Combined MET Inhibition and Topoisomerase I Inhibition Block Cell Growth of Small Cell Lung Cancer

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Abstract

Small cell lung cancer (SCLC) is a devastating disease, and current therapies have not greatly improved the 5-year survival rates. Topoisomerase (Top) inhibition is a treatment modality for SCLC; however, the response is short lived. Consequently, our research has focused on improving SCLC therapeutics through the identification of novel targets. Previously, we identified MNNG HOS transforming gene (MET) to be overexpressed and functional in SCLC. Herein, we investigated the therapeutic potential of combinatorial targeting of MET using SU11274 and Top1 using 7-ethyl-10-hydroxycamptothecin (SN-38). MET and TOP1 gene copy numbers and protein expression were determined in 29 patients with limited (n = 11) and extensive (n = 18) disease. MET gene copy number was significantly increased (>6 copies) in extensive disease compared with limited disease (P = 0.015). Similar TOP1 gene copy numbers were detected in limited and extensive disease. Immunohistochemical staining revealed a significantly higher Top1 nuclear expression in extensive (0.93) versus limited (0.15) disease (P = 0.04). Interestingly, a significant positive correlation was detected between MET gene copy number and Top1 nuclear expression (r = 0.5). In vitro stimulation of H82 cells revealed hepatocyte growth factor (HGF)-induced nuclear colocalization of p-MET and Top1. Furthermore, activation of the HGF/MET axis enhanced Top1 activity, which was abrogated by SU11274. Combination of SN-38 with SU11274 dramatically decreased SCLC growth as compared with either drug alone. Collectively, these findings suggest that the combinatorial inhibition of MET and Top1 is a potentially efficacious treatment strategy for SCLC. Mol Cancer Ther; 13(3); 576–84. ©2013 AACR.

Introduction

In the year 2012, there were an estimated 226,160 new cases and 160,340 deaths from lung cancer (1). Approximately 13% of prevalent lung cancer cases are small cell lung cancer (SCLC; ref. 2). Although SCLC comprises a small percentage of the total overall lung cancer cases, it presents as a very aggressive disease with a median overall survival of 2–4 months from the time of diagnosis.
repeat domain. Hepatocyte growth factor/scatter factor (HGF) is the cognate ligand for MET (20). HGF binds to the SEMA domain of MET, which induces the autophosphorylation of the intracellular tyrosine residues within the tyrosine kinase domain. This stimulation of MET by HGF leads to a plethora of biologic and biochemical effects in the cell. In fact, the HGF/MET axis plays an important role in embryological development, growth, motility, invasion, metastasis, angiogenesis, wound healing, and tissue regeneration (21).

Novel therapeutic modalities that target MET kinase activity have focused on the development of small molecule inhibitors, such as SU11274 (22–24). This compound is 50 times more selective for MET compared with other tyrosine kinases (24). In vitro studies using SU11274 demonstrated selective inhibition of MET tyrosine kinase activity in lung cancer cell lines expressing MET (25). Moreover, MET autophosphorylation at the activation loop, tyrosine phosphorylation, and downstream phosphorylation events were all inhibited by SU11274, highlighting the potential therapeutic benefits of MET inhibition on the growth of lung tumor and metastasis.

The standard therapy for SCLC is etoposide, a topoisomerase II (Top2) inhibitor, and cisplatin (26). However, in response to this regimen is short lived and overall survival is still on the order of months. Thus, there is intense focus on discovering new agents or combinations of therapies that are efficacious. A novel therapeutic approach in SCLC, particularly in refractory or relapsed disease, involves the use of Top1 inhibitors (27). These agents, primarily consisting of camptothecin analogs, irinotecan, and topotecan, stabilize the Top1/DNA complex during the process of DNA replication. In doing so, the Top1-induced DNA single-strand breaks cannot be resealed and DNA synthesis is halted, thereby initiating apoptotic cell death (28). In extensive stage disease, irinotecan combined with platinum-based agents increases overall survival compared with the combination of platinum and etoposide (27, 29). Irinotecan is a water-soluble compound that is metabolized into 7-ethyl-10-hydroxycamptothecin (SN-38) by the liver. SN-38 has a 100-fold greater antitumor effect over irinotecan (30).

In this investigation, we determined the relationship between MET and Top1 in SCLC. MET and TOP1 gene copy numbers as well as protein expression were determined in 29 SCLC patient tumor tissues—11 with limited disease and 18 with extensive disease. MET gene copy numbers and nuclear expression of Top1 were increased in extensive disease. Interestingly, there was a correlation between MET gene copy number and nuclear Top1 expression. In vitro cell culture modeling revealed modulation of Top1 activity via activation of the HGF/MET axis. We next evaluated the therapeutic benefits of the novel combination of the Top1 inhibitor, SN-38, and the small molecule MET inhibitor, SU11274. HGF stimulation induced nuclear colocalization of p-MET and Top1. Moreover, HGF stimulation enhanced Top1 activity, which was abrogated by MET inhibition using SU11274. Combined MET and Top1 inhibition decreased cell viability in two SCLC cell lines, H69 and H82. Collectively, these findings highlight the potential for cotoargeting MET and Top1 as a novel therapeutic modality for SCLC.

Materials and Methods

Obtaining patient samples and clinical information

The Institutional Review Board at The University of Chicago (Chicago, IL) approved all of the human subjects research performed in this study. Written informed consent was obtained from the patients before the harvest of tumor and paired adjacent normal lung tissues. The tissues used in this study were obtained from patients who were treated for SCLC at The University of Chicago Medical Center.

Gene copy number analysis by quantitative PCR

Genomic DNA was isolated from formalin-fixed paraffin-embedded (FFPE) tumor tissues using a protocol standardized in our laboratory (31), and cell line genomic DNA was isolated using the Qiagen Kit (Qiagen). In brief, 30 to 50 ng of genomic DNA was PCR amplified using FastSYBR green 2X MasterMix (Applied Biosystems) and ABI StepOnePlus (Applied Biosystems). MET and TOP1 gene copy numbers were determined using the primers listed in Supplementary Table 1 and the following reaction conditions: 1 cycle, 95°C for 10 seconds; 40 cycles, 95°C for 10 seconds, 60°C for 30 seconds, and 72°C for 30 seconds. Samples were assayed in triplicate for the gene of interest (GOI) being analyzed, as well as LINE1 as an internal control for the normalization of quantity values. Control genomic DNA that was not amplified for the GOI was used to normalize and calculate GOI amplification using the following equations:

\[
\text{Quantity (sample-normalized)} = \frac{\text{quantity (sample-GOI)}}{\text{quantity (sample-LINE1)}}
\]

\[
\text{Quantity (control-normalized)} = \frac{\text{quantity (control-GOI)}}{\text{quantity (control-LINE1)}}
\]

\[
\text{Gene copy number} = \frac{\text{[quantity (sample-normalized)]}}{\text{[quantity (control-normalized)]}}
\]

Immunohistochemistry

FFPE tissues from 29 patients with SCLC diagnosed at The University of Chicago Medical Center were utilized. Immunohistochemical (IHC) staining was performed using standard techniques previously described (25) with antibodies against the following proteins: MET (Invitrogen), phospho-MET (BioSource International), and Top1 (Abcam). In brief, tissue cores from normal and tumor tissues from each patient were obtained and arranged into a tumor tissue microarray using the ATA-27 Arrayer (Beecher Instruments). Slides were reviewed and scored by two independent pathologists on a scale of 0 to 3: 0, no staining, no expression; 1, weak staining, low expression;
Selective reaction monitoring

Cells (10^7) were washed, fixed with 10% buffered formalin, and solubilized to tryptic peptides by Liquid Tissue processing. The soluble mixtures were analyzed by selective reaction monitoring (SRM) on a Thermo Vantage mass spectrometer. The quantification of MET expression was achieved by spiking in a heavy isotope-labeled MET peptide into the samples, for the comparison of the area under the curve (AUC) to the endogenous MET analyte.

Immunofluorescence and confocal microscopy

H82 cells were deprived of growth factors by incubation in serum-free medium containing 0.5% bovine serum albumin (BSA; Sigma) for 16 hours. The cells were stimulated with HGF (Calbiochem) at 40 ng/mL for 10 minutes. The cells were plated on poly-L-lysine-coated glass cover slips, then fixed using 4% paraformaldehyde (Millipore), and permeabilized with 0.1% TritonX-100 (Sigma) in PBS. Fixed cells were washed with ice-cold PBS plus 0.1% Tween-20 and nonspecific binding was inhibited using 2.5% BSA in PBS, then incubated with the appropriate primary antibodies: anti-MET (Abcam), anti-pY1349/Y1350-MET (Cell Signaling), and anti-Top1 (Abcam) in PBS with 1% BSA. Secondary antibodies conjugated with fluorescein (Cy3 and Cy5) were utilized to detect the binding of primary antibodies. The cover slips were mounted and images were captured using a laser scanning confocal microscope. Cell nuclei were visualized by 4',6-diamidino-2-phenylindole (DAPI) staining.

Top1 activity assays of nuclear extracts

Nuclear extracts were prepared as described by Deffie and colleagues (32). In brief, H82 cells were collected by centrifugation and washed once with ice-cold buffer made of: 10 mmol/L of Tris–HCl, pH 7.5, 1 mmol/L of EDTA, 4 mmol/L of MgCl2, and 0.5 mmol/L of phenylmethylsulfonylfluoride. Cells were subsequently suspended in 1 mL of same buffer for 10 minutes and then centrifuged at 1,500 g for 10 minutes. The nuclear pellet was resuspended in 20 μL of above buffer lacking MgCl2 but supplemented with 1 mol/L NaCl and placed on ice for at least 30 minutes, and then centrifuged at 15,000 × g for 15 minutes. The supernatant was collected as the nuclear extract. Top1 enzymatic activity in the nuclear extracts was measured using a DNA-relaxation assay as per the manufacturer’s instructions (TopoGen). Supercoiled plasmid DNA in a reaction mixture (20 μL) containing 10 mmol/L of Tris–HCl, pH 7.9, 1 mmol/L of EDTA, 150 mmol/L of NaCl, 0.1% BSA, 0.1 mmol/L of spermidine, and 5% glycerol was incubated at 37°C for 30 minutes with neat and serially diluted (1:4) nuclear
extracts, purified recombinant human Top1 (positive control), or assay diluent (negative control). The reactions were terminated by addition of 5 μL of 5X Loading Buffer (5% SDS and 0.3% bromophenol blue). Samples were resolved on a 1% agarose gel and imaged using the BioRad GelDoc (BioRad). The conditions assayed were as follows: (i) unstimulated cells (Media), cells that were cultured in media alone; (ii) HGF-stimulated cells, cells were stimulated for 15 minutes with 50 ng/mL of HGF and then harvested; (iii) SU11274-treated cells (SU11274), cells were cultured for 4 hours with 5 μmol/L of SU11274 and then harvested; and (iv) HGF stimulation and SU11274 treatment (HGF/SU11274), cells were cultured for 4 hours with 5 μmol/L of SU11274 and then stimulated for 15 minutes with 50 ng/mL of HGF before harvesting.

Cell viability assay
H69 and H82 cells (1 × 10^4 cells/well in a 96-well plate) were cultured overnight in RPMI-1640 supplemented with 1% FBS. The next day, the cells were treated with SU11274 alone, SN-38 alone, or SU11274 and SN-38 in combination for 72 hours. Cell viability was estimated using Alamar blue (final concentration of 10% v/v), a nonradioactive, nontoxic compound that is reduced by viable cell such that the amount of reduced Alamar blue is proportional to the metabolic activity of the cells. Plates were incubated at 37°C for 4 to 5 hours and fluorescence was measured using a plate reader (530/590 nm for excitation/emission). Cell viability represents the percentage of cells affected by drug treatment following normalization to cells cultured in media alone.

Statistical analysis
A Wilcoxon signed ranks test was performed to compare differences in the gene copy numbers between MET and Top1 in cell lines and patient samples. Mann–Whitney testing was performed to compare protein expression by stage. Correlational analysis was performed using a Pearson correlation. All statistical analyses were conducted using SPSS 17.0 (SPSS Inc.), with statistical significance set at P < 0.05.

Results
MET and Top1 gene copy number and protein expression in SCLC tumors
Tumor samples were obtained from 29 patients treated for SCLC at The University of Chicago (Supplementary Table 2). There were 11 patients with limited stage disease and 18 patients with extensive stage disease. Gene copy numbers for MET and Top1 were determined using genomic DNA isolated from patient tumor samples (Fig. 1A). MET gene copy number was increased (>6 copies) in 9 of 29 patient samples. In 21 of the 29 patients, there was a
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Table 1. Correlation of gene copy number with protein expression

<table>
<thead>
<tr>
<th>IHC staining</th>
<th>Pearson correlation $r$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MET gene copy number</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c-Met nuc</td>
<td>-0.038</td>
<td>0.221</td>
</tr>
<tr>
<td>c-Met cyto</td>
<td>-0.232</td>
<td>0.425</td>
</tr>
<tr>
<td>p-c-Met nuc</td>
<td>-0.267</td>
<td>0.336</td>
</tr>
<tr>
<td>p-c-Met cyto</td>
<td>-0.182</td>
<td>0.500</td>
</tr>
<tr>
<td><strong>TOP1 gene copy number</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c-Met nuc</td>
<td>0.553</td>
<td>0.026</td>
</tr>
<tr>
<td>TOP1 cyto</td>
<td>-0.275</td>
<td>0.300</td>
</tr>
<tr>
<td>p-c-Met(Y1003) nuc</td>
<td>-0.226</td>
<td>0.417</td>
</tr>
<tr>
<td>p-c-Met(Y1003) cyto</td>
<td>-0.063</td>
<td>0.824</td>
</tr>
</tbody>
</table>

NOTE: Bold type indicates statistically significant correlation ($P < 0.05$).

statistically significant greater MET gene copy number compared with TOP1 gene copy number ($P = 0.005$). When patients were grouped by disease stage (limited or extensive), there was a statistically significant difference between the mean MET gene copy number for limited disease (2.7) and extensive disease (7.9; $P = 0.015$). No difference was observed for TOP1 gene copy number (Fig. 1B).

The expression and distribution of MET and Top1 was determined by IHC in 29 patient tumor samples. Figure 2A shows representative IHC images of MET and Top1 staining in limited and extensive disease stage tumors. Nuclear Top1 expression was significantly higher in extensive stage disease than in limited stage disease ($P = 0.04$); cytoplasmic Top1 was not differentially expressed based on disease stage (Fig. 2B). Moreover, there was no difference in the expression or distribution of MET and p-MET based on disease stage.

We next sought to determine whether MET or TOP1 gene copy number correlated with protein expression/distribution of MET, p-MET, and Top1 (Table 1). Having shown that MET gene copy number and nuclear Top1 were increased in extensive disease compared with limited disease, it was interesting to determine whether MET gene copy number was correlated with increased nuclear Top1 expression ($r = 0.5$; Fig. 2C).

**MET and TOP1 gene copy number and protein expression in SCLC cell lines**

MET and TOP1 gene copy number was determined in 20 SCLC cell lines (Fig. 3A). MET gene copy number was increased (>6 copies) in 4 of 20 cell lines and TOP1 was increased (>6 copies) in 2 of 20 cell lines. In 18 of the 20 cell lines, MET gene copy number was greater than the TOP1 gene copy number. In fact, the mean MET gene copy number (4.6) was significantly higher than the mean TOP1 gene copy number (2.2; $P = 0.004$).

We next determined MET and Top1 protein expression in a panel of 8 SCLC cell lines by immunoblotting and SRM. Figure 3B shows high levels of MET expression in H69 and H345, whereas moderate expression was detected in H82, H249, and H526 cells. In contrast, MET expression was low or undetectable in H184, H446, and H2171 cells. The expression pattern of MET in the cell lines was largely recapitulated using SRM technology (Fig. 3C). Highest MET expression was detected in H69 (255.09 ± 8.5 amol/mg) and H345 (244.03 ± 11.59 amol/mg). Moderate levels were detected in H82 (158.63 ± 10.27 amol/mg), H249 (115.66 ± 8.77 amol/mg), and H526 (134.69 ± 18.49 amol/mg), and low to undetectable levels were detected in H184 (0 amol/mg) and H446 (88.53 ± 8.24 amol/mg). The only exception was the detection of...
moderate levels of MET expression in H2171 (148.25 ± 12.65 amol/mg) by SRM compared with a relatively low expression by immunoblotting.

Modulation of Top1 activity via the HGF/MET axis

The modulation of Top1 expression by the HGF/MET axis was investigated in H82 cells. Figure 4A shows low basal expression of p-MET and Top1 in H82 cells. HGF stimulation increased the expression of pMET as well as Top1. Moreover, p-MET and Top1 colocalized in the nucleus of HGF-stimulated cells.

DNA relaxation assays were performed to determine the induction of Top1 activity in response to HGF stimulation (Fig. 4B). Increasing amounts of nuclear extracts from H82 cells stimulated with HGF in the absence or presence of SU11274 were incubated with supercoiled plasmid DNA. SU11274 decreased Top1 activity as evidenced by the presence of strong supercoiled bands in the SU11274-treated cells compared with HGF-treated and control cells. The addition of SU11274 to HGF-stimulated cells reduced Top1 activity compared with cells treated with HGF alone, suggesting that activation of the HGF/MET axis mediated Top1 activity.

SU11274 and SN-38 synergize to decrease cell viability

We investigated the potential synergism between SU11274 and SN-38 to decrease cell viability in H69 and H82 cells. The cell lines were treated with SU11274 and SN-38 alone or in combination, and cell viability was determined using the standard Alamar blue assay. H69 cells (R988C MET mutation) were highly sensitive to SU11274 alone and SN-38 alone across the concentrations investigated (Fig. 5A). Moreover, SU11274 and SN-38 combined to significantly decrease cell viability compared with either SU11274 alone or SN-38 alone. In contrast, H82 cells (wild-type MET) were less sensitive to SU11274 and SN-38 inhibition. However, SU1127 and SN-38 worked in combination at the lower doses of SU11274 and SN-38 to significantly decrease cell viability (Fig. 5B).

Discussion

SCLC is an aggressive malignancy for which novel therapies are desperately needed. Herein, we show that MET can be specifically inhibited with a novel small molecule inhibitor SU11274 in SCLC cell lines, and that SN-38, a Top1 inhibitor, can synergize with SU11274. This synergism was most evident in the H69 SCLC cell line that expresses the R988C mutation in the MET juxtamembrane domain, which renders MET constitutively active (16). Further support for the MET/HGF axis modulation of Top1 activity is evidenced by the association of Top1 with p-MET and the nuclear colocalization of MET and Top1 in response to HGF stimulation. Moreover, MET inhibition by SU11274 decreased the activity of Top1 leading to less relaxed DNA in the Top1 activity assay. Taken together, these data show a link between the activation of the HGF/MET axis and Top1 activity in the nucleus.

We have previously shown that MET is expressed in a variety of SCLC cell lines, with abundant expression in H69 and moderate expression in H82 cells (16). Activity along the HGF/MET axis has been shown to be critical for
Amplification of the \textit{MET} gene has been more commonly associated with metastatic disease (23). Although we detected increased \textit{MET} gene copy number in primary tumor samples in this study, we cannot rule out similar increases in metastatic tissues. However, we found an association between increased \textit{MET} gene copy number and advanced stage disease. It is likely that increased \textit{MET} gene copy number and activation of \textit{MET} in SCLC may lead to enhanced Top1 activity and disease progression. Specifically, inhibiting the HGF/MET pathway through the use of targeted molecular therapies holds significant promise, particularly for patients with \textit{MET} overexpression or activating mutations.

SU11274 was utilized for this study given its higher selectively (50-fold) for \textit{MET} compared with other tyrosine kinases such as epidermal growth factor receptor (EGFR), platelet-derived growth factor receptor (PDGFR), and fibroblast growth factor receptor-1 (FGFR-1; ref. 36). Through such targeted inhibition, SU11274 has been shown to abrogate HGF-induced tyrosine phosphorylation of the \textit{MET} autophosphorylation sites at amino acid residues Y1230/1234/1235, as well as downstream phosphorylation of AKT and extracellular signal-regulated kinase (ERK) 1/2, in a dose-dependent manner in SCLC (22). However, work with this compound stimulated the development of other compounds based on an indolinone core, such as PF2341066 (Crizotinib, Pfizer). It is to be noted that crizotinib has both anti-\textit{MET} activity and anti-\textit{EML4-ALK} activity in lung cancer. Other small molecule inhibitors such as ARQ197 and \textit{MET} monoclonal antibody (onartuzumab) are also in clinical testing (22). The proliferation of anti-\textit{MET} therapeutics for the treatment of lung cancer, and their success in the treatment of SCLC, validates \textit{MET} as a key player in SCLC tumorigenesis.

To date, Top inhibition is one of the cytotoxic therapies for SCLC. As shown initially by the Japanese Cooperative Oncology Group (29) and subsequently by Hermes and colleagues (27), the Top1 inhibitor irinotecan in combination with a platinum-based agent improved median survival and the 1-year survival rate, without causing additional toxicity in patients with extensive SCLC. In the Hermes phase III study, 220 patients were randomized to receive irinotecan plus carboplatin (IC) or etoposide plus carboplatin (EC). The median survival was 8.5 months in the IC arm compared with 7.1 months in the EC arm. Although the study size was small, this study suggested that Top1 inhibition was more effective than previously considered treatments of metastatic SCLC.

It is appreciated from the imatinib studies in SCLC that a single novel therapy may not be sufficient to eradicate SCLC. Keeping this view in mind, we utilized SN-38, which is the active metabolite of irinotecan in this study to determine whether there was synergism with SU11274. Our results showed that SU11274 does synergize with SN-38 to inhibit the growth of SCLC cells \textit{in vitro}. This seems to be a potential unique pathway that can be targeted in SCLC expressing \textit{MET}. We observed synergism between SU11274 and SN-38 in two SCLC cell lines; however, the
extent of synergism varied between H69 and H82 cells. The drugs synergized at much lower doses in H69 cells compared with H82 cells, with H82 cells having a strong trend toward antagonism at higher doses. The postulated reason for this difference is that the H69 cell line harbors a mutation, R988C in the exon encoding the juxtamembrane region of MET, whereas H82 expresses wild-type MET. The fact the R988C mutations make MET constitutively active renders cells expressing this mutation much more susceptible to targeted MET inhibition, and by extension cotargeted therapies.

In summary, the studies described here have established the in vitro effects of MET inhibition, on HGF-induced signal transduction, as well as demonstrated the benefits of combined therapy with the clinically efficacious Top1 inhibitor. This is a novel treatment modality because it not only targets the growth factor addiction that is characteristic of many tumors via the inhibition of the HGF/MET axis, it also targets a putative downstream effector molecule, Top1. These results also highlight the impact of mutations on the efficacy of molecularly targeted drugs, as well as emphasize the potential synergistic effects of combining therapeutics to treat SCLC. It would now be useful to investigate this phenomenon in other cancers such as NSCLC, breast carcinoma, and head and neck malignancies, in which MET has been shown to play an integral role in tumorigenesis. Furthermore, it would also be beneficial to study other MET mutations in SCLC, which may influence the efficacy of this and other drug combinations.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors’ Contributions

Conception and design: C.E. Rolle, R. Kanteti, S. Nandi, S. Yala, R. Salgia
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): C.E. Rolle, S. Yala, M. Tretiakova, T. Hembrough, A.N. Husain
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): C.E. Rolle, R. Kanteti, M. Surati, S. Yala, Q. Arif, T. Hembrough, T.M. Brand, E.E. Vokes, A. Bharti
Writing, review, and/or revision of the manuscript: C.E. Rolle, R. Kanteti, M. Surati, T.M. Brand, D.L. Wheeler, E.E. Vokes, R. Salgia
Administrative, technical, or material support (i.e., reporting and organizing data, constructing databases): C.E. Rolle, M. Tretiakova

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