. Antibodies to EGFR ligands were purchased from R&D Systems, Inc. (Minneapolis, MN). Antibody directed against the cytoplasmic domain of tumor necrosis factor α-converting enzyme was from Imgenex (San Diego, CA). All other antibodies were purchased from Santa Cruz Biotechnology (Santa Cruz, CA). LipofectAMINE was purchased from Invitrogen. Purified lipoteichoic acid (LTA) from Staphylococcus aureus and all other reagents were purchased from Sigma.

Mice—Six specific-pathogen-free C57 black mice (8 weeks old, Charles River Laboratories, Wilmington, MA) were treated intranasally with the metalloproteinase inhibitor GM6001 or saline solution prior to exposure to smoke in a specially designed chamber (9).

Cell Culture and Assay for Cell Density—Primary human airway epithelial cells were obtained from Clonetics (San Diego, CA) and were cultured under conditions recommended by the vendor. NCI-H292 (mucoepidermoid carcinoma) cells were also used. NCI-H292 cells were maintained in RPMI 1640 medium containing 10% fetal bovine serum, 100 units/ml penicillin, and 0.1 mg/ml streptomycin. For cell proliferation assays, cell density was assayed 24 or 48 h after a 4-h treatment with serum-free medium (SFM), smoke-containing medium, or EGF using Cell Titer 96® Aqueous One reagent (Promega, Madison, WI) according to the manufacturer’s instructions.

Immunoprecipitation and Immunoblotting—Cells were lysed in 20 mM Tris-HCl, 150 mM NaCl, 0.5% Triton X-100, 0.1% SDS, 1 mM EDTA, and 1 mM sodium orthovanadate. The samples were pre-cleared by centrifugation at 10,000 rpm for 10 min at 4 °C, and total protein concentrations were determined using the Bradford protein assay (Bio-Rad). For detection of ADAM (a disintegrin and metalloproteinase) proteins, we used lysates from cells that had or had not been transfected with morpholin antisense oligonucleotides. Lysis buffer contained 10 mM 1,10-orthophenanthroline to prevent autolysis of the ADAMs. For detection of EGFR ligands shed into cell culture medium, we concentrated the medium 10× using Amicon Centrifil filters with a cutoff of 3 kDa. For determination of the phosphorylation state of EGFR, we incubated equal amounts of lysate with anti-EGFR antibody and Protein A-agarose beads overnight at 4 °C. The lysate-antibody-bead complex was spun down and washed three times with lysis buffer. Following the final wash, 40 μl of SDS gel-loading buffer was added, the mixture was heated at 100 °C for 3 min, and proteins were resolved by SDS-PAGE. For immunoblot analysis of the samples listed above, proteins were transferred to nitrocellulose membranes using the Bio-Rad Mini Trans-Blot electrophoretic transfer cell. Membranes were blocked

This work was supported by National Institutes of Health Grants RO-1 HL-43762 and PO-1 HL-24136 (to C. B.) and a grant from the Tobacco-Related Diseases Research Program of the State of California (to C. B.). The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby advertisement “in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

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The abbreviations used are: EGFR, epidermal growth factor receptor; LTA, lipoteichoic acid; ADAM, a disintegrin and metalloproteinase; ROS, reactive oxygen species; SFM, serum-free medium; TNFα, tumor necrosis factor α; TGFα, transforming growth factor α; HBEGF, heparin-binding epidermal growth factor; H2DCFDA, 2’,7’-dichlorodihydrofluorescein diacetate.

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for 1 h at room temperature in phosphate-buffered saline containing 0.1% Tween 20 (PBS/Tween) and supplemented with 5% BSA, then washed with PBS/Tween and incubated with the appropriate antibody overnight at 4 °C. After removing primary antibody with several washes of PBS/Tween, the blot was placed in the appropriate horseradish peroxidase-conjugated secondary antibody for 45 min. After several washes, the antibody-antigen complexes were visualized using the ECL chemiluminescence detection system (Amersham Biosciences). The cell lysates were immunoprecipitated with anti-EGFR antibody, immunoblotted with anti-phosphotyrosine antibody, and visualized by chemiluminescence. The lower panel shows results after the blot was stripped and reprobed with anti-EGFR antibody. Same experiment as in A using NCIH292 cells. C, NCIH292 cells grown on coverslips were incubated for 15 min at 37 °C with or without smoke-containing medium or EGF (100 ng/ml). Cells were then fixed, permeabilized, and immunostained with anti-EGFR antibody and fluorescein isothiocyanate-conjugated sheep anti-mouse IgG prior to viewing.

**FIG.2.** Smoke stimulates phosphorylation of EGFR. A, primary human bronchial epithelial cells were incubated with SFM, smoke-containing SFM (SMK), or EGF (10 ng/ml)-containing SFM for 10 min. Cell lysates were immunoprecipitated with anti-EGFR antibody, immunoblotted with anti-phosphotyrosine antibody, and visualized by chemiluminescence. The lower panel shows results after the blot was stripped and reprobed with anti-EGFR antibody. B, same experiment as in A using NCIH292 cells. C, NCIH292 cells grown on coverslips were incubated for 15 min at 37 °C with or without smoke-containing medium or EGF (100 ng/ml). Cells were then fixed, permeabilized, and immunostained with anti-EGFR antibody and fluorescein isothiocyanate-conjugated sheep anti-mouse IgG (Amersham Biosciences) prior to viewing with a Nikon Eclipse E600 microscope using an NCF Fluor 40 objective lens.

**Morpholino Antisense Oligonucleotides**—NCIH292 cells were transfected according to the manufacturer’s instructions with 2 μM solutions of morpholino antisense oligonucleotides (Gene Tools LLC, Philomath, OR) corresponding to ADAM10, 5’-AAATAACACTCTACGACCAAC-CATC-3′; ADAM15, 5’-AAGACGACGCCGAGCCCGATGCCAGC-3′; ADAM 9, 5’-GAAAGCGCCGGCCAGACCACCTC-3′; or ADAM 17, 5’-TCAGGATAGGAGACTGCTTC-3′). Thirty hours later, cells were lysed for ADAM immunoblot or stimulated with smoke or EGF. ADAM immunoblots were normalized for loading differences using β-actin and analyzed by densitometry (Image J 1.27 software). Stimulated cells were used for immunoprecipitation and phospho-EGFR immunoblot as described above.

**RESULTS**

To approach the question of how smoke stimulates cell proliferation, we exposed both primary human bronchial epithelial cells and the lung tumor cell line NCIH292 to serum-free medium with or without smoke components (9) for 4 h. Cell counts 48 h later revealed that cell number increased as a consequence of smoke exposure (Fig. 1, A and B). Associated with this was phosphorylation of the EGFR, which occurred during the first several minutes of smoke exposure (Fig. 2, A and B). That this was required for the stimulatory effect of smoke was indicated by a reduction of cell number in the presence of the EGFR kinase inhibitor, AG 1478 (Fig. 1, A and B). These effects occurred in the absence of extracellular ligand.

Although there have been prior reports of "ligand-independent" EGFR activation, the mechanism of activation is unclear. Following smoke exposure, we observed oligomerization and internalization of EGFR (Fig. 2C) with the same kinetics as...
that seen following administration of EGF itself (not shown). Oligomerization implies that smoke induces autophosphorylation of the receptor, a mode of activation inhibitable by AG 1478. It has only recently been appreciated that receptor activation in the absence of exogenous growth factor can nonetheless be growth factor-dependent. Thus, Ullrich and co-workers (10) showed that the transactivation of EGFR by G proteincoupled receptors was mediated by the metalloproteinase-dependent cleavage of HBEGF and its subsequent binding to EGFR. We recently showed that transactivation of EGFR by the bacterial outer membrane component LTA occurs by a similar mechanism (11). To examine the mechanism induced by smoke, we first asked whether ligand binding was required for the response. Results showing attenuation of receptor phosphorylation by antibody blockade of the ligand-binding site indicated that despite the absence of an extracellular ligand, ligand-receptor interaction was required for the response (Fig. 3A).

Because EGFR ligands (amphiregulin, betacellulin, EGF, TGFα, HBEGF, and epiregulin) originate as transmembrane proteins that are cleaved and “shed” prior to receptor binding (12–15), we next sought evidence for the possibility that smoke stimulated the shedding of ligand into the cell culture medium.

The breast cancer cell line SKBR3 shows EGFR phosphorylation in response to soluble ligand but not to smoke, making the cells suitable “reporters” for smoke-induced ligand shedding. As shown (Fig. 3B), SKBR3 cells displayed strong receptor phosphorylation in response to the conditioned medium from smoke-exposed, but not unexposed, NCIH292 cells. This suggested that NCIH292 cells proteolytically cleaved and released ligand upon smoke exposure and that this ligand was transferred to SKBR cells in the conditioned medium.

The cleavage of EGFR ligands is mediated, at least in some cases, by transmembrane metalloproteinases called ADAMs (16, 17). Consistent with the view that smoke stimulates ligand cleavage and release, we found that the metalloproteinase inhibitor GM6001 inhibited the phosphorylation of EGFR by smoke but not EGF (Fig. 4A). When we exposed NCIH292 cells to smoke in the presence of antisense oligonucleotides corresponding to various ADAMs, we found that antisense ADAM 17 (tumor necrosis factor α converting enzyme) but not antisense ADAMs 9, 10, or 15 (data not shown for ADAMs 9 and 15) strongly attenuated smoke-induced phosphorylation of EGFR (Fig. 4B). Immunoblots monitoring the amount of ADAM present in the same cells confirmed that antisense inhibition was appropriate and specific (Fig. 4C). This implicated ADAM 17 in the response to smoke contrasting with earlier data implicating ADAM 10 in the response of the same cells to bacterial LTA (11).

Although the basis for substrate specificity of the ADAMs is unclear, it is recognized that individual ADAMs may cleave more than a single substrate. ADAM 17 in particular has been shown to cleave several surface molecules including both TNFα and TGFα (18). To identify the ligand cleaved in response to smoke, we prepared immunoblots of medium from smoke-exposed NCIH292 cells. Although negative for the EGFR ligands epiregulin, HBEGF, betacellulin, and EGF, the blots showed that smoke but not LTA strongly stimulated the release of amphiregulin. The reverse was true for HBEGF (Fig. 4D). Small amounts of TGFα were also released by smoke (not shown). As expected, the presence of antisense ADAM 17 inhibited the ability of smoke to stimulate amphiregulin release (Fig. 4E).

We next addressed the question of how smoke stimulates ADAM 17. Because both EGFR phosphorylation and metalloproteinase activation are known to be redox-sensitive (19–23), we asked whether oxygen radicals stimulate ADAM 17 to cleave amphiregulin. As shown (Fig. 5A), smoke exposure...
Fig. 4. EGFR activation by smoke requires amphiregulin cleavage by ADAM 17 (tumor necrosis factor α-converting enzyme). A, NCIH292 cells were preincubated with metalloproteinase inhibitor GM6001 (40 μM) for 1 h prior to stimulation with smoke (SFM- or EGF (10 ng/ml)-containing SFM for 5 min, then immunoprecipitated and immunoblotted as in Fig. 2. B, NCIH292 cells were transfected with 2 μM solutions of morpholino antisense oligonucleotides as indicated prior to stimulation with smoke- or EGF (10 ng/ml)-containing SFM, immunoprecipitated and immunoblotted as in Fig. 2. C, left panel, NCIH292 cell immunoblots showing the amount of ADAMs 10 and 17 present with different antisense oligonucleotide treatments; CON, control (no antisense oligonucleotide); actin is immunoblotted as a loading control; p, pro-enzyme; m, mature enzyme; right panel, densitometric analysis of gel in left panel. The expression of ADAM 10 and ADAM 17 is inhibited by the appropriate morpholino antisense treatment, shown as percent of value from untreated (control) cells. Data points have been normalized for loading differences using immunoreactive actin signals for each lane. D, NCIH292 cells were exposed to SFM-containing smoke or purified LTA from S. aureus (50 μg/ml) or to SFM alone for 5 min. Culture medium was collected and incubated with heparin-Sepharose to precipitate EGFR ligands. Immunoblot was carried out with antibodies to all six EGFR ligands with only amphiregulin and HBEGF showing significant reactivity. The blot was probed with anti-amphiregulin prior to stripping and reprobing with anti-HBEGF. E, smoke was administered as in D in the presence or absence of antisense oligonucleotides directed against ADAM 10 or 17.

raised the levels of ROS in NCIH292 cells. Moreover, antioxidants N-acetyl-l-cysteine (a precursor of glutathione) or dimethylthiourea (an oxygen-radical scavenger) inhibited both ligand release and receptor activation (Fig. 5, B and C).

Although the appearance of oxygen radicals in nonphagocytic cells is often associated with the diversion of oxygen species from mitochondrial electron transport, recent data show that intracellular radicals may also derive from a low activity NADPH oxidase (24). To examine the relative importance of these two oxidant sources, we exposed cells to smoke in the presence of drugs known to inhibit electron transport (rotenone and antimycin A) or NADPH oxidase (diphenylidodium chloride). The absence of detectable ROS in diphenylidodium chloride-treated cells (Fig. 5D) implicated NADPH oxidase in the critical early response to tobacco smoke. Data in Fig. 5 collectively suggest that activation of this oxidase results in amphiregulin cleavage and EGFR phosphorylation, which was shown in Fig. 1 to be necessary for cell proliferation.

To test the relevance of the above findings in an animal model, we exposed mice to smoke in a specially designed chamber (9). Consistent with results in vitro, tracheal lysates from mice exposed to smoke alone showed elevated phosphorylation of EGFR, whereas lysates from animals exposed to smoke in the presence of the metalloproteinase inhibitor GM6001 did not (Fig. 6; compare with data in Fig. 4).

DISCUSSION

These findings reveal mechanisms by which smoke stimulates the proliferation of human lung cells in vitro. Based on the results of experiments in animals, it seems likely that these findings mirror events in the lungs of human smokers (Fig. 6). The results fill a gap in our understanding of mechanisms mediating hyperproliferation in smokers’ lungs (5) and, based on the link between proliferation and neoplasia (25–28), contribute to our understanding of the pathogenesis of lung cancer.

These studies also indicate that the ability of EGFR to integrate responses to diverse environmental stimuli depends on stimulus-specific activation of the various ADAMs. When epithelial cells activate EGFR in response to both bacteria (11) and tobacco smoke (this study), they do so by different mechanisms (Fig. 7). In both cases, ADAMs are required, but one involves ADAM 10 and the other ADAM 17. Although the activation mechanisms for these proteases are unknown, our data, obtained in the same cell type using two different stimuli, indicate that these mechanisms are stimulus-specific. Whereas the choice of ADAM itself depends on the nature of the stimulus, the choice of transmembrane ligand would appear to depend upon (a) phenotype-dependent ligand expression and (b) substrate specificity of the activated ADAM. Our data clearly show that both HBEGF and amphiregulin are expressed in NCIH292 cells. Therefore, results showing that LTA elicits cleavage of HBEGF but not amphiregulin (11) and that smoke does the opposite (this study) imply that HBEGF, but not amphiregulin, is a substrate for ADAM 10 and that amphiregulin, but not HBEGF, is a substrate for ADAM 17. Although these findings are in general agreement with evidence linking...
ADAM 17 to amphiregulin (29) and ADAM 10 to HBEGF (30), they are somewhat at odds with data showing that ADAM 17 is capable of cleaving both amphiregulin and HBEGF (29). Notably, however, the two sets of data were obtained from different cell types (mouse keratinocytes versus human lung epithelial cells). Phenotypic differences with respect to the abundance and location of ADAMs, ligands, and signaling molecules eliciting ADAM activity can be expected to affect the probability of any given cleavage reaction.

Some disparity can be seen in our own results comparing the degree to which treatment of cells with antisense ADAM 17 inhibited smoke-induced EGFR phosphorylation (Fi. 4B, almost complete response) versus ADAM 17 protein levels (Fig. 4C, ~50% response). We attribute this to one or both of the following. 1) Western blot results are not necessarily linear with protein concentration, and 2) because of the (as yet unknown) subcellular distribution of ADAM 17, amphiregulin, and EGFR in NCIH292 cells, there may be a threshold concentration of ADAM 17 below which amphiregulin cleavage is insufficient to activate EGFR.

In addition to implicating ADAM 17 in the response of lung cells to tobacco smoke, our findings also illustrate that the relevant activation mechanism is oxygen radical-dependent. Oxygen radical production in the setting of smoke exposure appears to be a result of the activation of NADPH oxidase. One possible scenario by which smoke could stimulate this enzyme is suggested by the finding that tobacco smoke induces mitochondrial depolarization (31). This would induce a transient deficiency in ATP production and stimulate compensatory glu-
The conversion of glucose to bisphosphoglycerate would then lead to the production of NADH, which, via the action of a transhydrogenase enzyme, contributes to the formation of NADPH. This serves as a substrate and stimulus for NADPH oxidase.

The uniformity of results obtained in both primary and tumor cells confirms the fundamental nature of the effect of smoke on EGFR and cell proliferation. Although it remains possible that details of the response to smoke differ in normal versus tumor cells, our data suggest that such differences are subtle. This is based on results showing that (a) smoke stimulates proliferation of both non-tumor and tumor cells (Fig. 1, A and B), (b) smoke stimulates EGFR phosphorylation in both cell types (Fig. 2, A and B), (c) there is a causal relationship between smoke-induced EGFR phosphorylation and cell proliferation in both cell types (Fig. 1, A and B), and (d) the mechanism of receptor activation by smoke is metalloproteinase-dependent in both tumor cells in vitro and in mouse tracheal epithelial cells in vivo (Figs. 4 and 6).

In addition to their usefulness as a model, the tumor cell (NCH229) experiments may directly indicate how smoke stimulates the growth of nascent tumors prior to a diagnosis of lung cancer. An understanding of these signals may suggest strategies to limit the tumorigenic effects of smoke on the lung.

Finally, the phosphorylation of EGFR can be induced by an increasingly long list of environmental stimuli. Because of the role of EGFR in cell proliferation and the relationship between hyperproliferation and malignant transformation, elevated levels of EGFR phosphorylation in a tissue biopsy may identify tissues at risk for malignant transformation. In conjunction with this, it may be possible to identify tumor promoters based on their ability to stimulate the phosphorylation of EGFR in model systems.

Acknowledgments—We thank Kent Pinkerton, Ph.D., and Dale Uyeminami, Ph.D., for providing smoke condensate-containing filters for this study.

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J. Biol. Chem. 2003, 278:26202-26207.  
doi: 10.1074/jbc.M207018200 originally published online April 23, 2003

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