Small cell lung carcinoma (SCLC) accounts for 20–25% of primary lung cancers and is rapidly growing, widely metastatic, and rarely curable. Autocrine stimulation of multiple G protein-coupled neuropeptide receptor systems contributes to the transformed growth of SCLC. The ability of neuropeptide receptors to stimulate phospholipase C and mobilize intracellular Ca\(^{2+}\) indicates that G\(_q\) family members of heterotrimeric G proteins are a convergence point mediating autocrine signaling by multiple neuropeptides in SCLC. Expression of a GTPase-deficient, constitutive active form of an \(\alpha_q\) family member, \(\alpha_{16}Q212L\), in SCLC markedly inhibited growth of the cells in soft agar and tumor formation in nude mice. SCLC lines expressing \(\alpha_{16}Q212L\) exhibited 2- to 4-fold elevated basal phospholipase C activity, but neuropeptide- and hormone-regulated intracellular Ca\(^{2+}\) mobilization was nearly abolished. The data suggest that Ca\(^{2+}\) mobilization is an obligatory signal in neuropeptide-stimulated growth of SCLC. In addition, the proline-directed c-jun NH\(_2\)-terminal kinases/stress-activated protein kinases, which are members of the mitogen-activated protein kinase family, were stimulated 2-fold in parental SCLC in response to exogenous neuropeptides and muscarinic agonists and were constitutively activated to the same degree in \(\alpha_{16}Q212L\)-expressing SCLC. Thus, \(\alpha_{16}Q212L\) expression induced desensitization of neuropeptide-stimulated Ca\(^{2+}\) signaling and persistent activation of the c-jun NH\(_2\)-terminal kinase/stress-activated protein kinase pathway. We propose that the induction of discordant signaling by selective perturbation of receptor-regulated effector systems leads to the inhibition of SCLC cell growth.

Small cell lung carcinoma (SCLC)\(^1\) displays neuroendocrine features exemplified by the presence of cytoplasmic neurosecretory granules containing a wide variety of mitogenic neuropeptides including gastrin-releasing peptide, arginine vasoressin, neurotensin, cholecystokinin, and many others (1, 2). Significantly, SCLC also expresses receptors for these neuropeptides, thereby establishing autocrine-stimulated cell growth (3). The number and variability of neuropeptides released from individual small cell carcinomas hampers effective blockade of mitogenic signaling at the level of ligand/receptor binding using specific neuropeptide antagonists. This redundancy at the level of receptor signaling highlights the importance of defining the intracellular components involved in mitogenic signal transduction in SCLC where convergence of multiple neuropeptide receptor systems into common pathways would be anticipated.

Molecular cloning of the receptors for gastrin releasing peptide, vasopressin, and gastrin/cholecystokinin reveals that they are members of the superfamily of seven membrane-spanning receptors (4–8). As a class, these receptors initiate signaling in response to ligand binding by interacting with heterotrimeric G proteins. Although the repertoire of G proteins potentially involved in neuropeptide signaling in SCLC is quite large, the failure of pertussis toxin to appreciably inhibit in vitro growth of SCLC (9) suggests that the pertussis toxin-sensitive G\(_i\) and G\(_q\) proteins are unlikely to be dominant components of mitogenic signaling in SCLC. In fact, the prominence of phospholipase C activation and Ca\(^{2+}\) mobilization (10–12) by neuropeptides in SCLC points to the pertussis toxin-insensitive G\(_q\) proteins as likely candidates for mediating autocrine signaling in SCLC because the G\(_q\) family of G proteins are known to stimulate several of the phospholipase C\(_\beta\) isoforms (13, 14).

To examine the role of G\(_q\) proteins in SCLC growth pathways, we have used retrovirus-mediated gene transfer to express a GTPase-deficient, constitutively active form of the \(\alpha_q\) family member, \(\alpha_{16}\), in SCLC lines. We find that expression of GTPase-deficient \(\alpha_{16}\) in SCLC markedly inhibits their growth and oppositely affects two signal transduction pathways normally engaged by neuropeptides and muscarinic agonists in SCLC; Ca\(^{2+}\) mobilization was inhibited, and the c-jun NH\(_2\)-terminal kinase/stress-activated protein kinase pathway was constitutively activated. The data indicate that derangement of coordinated neuropeptide signaling in SCLC leads to strong inhibition of growth.

**MATERIALS AND METHODS**

Retrovirus-mediated Gene Transfer and Cell Culture—The PA317 packaging cell line (15) was infected with ecotropic retrovirus secreted from GP+E-86 cell lines (16) that had been stably transfected with LNCX or LNCX-\(\alpha_{16}Q212L\) (17). Following selection in G418, individual PA317 clones were screened for expression of \(\alpha_{16}Q212L\) polypeptide by immunoblotting. The PA317 packaging cell lines expressing LNCX or LNCX-\(\alpha_{16}Q212L\) were allowed to secrete virus into Dulbecco’s modified Eagle’s medium containing 10% fetal bovine serum for 16–24 h. The medium was collected, supplemented with 8 \(\mu\)g/ml polybrene, filtered through a 0.45- \(\mu\)m filter, and incubated undiluted with the indicated lung cancer cell lines for 16–24 h. The next day, the virus-containing medium was removed from the lung cancer cells and replaced with fresh virus for another 16–24 h. Following the second virus exposure, the lung cancer cell lines were placed in their normal growth medium.
supplemented with 0.5 mg/ml G418. SCLC cells lines H345 and H1048 were cultured in HITES (RPMI 1640 medium containing 10 mg hydrocortisone, 5 µg/ml insulin, 10 µg/ml transferrin, 10 ng/µl estradiol, 30 ng sodium selenite, and 0.1% bovine serum albumin), and SCLC cell lines H169 and N417 and NSCLC lines H157 and H2122 were cultured in RPMI 1640 medium containing 10% fetal bovine serum. The studies described herein were performed with pooled populations of G418-resistant cells.

Immunoblot Analysis of αq/Q212L Expression—The indicated lung cancer cell lines were collected in phosphate-buffered saline and lysed in 10 mM Tris-Cl (pH 7.4), 1 mM EDTA, 0.5% Triton X-100. Following a 5-min microcentrifugation (10,000 × g), soluble proteins (100 µg) were resolved on 10% SDS-polyacrylamide gel electrophoresis, transferred electrophoretically to nitrocellulose, and probed with a rabbit polyclonal anti-αq antisemur (17). The immobilized antibodies were visualized with [125I]-protein A and autoradiography.

Determination of Soft Agar Cloning Efficiency—Single-cell suspensions of the nonadherent SCLC cell lines were prepared by passage through a 20-gauge needle syringe (H69, H345, N417, and H1048) or mild trypsinization of the adherent NSCLC lines (H157 and H2122). The cells were counted with a hemacytometer and 10,000 cells (H345, N417, H157, and H2122) or 25,000 cells (H69 and H1048) were diluted in 1.5 ml of growth medium containing 0.3% agar (Difco) and plated in triplicate on a 2-ml base of growth medium containing 0.5% agar nobel in 35-mm wells of six-well plates. The plates were placed in a humidified CO2 incubator, and the colonies were counted after 3–4 weeks with a microscope using a 4× objective.

Analysis of Total Inositol Phosphates—The SCLC lines infected with LNMX or LNMX-αq/Q212L were incubated for 24 h in RPMI 1640 medium containing 0.1% bovine serum albumin and 1 µCi/ml [3H]inositol. The NSCLC lines were incubated in inositol-free Dulbecco’s modified Eagle’s medium containing 1 µCi/ml [3H]inositol due to low uptake and incorporation of inositol by these lines relative to the SCLC lines. The cells were washed twice with RPMI 1640 medium containing 0.1% bovine serum albumin and once with the same containing 20 mM LiCl. The cells were then incubated in 1 ml of medium containing 20 mM LiCl for 30 min at 37°C, quenched with 2 ml of MeOH:HCI (100:1), 1 ml of diethyl ether, and 1 ml of CHCl3. Total inositol phosphates in the aqueous phase were purified by ion exchange chromatography as described previously (18).

Determination of Intracellular Ca2+ Levels—Plates—Plateau phase H345 and H1048 cells infected with LNMX or LNMX-αq/Q212L in HITES medium were washed, and single cell suspensions were prepared. The cells were loaded with the calcium indicator Indo-1 AM (Molecular Probes, Eugene, OR) as described (12, 19). The intracellular increases in intracellular Ca2+ levels were determined with an EPICS752 sorter (Coulter Electronics, Hialeah, FL) by quantitating the ratio of fluorescence at 410–490 nm using an excitation wavelength of 360 nm.

Assay of MAP Kinase and c-jun NH2-terminal Kinase Activities—Plates—Phase H345 cells expressing αq/Q212L or the empty LNMX vector were cultured in centrifugation medium (1000 xg) and lysis buffer (0.5% Triton X-100, 50 mM β-glycerophosphate (pH 7.2), 0.1 mM sodium vanadate, 2 mM MgCl2, 1 mM EGTA, 1 mM dithiothreitol, 2 µg/ml leupeptin, and 4 µg/ml aprotenin). In addition, H345 cells expressing the empty vector were incubated (37°C) for 10 min with 100 µM 12-O-tetradecanoylphorbol-13-acetate, collected by centrifugation and lysed as described above. Following a 5-min centrifugation (10,000 × g) to remove nuclei and cell debris, portions of the soluble extracts (0.5 ml, 1 mg protein) were applied to a Pharmacia HR5/5 MonoQ column equilibrated in 50 mM β-glycerophosphate (pH 7.2), 0.1 mM sodium vanadate, 1 mM EGTA, and 1 mM dithiothreitol and eluted with a 30-ml gradient of 0–350 mM NaCl in the same buffer. Fractions (1 ml) were collected and assayed for MAP kinase activity using [γ-32P]ATP, EGFR662–681 peptide (20). Aliquots (20 µl) of the fractionated extracts were mixed with 20 µl of 50 mM β-glycerophosphate (pH 7.2), 0.1 mM sodium vanadate, 20 mM MgCl2, 200 µM [γ-32P]ATP (5000 cpm/ml), 50 µg/ml 1-20 (TMYADFXSGTRGSRNAIH), 1 mM EGTA, and 400 µM EGFR662–681 peptide (RELVEFLPTSPGEAPNQLR). The kinase reactions were performed for 15 min at 30°C and terminated by addition of 25% trichloroacetic acid, and EGFR662–681 peptide phosphorylation was assessed by binding to phosphocellulose filters as described (20).

The activity of c-jun NH2-terminal kinases was determined essentially as described (21). SCLC cells were collected by centrifugation (5 min, 1000 × g) and lysed (4°C, 30 min) in 0.5 ml of 25 mM HEPES (pH 7.7), 20 mM β-glycerophosphate, 0.2% sodium vanadate, 0.1% Triton X-100, 0.3% NaCl, 1.5 mM MgCl2, 0.2% MEATDA, 0.5 mM dithiothreitol, 2 µg/ml leupeptin, and 4 µg/ml aprotenin. Following a 5-min microcentrifugation (10,000 × g), aliquots of the soluble extracts containing 400 µg of protein were incubated for 2 h at 4°C with GST-c-jun un(1–79) adsorbed to glutathione-agarose as described (21). The GST-c-jun un(1–79) beads were washed four times by repetitive centrifugation in 20 mM HEPES (pH 7.7), 50 mM NaCl, 2.5 mM MgCl2, 0.1 mM EDTA, and 0.05% Triton X-100 and then incubated for 20 min at 30°C in 40 µl of 50 mM β-glycerophosphate (pH 7.6), 0.1 mM sodium vanadate, 10 mM MgCl2, 1 mM EGTA, and 0.5 µM γ-[32P]ATP (25,000 cpm/ml). The reactions were terminated with 10 µl of SDS-polyacrylamide gel electrophoresis sample buffer,-boiled, and submitted to 10% SDS-polyacrylamide gel electrophoresis. The GST-c-jun un(1–79) polypeptides were identified in Coomassie-stained gels, excised, and counted in a scintillation counter.

RESULTS AND DISCUSSION

To test the role of Gq family members in SCLC growth, we analyzed the effects of expression of GTPase-deficient forms of αq family members on neurotensin-stimulated signaling and growth in SCLC lines. We have previously used retrovirus-mediated gene transfer as a standard method to express exogenous gene products in many different cell lines (17, 20). However, repeated attempts to establish a stable PA317 retroviral packaging line expressing the GTPase-deficient form of αq (αq/Q209L) failed, suggesting that the αq/Q209L polypeptide was cytotoxic in these lines and did not permit retroviral packaging. Subsequent attempts with the GTPase-deficient form of the αq family member, αq/Q212L, were successful such that a stable PA317 retroviral packaging line that secreted virus encoding the αq/Q212L polypeptide was established.

Retrovirus encoding the αq/Q212L polypeptide as well as the vector, LNMX, lacking a cDNA insert were used to infect four SCLC lines (H69, H345, N417, and H1048) as well as two NSCLC cell lines (H157 and H2122). Stable populations of tumor cells were selected for resistance to G418. Immunoblotting with an αq-specific antibody verified that an αq polypeptide was indeed expressed in the αq/Q212L-transfected lines (Fig. 1A) relative to the LNMX-transfected controls. The lung cancer cell lines lack detectable endogenous αq because it is normally restricted in expression to cells of hematopoietic origin (22). As predicted for an αq family member, expression of the αq/Q212L polypeptide in the SCLC and NSCLC lines persisted to stimulate basal phospholipase C activity at least 10-fold. Repeated attempts to stably express αq/Q212L in another extraneous small cell line (HS10) failed, suggesting that small cell carcinomas of extrapulmonary origin may be particularly sensitive to αq/Q212L. Thus, the data show that αq/Q212L was functionally expressed in SCLC and NSCLC lines and constitutively activated phospholipase C activity.

Colony formation in semi-solid medium was used to monitor the transformed phenotype of SCLC and NSCLC expressing αq/Q212L. The ability of the αq/Q212L-expressing SCLC to form colonies in soft agar was inhibited approximately 70% with respect to lines infected with the vector containing no cDNA insert (Fig. 2). In contrast, αq/Q212L expression did not influence the growth of two NSCLC lines (H157 and H2122). Note that the absolute cloning efficiency of the different lung cancer cell lines varied considerably, although the percentage of inhibition of soft agar cloning efficiency by αq/Q212L was similar. The soft agar cloning efficiencies of H345 cells expressing GTPase-deficient forms of αq and αi were 96 and 139%, respectively, of the cloning efficiency of H345 cells infected with LNMX (data not shown), indicating that inhibition of SCLC growth is specific for the αq family members. This finding is consistent with the inability of pertussis toxin to significantly stimulate or inhibit the in vitro growth of SCLC lines (9). As a
more stringent indicator of the transformed growth properties of SCLC lines expressing \( \alpha_{16}{ }^{16Q212L} \), the H1048 lines infected with LNCX or \( \alpha_{16}{ }^{16Q212L} \) were implanted in the flanks of nude mice. Of the three mice injected with H1048-LNCX cells (107 with LNCX or \( \alpha_{16}{ }^{16Q212L} \) respectively. The H1048-LNCX cells also exhibit a measurable response following exposure to exogenous cholecystokinin (Fig. 3) and the muscarinic agonist, carbachol (Fig. 3). The inhibition of SCLC growth observed with \( \alpha_{16}{ }^{16Q212L} \) expression is likely to be related, at least in part, to loss of Ca\(^{2+} \) signaling, indicating that the Ca\(^{2+} \) mobilization is a major mitogenic signal in SCLC. However, it seemed possible that additional signal pathways involved in regulation of growth and differentiation were being regulated in response to expression of \( \alpha_{16}{ }^{16Q212L} \), especially in relation to altered cellular morphology. The activity of the p42/44 MAP kinases was assessed because they have been previously shown to be persistently stimulated in morphologically differentiated PC12 cells (20). Extracts from LNCX and \( \alpha_{16}{ }^{16Q212L} \)-expressing H345 cells were fractionated on MonoQ fast protein liquid chromatography and analyzed for MAP kinase activity with an EGFR662–681 peptide phosphorylation assay. The data in Fig. 4 reveal that increased p42/44 MAP kinase activity relative to control cell extracts was not observed in fractionated extracts from \( \alpha_{16}{ }^{16Q212L} \)-expressing H345 cells. In addition, incubation of the various SCLC lines with neuropeptides including bombesin and vasopressin failed to significantly stimulate p42/44 MAP kinase activity (data not shown), although treatment of H345 cells with the phorbol ester 12-O-tetradecanoylphorbol-13-acetate markedly increased MAP kinase activity (Fig. 4).

The recently defined c-Jun NH\(_2\)-terminal kinases or stress-activated protein kinases are members of the MAP kinase family that exhibit homology to the p42/44 MAP kinases (26, 27) and are strongly activated by exposure to heat shock and ultraviolet light (21). Analysis of c-Jun NH\(_2\)-terminal kinase activity using an immobilized GST-c-Jun(1–79) assay revealed a statistically significant 1.8-fold increase in c-Jun NH\(_2\)-terminal kinase activity in extracts from H345 cells expressing \( \alpha_{16}{ }^{16Q212L} \) relative to control cells (Fig. 5A). The magnitude of c-Jun NH\(_2\)-terminal kinase activation by \( \alpha_{16}{ }^{16Q212L} \) is similar to the level of activation observed in response to acute treatment of H345 cells with a neuropeptide, bombesin, or a muscarinic agonist, carbachol (Fig. 5B). Furthermore, c-Jun NH\(_2\)-terminal kinase activity is strongly stimulated (−10-fold) by exposure of H345 cells to ultraviolet irradiation (UV-C, 96 J/M\(^2\)), but not by strong activation of protein kinase C with 12-O-tetradecanoylphorbol-13-acetate (Fig. 5C) that leads to marked p42/44 MAP kinase activation (Fig. 4). Thus, the findings demonstrate a significant activation of protein kinases characteristic of c-Jun NH\(_2\)-terminal kinases/stress-activated protein kinases but not the p42/44 MAP kinases following expression of \( \alpha_{16}{ }^{16Q212L} \) in a SCLC line. Elevated cAMP and activation of cAMP-dependent protein kinase are growth inhibitory in many cell systems. It has been previously established that expression of \( \alpha_{16}{ }^{16Q212L} \) in Swiss 3T3 fibroblasts significantly stimulates cAMP-dependent protein kinase through a protein kinase C-dependent mechanism (17), a finding that may be partially responsible for the growth inhibition observed in Swiss 3T3 cells. However, the basal activity of cAMP-dependent protein kinase in \( \alpha_{16}{ }^{16Q212L} \)-expressing H345 and H69 cells was 85 and 117% of LNCX-
expressing $\alpha_{16}Q212L$ cells, respectively, indicating that the cAMP-dependent protein kinase pathway is not involved in the $\alpha_{16}Q212L$-induced growth inhibition observed in SCLC lines.

The results show that cellular expression of $\alpha_{16}Q212L$ inhibits the growth of SCLC but not NSCLC. The selective inhibition of SCLC growth relative to NSCLC growth is likely to be explained by the different cellular pathways that exert dominance in growth regulation in the two lung cancer cell types. Oncogenic activation of Ras is frequently observed in NSCLC. In fact, H157, a squamous cell carcinoma, and H2122, an adenocarcinoma, have been previously shown to express mutated forms of Ki-Ras (28). In addition, NSCLC frequently overexpress specific receptor tyrosine kinase systems such as the epidermal growth factor receptor (29). In contrast, SCLC is characterized by the notable absence of GTPase-deficient forms of Ras, and overexpression of epidermal growth factor receptors is rare (28, 29). Instead, neuropeptide autocrineloops utilizing seven membrane-spanning receptors and heterotrimeric G proteins are proposed to be the primary mitogenic inputs in SCLC. Previous findings that $\alpha_{Q}Q209L$ expression in NIH 3T3 fibroblasts leads to cellular transformation (30, 31) is consistent with a role for $G_{q}$ proteins, phospholipase $C_{q}$, and $Ca^{2+}$ mobilization in mitogenic signaling. However, other studies revealed that $\alpha_{16}Q212L$ expression in Swiss 3T3 fibroblasts profoundly inhibited bombesin (gastrin-releasing peptide) signal transduction including calcium mobilization, MAP kinase acti-
vation, and arachidonic acid release. The net effect was a nearly complete inhibition of bombesin (gastrin-releasing peptide)-stimulated DNA synthesis (17). Similar to the latter studies, our findings show that expression of $\alpha_{16}$Q212L in SCLC lines resulted in strong inhibition of neuropeptide-regulated Ca$^{2+}$ mobilization (Fig 3) and dramatically reduced the ability of the cells to grow in soft agar (Fig. 2). These conflicting results concerning cellular actions of GTPase-deficient Goq proteins may reflect different levels of expression of the Goq subunits in the various cell lines where low expression results in transformation and high expression leads to negative modulation of intracellular signaling pathways and growth arrest. Alternatively, the ability of Goq phospholipase C$\beta$, and Ca$^{2+}$ mobilization to stimulate DNA synthesis may be quite variable among different cell types.

Expression of GTPase-deficient $\alpha_{16}$Q212L oppositely affected two signal transduction pathways normally engaged by neuropeptides and muscarinic agonists in SCLC; Ca$^{2+}$ mobilization was inhibited, and the c-jun NH$_2$-terminal kinase/stress-activated protein kinase pathway was constitutively activated. Thus, $\alpha_{16}$Q212L expression induced discordant signaling in SCLC. We have found that $\alpha_{16}$Q212L expression also constitutively activates the c-jun NH$_2$-terminal kinase/stress-activated protein kinase pathway in PC12 cells where growth arrest and neuronal differentiation is observed. The failure of phorbol esters to significantly activate the c-jun NH$_2$-terminal kinase/stress-activated protein kinase pathway in PC12 cells where growth arrest and neuronal differentiation is observed. The failure of phorbol esters to significantly activate the c-jun NH$_2$-terminal kinase/stress-activated protein kinase pathway in PC12 cells is due to the lack of a strong growth inhibitory response resulting from activated c-jun expression, which will inhibit cell death in several fibroblast systems and differentiation of PC12 cells. Expression of activated MEK kinase-1 leads to cell death in several fibroblast systems and differentiation of PC12 cells similar to the phenotype observed with activated c-jun members such as $\alpha_{16}$Q212L. Thus, the MEK kinase/c-jun NH$_2$-terminal kinase regulatory pathways may contribute to growth inhibition and possibly cell death, a sharply contrasting phenotype from that observed with activated Raf expression.

These findings indicate that it is possible to inhibit cell growth of selected tumor cell types by selectively disrupting coordinated signal transduction pathways. Increasing awareness that signals controlling growth and apoptosis are overlapping is insightful in regards to these results. We suggest that the balance and magnitude of specific signal transduction pathways regulated by hormones and growth factors can determine commitment to tumor cell growth or arrest. Identifying tumors that have a strong growth inhibitory response resulting from activated c-jun expression will allow a new pharmacologic and genetic approach to cancer therapeutics. The ability of Goq family members of G proteins to regulate the c-jun NH$_2$-terminal kinase/stress-activated protein kinase pathway and to cause growth inhibition in SCLC and some fibroblasts focuses our attention on the $\alpha_{16}$ effects capable of inhibiting tumor cell growth.

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Discordant Signal Transduction and Growth Inhibition of Small Cell Lung Carcinomas Induced by Expression of GTPase-deficient G

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