ERK Signal Suppression and Sensitivity to CH5183284/Debio 1347, a Selective FGFR Inhibitor

Yoshito Nakanishi, Hideaki Mizuno, Hitoshi Sase, Toshihiko Fujii, Kiyooki Sakata, Nukinori Akiyama, Yuko Aoki, Masahiro Aoki, and Nobuya Ishii

Abstract

Drugs that target specific gene alterations have proven beneficial in the treatment of cancer. Because cancer cells have multiple resistance mechanisms, it is important to understand the downstream pathways of the target genes and monitor the pharmacodynamic markers associated with therapeutic efficacy. We performed a transcriptome analysis to characterize the response of various cancer cell lines to a selective fibroblast growth factor receptor (FGFR) inhibitor (CH5183284/Debio 1347), a mitogen-activated protein kinase (MEK) inhibitor, or a phosphoinositide 3-kinase (PI3K) inhibitor. FGFR and MEK inhibition produced similar expression patterns, and the extracellular signal–regulated kinase (ERK) gene signature was altered in several FGFR inhibitor–sensitive cell lines. Consistent with these findings, CH5183284/Debio 1347 suppressed phosho-ERK in every tested FGFR inhibitor–sensitive cell line. Because the mitogen-activated protein kinase (MAPK) pathway functions downstream of FGFR, we searched for a pharmacodynamic marker of FGFR inhibitor efficacy in a collection of cell lines with the ERK signature and identified dual-specificity phosphatase 6 (DUSP6) as a candidate marker. Although a MEK inhibitor suppressed the MAPK pathway, most FGFR inhibitor–sensitive cell lines are insensitive to MEK inhibitors and we found potent feedback activation of several pathways via FGFR. We therefore suggest that FGFR inhibitors exert their effect by suppressing ERK signaling without feedback activation. In addition, DUSP6 may be a pharmacodynamic marker of FGFR inhibitor efficacy in FGFR-addicted cancers.

Introduction

Several tyrosine kinase-targeting agents have recently been developed. Each of these agents has demonstrable efficacy when used in patient cohorts that are stratified based on the genetic status of their respective molecular targets. The fibroblast growth factor receptors (FGFR) are tyrosine kinases that are constitutively activated in a subset of tumors by genetic alterations such as gene amplification, point mutation, or chromosomal translocation/rearrangement (1, 2). Genetic alterations of FGFR may also be predictive indicators of patient response to FGFR inhibitors (2, 3). For instance, dovitinib, a multitargeted kinase inhibitor that inhibits FGFRs, produced three unconfirmed partial responses in breast cancer harboring FGFR1 gene amplification (4). Although genetic alterations could predict drug efficacy, acquired genetic alterations confer resistance to molecular-targeted drugs. Acquired mutations in target genes or downstream components are major mechanisms of resistance (5–13). Although acquired FGFR mutations have not yet been identified in patients, several FGFR mutations that confer resistance to FGFR inhibitors have been reported (7, 14). Because cancer cells continue to utilize the pathway to which they are originally addicted, they acquire some genetic alterations to reactivate the pathway. Therefore, monitoring of changes in the pathways utilized by cancer cells could be used to predict the efficacy of an inhibitor in tumors.

The FGFR family consists of FGFR1, FGFR2, FGFR3, and FGFR4, each of which is bound by a subset of 22 fibroblast growth factor (FGF) ligands. FGFRs are activated by ligand-dependent or ligand-independent dimerization that leads to intermolecular phosphorylation. FGFR substrate 2 (FRS2) is a key adaptor protein that is phosphorylated by FGFR. Phosphorylated FRS2 recruits several other adaptor proteins and activates the mitogen-associated protein kinase (MAPK) or PI3K/AKT pathways (1). However, the pathway associated with effective FGFR suppression in FGFR-addicted cancers has not yet been identified. Gaining an understanding of the FGFR pathway by studying its function in the presence of FGFR inhibitors will enable identification of candidate pathways utilized by FGFR-addicted cancers and the pharmacodynamic markers of these pathways.

In a previous study, we analyzed the signaling pathway of an FGFR fusion kinases, FGFR3-BAIAP2L1 (15). A Rat-2 cell line stably expressing FGFR3-BAIAP2L1 exhibited potent tumorigenic activity. Gene expression analysis revealed strong upregulation of genes downstream of the MAPK pathway, and upregulation of the MAPK pathway was validated by Western blotting; in contrast, the PI3K/AKT pathway was not activated by FGFR3-BAIAP2L1. Therefore, we suggested that MAPK pathway activation is essential to
the tumorigenic activity of FGFR3-BAIAP2L1. To generalize the MAPK pathway dependency of FGFR, we characterized the pathway modulation by CH5183284/Debio 1347, a selective FGFR inhibitor, in several FGFR genetically altered cancer cell lines. We analyzed differential transcript expression by microarray analysis and found that MAPK pathway modulation was associated with the efficacy of CH5183284/Debio 1347. We identified the dual specificity phosphatase 6 (DUSP6) gene, which lies downstream of MAPK, as a candidate pharmacodynamic marker of FGFR inhibitor efficacy. Finally, we applied a MEK inhibitor to FGFR genetically altered cancer cells to validate the significance of MAPK pathway modulation by FGFR inhibition.

Materials and Methods

Reagents and cell lines

CH5183284/Debio 1347 (FGFR inhibitor), CH4987655 (MEK inhibitor), CH5126766 (RAF-MEK inhibitor), and CH5132799 (PI3K inhibitor) were synthesized at Chugai Pharmaceutical Co. Ltd., as previously described (7, 16–18). AZD4547 was synthesized at Chugai Pharmaceutical Co. Ltd. (patent publication WO2008075068). PD173074, PD0325901, and selumetinib were purchased from Sigma-Aldrich and Selleck Chemicals. The DMS-114, NCI-H520, NCI-H1581, NCI-H716, KATO-III, SNU-16, AN3 CA, RT-4, NCI-N87, ZR-75-1, and HCT116 cell lines were purchased from the American Type Culture Collection (Manassas, VA, USA). The KMS-11 cell line was purchased from the Health Science Research Resources Bank. MFE-296 and UM-UC-14 cell lines were purchased from Health Protection Agency Culture Collections. The MFE-280 cell line was purchased from Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH. The HSC-39 and MNK-45 cell lines were purchased from Immuno-Biological Laboratories, and the SUM-52PE cell line was purchased from Asterand. All cell lines were obtained more than one year prior to the experiments and were propagated for less than 6 months after thawing and cultured according to supplier instructions.

Microarray

Cells were treated with 1 μM/1 inhibitor doses and incubated for 24 hours at 37°C. Total RNA was purified with the RNeasy Kit (Qiagen). Total RNA was reverse transcribed, labeled, and hybridized to Human Genome U133 Plus 2.0 arrays (Affymetrix) according to the manufacturer’s instructions. The microarray data were deposited in the GEO database (GEO number: GSE73024). The expression value for each probe was calculated using the guanine-cytosine robust multiarray analysis (GC-RMA) algorithm (19). To reduce noise from the low-signal range, probes with a median signal of <10 across samples were filtered out. The log ratio of expression relative to dimethyl sulfoxide (DMSO)-treated samples was calculated to identify downregulated genes (<50% expression) and upregulated genes (>200% expression). Cluster 3.0 was used for clustering and Java Treeview was used for heatmap construction (20).

Signature analysis

The microarray dataset from human keratinocytes treated with extracellular signal–regulated kinase 1/2 (ERK1/2) siRNA (GSE15417; ref. 21) was obtained from the Gene Expression Omnibus. This dataset consists of profiles from two independent siRNA experiments (set A and B). Both profile sets and the log-transformed expression data for each probe were analyzed by a t test comparison against the control. Then, significantly downregulated probes with t test P < 0.01 in both comparisons were selected. We used 672 of 22,277 probes as an ERK1/2-inducible gene signature.

For the datasets in the “Microarray” section, the log ratios for the replicated experiments were averaged. Then, distributions of the log ratios for probes in the signature and not in the signature were plotted as a histogram. Differences in their distribution patterns indicate a coordinated change in expression for the gene signature. R (http://www.r-project.org/) was used for calculation.

Results

FGFR inhibition affects gene expression via the MAPK pathway in an FGFR1 gene-amplified cancer

The MAPK and PI3K/AKT pathways are the main downstream effectors of FGFR (1). We investigated the effects of
CH5183284/Debio1347 and AZD4547 (both FGFR inhibitors), CH4987655 (MEK inhibitor), and CH5132799 (PI3K inhibitor) on the transcriptome of the NCI-H1581 lung cancer cell line harboring FGFR1 gene amplification. We determined the effects of a 24-hour exposure on gene expression. Expression values are presented relative to the DMSO control and clustered by similarity (Fig. 1A). We identified 2850 probes that were modulated by CH5183284/Debio 1347. Of these, 2273, 1675, and 158 were also affected by AZD4547, CH4987655, and CH5132799, respectively. Because FGFR inhibition and MEK inhibition produced similar differential expression patterns, we analyzed our data in the context of the gene set associated with ERK siRNA-mediated changes (GSE15417). To analyze the coordinated change in expression of the gene signature, the log ratio to the control was calculated and distributions of log ratios for probes in the signature (blue) and not in the signature (red) were plotted as a histogram. The FGFR and MEK inhibitors, but not the PI3K inhibitor, showed differential gene expression patterns regulated by ERK (Fig. 1B). These results suggest that the FGFR inhibitor mainly modulates the MAPK pathway and not the PI3K pathway.

ERK signal suppression is associated with sensitivity to FGFR inhibition

We investigated the effect of CH5183284/Debio 1347 on the MAPK pathway in 14 cancer cell lines harboring other FGFR alterations. Thirteen of the cell lines were sensitive to CH5183284/Debio 1347 and harbored FGFR genetic alterations such as NCI-H716, KATO-III, HSC-39, SNU-16, MFE-280, MFE-296, AN3CA, DMS-114, NCI-H520, NCI-H1581, KMS-11, UMC-14, and RT-4; the other cell line, NCI-N87, was insensitive to CH5183284/Debio 1347 and had no FGFR alterations. Data on genetic status and sensitivity to CH5183284/Debio 1347 are available elsewhere (7) or in Supplementary Table S1. We determined the effects of a 24-hour exposure to 1 μmol/L CH5183284/Debio 1347 on gene expression relative to the DMSO control. We confirmed that the ERK (GSE15417) and MEK signatures (23) were suppressed by CH5183284/Debio 1347 only in sensitive cell lines harboring FGFR alterations (Fig. 2A and Supplementary Fig. S1). Consistent with this, suppression of phospho-ERK by a 2-hour treatment with CH5183284/Debio 1347 was observed in seven cancer cell lines harboring FGFR alterations (Fig. 2B). However, phospho-AKT was suppressed only in four cell lines (NCI-H1581, SNU-16, KATO-III, and SUM-52PE), suggesting that

Figure 1.
Differential expression in the presence of several pathway inhibitors in NCI-H1581, an FGFR1-amplified cancer cell line. A, heatmap showing expression log ratio to control (DMSO) for each probe after a 24-hour treatment with 1 μmol/L CH5183284/Debio 1347, AZD4547 (FGFR inhibitor), CH4987655 (MEK inhibitor), or CH5132799 (PI3K inhibitor) in NCI-H1581 harboring FGFR1 gene amplification (n = 2). Probes were clustered by similarity at the left side of the panel. B, distributions of log ratio to control (geometric mean of DMSO-treated samples) were plotted as a histogram. The x-axis represents the log ratio; the y-axis represents the frequency. The distribution pattern for probes in the ERK1/2 signature is blue; distributions of other probes are red (n = 2)
FGFRs likely depend on the MAPK pathway and that ERK signal suppression is associated with sensitivity to FGFR inhibition.

Differential expression of DUSP6 and sensitivity to FGFR inhibition

Because FGFRs likely depend on the MAPK pathway, we searched for genes that could be modulated by and associated with sensitivity to CH5183284/Debio 1347 among the 672 genes of the ERK signature (GSE15417). We calculated the ratio of the geometric mean of each probe in 13 cell lines treated with DMSO and CH5183284/Debio 1347 (NCI-H716, KATO-III, HSC-39, SNU-16, MFE-280, MFE-296, AN3 CA, DMS-114, NCI-H520, NCI-H1581, KMS-11, UM-UC-14, and RT-4). We identified 47 genes (51 probes) that were significantly modulated ($P < 0.05; 2$-fold change) by treatment (Fig. 3A and Supplementary Table S2). The most significantly modulated gene was the DUSP6 gene. Expression of DUSP6 was suppressed by CH5183284/Debio 1347 in every sensitive cancer cell line that we tested but not in

**Figure 2.**
MAPK pathway suppression by CH5183284/Debio 1347 in FGFR-altered cancer cell lines. A, distributions of expression log ratio to control (geometric mean of DMSO-treated samples) were plotted as a histogram. The x-axis represents the log ratio; the y-axis represents the frequency. Distribution patterns for probes in the ERK1/2 signature are blue; other probes are red. Cells were treated with $1 \mu$mol/L CH5183284/Debio 1347 or DMSO for 24 hours. Total RNA was analyzed by microarray. IC50 concentrations of CH5183284/Debio 1347 in antiproliferative assay are provided. B, inhibition of ERK or AKT phosphorylation. After a 2-hour incubation with CH5183284/Debio 1347, cultures of DMS-114, NCI-H1581, SNU-16, KATO-III, SUM-52PE, UM-UC-14, and KMS-11 cells were lysed and analyzed by Western blotting. Ampl, amplification; mut, mutation.
Figure 3.
Modulation of DUSP6 expression in FGFR inhibitor–sensitive cancer cell lines. A, a volcano plot representation showing the magnitude (log2 ratio, x-axis) and significance (log10 P, y-axis) of all genes in the ERK signature. The red circles represent the significantly modulated probes and the white circles represent others. B, bar graphs show the ratio of probes that recognize DUSP6 vs. DMSO in 14 cancer cell lines. The black bars denote cell lines harboring FGFR alterations, and gray bars denote the FGFR wild-type cell line. C, inhibition of DUSP6 expression or ERK phosphorylation. After a 24-hour treatment with PD173074 (FGFR inhibitor) at 3 μmol/L or with PD0325901 (MEK inhibitor) at 1 μmol/L, cultures of NCI-H1581, DMS-114, AN3 CA, SNU-16, KMS-11, ZR-75-1, NCI-N87, and HCT116 cells were lysed and analyzed by Western blotting. D, pharmacodynamic response in in vivo models. Mice-bearing SNU-16, DMS114, NCI-N87, or MKN-45 cells were orally administered CH5183284/Debio 1347 at 100 mg/kg, and the tumors were collected and lysed at 4-hour postdosing (n = 2). Lysates were then analyzed by Western blotting. Ampli, amplification; Mut, mutation.

NCI-N87, which is insensitive to CH5183284/Debio 1347 (Fig. 3B and Supplementary Fig. S2). PD173074, another FGFR inhibitor, also suppressed phospho-ERK, resulting in decreased DUSP6 protein expression levels in the FGFR inhibitor–sensitive cell lines after a 24-hour treatment (Fig. 3C). As expected, phospho-AKT level was not constantly suppressed. Notably, one FGFR1 gene-amplified but FGFR inhibitor–insensitive cell line, ZR-75-1, did not show suppression of phospho-ERK and DUSP6 expression. PD0325901, a MEK inhibitor, reduced phospho-ERK and DUSP6 protein levels in the FGFR inhibitor–sensitive and -insensitive cell lines. To show the usefulness of DUSP6 as a pharmacodynamic marker of CH5183284/Debio 1347 in in vivo model, we obtained the tumor tissues 4 hours after the 11th daily administration of 100 mg/kg CH5183284/Debio 1347. We utilized SNU-16 and DMS-114 as a CH5183284/Debio 1347-sensitive model and NCI-N87 and MKN-45 as an insensitive model. The tumor growth inhibitory activities of CH5183284/Debio 1347 against those models are available (Supplementary Table S3). Consistent with the in vitro findings, CH5183284/Debio 1347 suppressed phospho-ERK and decreased DUSP6 protein expression levels in the FGFR inhibitor–sensitive xenograft models but not in the insensitive models (Fig. 3D). These data suggest that DUSP6 is the most reliable pharmacodynamic marker associated with the efficacy of FGFR inhibitors in FGFR genetically altered cancers.
MAPK pathway suppression without feedback activation of bypass pathways could be important for FGFR inhibitor activity in FGFR genetically altered cancers

To investigate the significance of MAPK pathway suppression by FGFR inhibitors, we tested the sensitivity of FGFR-addicted cancer cell lines to MEK inhibitors, such as CH4987655, CH5126766, or selumetinib. Although MEK inhibition suppressed DUSP6 protein expression in FGFR genetically altered cancer cell lines, these cell lines were not sensitive to the MEK inhibitor, whereas the B-RAF-mutated cell line (SK-MEL-1), a K-RAS-mutated cell line (HCT116), and NF-1-null cell line (MeWo) were sensitive to MEK inhibitors (Fig. 4). To clarify the mechanisms of innate resistance to MEK inhibitors, we treated the SNU-16 cell line harboring FGFR2 gene amplification with CH5183284/Debio 1347, CH5126766 (RAF-MEK inhibitor), or CH5132799 (PI3K inhibitor), either alone or in combination (Fig. 5). CH515183284/Debio 1347 suppressed phospho-FGFR, phospho-AKT, phospho-ERK, and DUSP6. In the presence of CH5126766-mediated suppression of phospho-ERK and DUSP6, we observed elevated phosphorylation of FGFR, MET proto-oncogene, receptor tyrosine kinase (MET), epidermal growth factor receptor (EGFR), AKT, SRC proto-oncogene, nonreceptor tyrosine kinase (SRC), and signal transducer and activator of transcription 3 (STAT3). Feedback activation by MEK inhibition was abrogated by CH5183284/Debio 1347. Thus, MAPK pathway suppression alone reactivated FGFR and induced potent activation of other pathways. CH5132799 did not produce this result. DUSP6 and Cdc25C suppression, and thus MAPK pathway inhibition, was stronger with CH515183284/Debio 1347 than with CH5126766. These results show that the FGFR inhibitor suppressed the MAPK pathway more effectively than the MEK inhibitor alone without feedback activation of other signals, thus leading to the efficacy of FGFR inhibitors in FGFR-addicted cancers.

Discussion

Investigations of the signaling pathways associated with oncogenes provide important information leading to combination therapies or increased understanding of resistance mechanisms. For instance, in an endocrine therapy–resistant hormone receptor–positive breast cancer, the PI3K/AKT pathway is abnormally activated and a downstream kinase, S6 kinase, independently phosphorylates, and activates the estrogen receptor ligand (24). Therefore, combination of endocrine therapy with letrozole and PI3K pathway inhibition by everolimus exhibits great clinical efficacy (25). The MAPK and PI3K/AKT pathways are the main downstream effectors of FGFR (1). Every FGFR-altered cancer cell line that was tested in this study was dependent on the MAPK pathway but not the PI3K/AKT pathway (Fig. 1, 2). This is consistent with several genetic profiling studies. FGFR and RAS mutations are mutually exclusive in bladder cancer and endometrial cancer (26, 27). In contrast, FGFR mutations are frequently associated with mutations in the PI3K/AKT pathway (26, 27). Conversely, when an FGFR-altered cancer also carries a KRAS mutation, FGFR inhibitors are ineffective (28), suggesting that FGFR and RAS likely activate the same pathway. Although MAPK is considered the main downstream effector of FGFR, we have shown that MEK inhibitors are not always effective in FGFR-altered cancer because of feedback activation (Fig. 5). Similarly, PI3K inhibition enhanced HER2 signaling in HER2 overexpressing breast cancer. In that context, the combined administration of PI3K and HER2 inhibitors produced superior antitumor activity in comparison to monotherapy (29). Therefore, the combination of FGFR and MEK inhibition could be another approach to treat patients harboring FGFR alterations.

DUSP6 is a member of the dual-specificity protein phosphatase subfamily that inactivates target kinases, such as ERK, by dephosphorylation. Overexpression of DUSP6 was observed in response to activated RAS or BRAF (30–34), representing an increase in negative feedback of the MAPK pathway. Therefore, DUSP6 expression could reflect activity of the MAPK pathway. In addition, a role of DUSP6 during early mouse development in response to FGF signaling has been suggested (35, 36). In mouse embryos, DUSP6 contributes as a negative feedback regulator of FGF-stimulated ERK signaling. The DUSP6 loss-of-function

Figure 4.
Sensitivity of FGFR-altered cancer cell lines to MEK inhibitors. Cells were seeded in 96-well plates and treated for 4 days with various concentrations of CH4987655 (MEK inhibitor), CH5126766 (RAF-MEK inhibitor), or selumetinib (MEK inhibitor) prior to viability assays.
Concentrations were 0.3 or 1 μmol/L. The drug gene amplification were lysed and analyzed by Western blotting. The drug inhibitor), or combinations thereof, (PI3K inhibitor), CH5126766 (RAF-MEK inhibitor), or combinations thereof, SNU-16 cancer cells harboring FGFR2 gene amplification were lysed and analyzed by Western blotting. The drug concentrations were 0.3 or 1 μmol/L.

ERK Signal Suppression and Sensitivity to FGFR Inhibitor

Figure 5.
Pathway biology upon MEK inhibitor treatment in FGFR2-amplified cancer cells. After a 24-hour treatment with CH5183284/Debio 1347, CH5132799 (PI3K inhibitor), CH5126766 (RAF-MEK inhibitor), or combinations thereof, SNU-16 cancer cells harboring FGFR2 gene amplification were lysed and analyzed by Western blotting. The drug concentrations were 0.3 or 1 μmol/L.

Mutant causes several symptoms, such as variably penetrant, dominant postnatal lethality, skeletal dwarfism, coronal craniosynostosis, and hearing loss. These phenotypes are also characteristic of FGFR active mutations. Therefore, we suggest that DUSP6 could be the most reliable pharmacodynamic marker of FGFR inhibition; the responsiveness of DUSP6 expression could predict the efficacy of FGFR inhibitors.

Studying pharmacodynamic biomarkers will help accelerate the development of molecular-targeted agents for the treatment of cancer (37, 38). In general, the gold-standard pharmacodynamic assay is immunohistochemistry on a tumor sample. Several clinical studies evaluated the phosphorylation status of the drug target or molecules on the downstream pathway (39, 40). Although the evaluation of differential phosphorylation could be used to assess inhibitor activity in the tumor, there are limitations to phospho-related assays. The loss of immunoreactive phospho-AKT and phospho-ERK during sample procurement has been reported (41). Therefore, we must consider multiple pre-analytical factors that influence the stability of phosphorylated proteins during procurement and preservation of clinical samples (42). Noninvasive samples such as circulating tumor cells and circulating tumor DNA obtained from a liquid biopsy could be the next-generation source of pharmacodynamic markers (43). In solid tumors, for instance, monitoring for ERK downstream signaling targets such as DUSPs and SPREADs (17). In FGFR-altered cancer cells, DUSP6 was more significantly suppressed by CH5183284/Debio 1347 than by CH5126766 (Fig. 5). CH5126766 suppressed phospho-ERK but not the downstream ERK effector DUSP6, suggesting that CH5126766 does not strongly suppress MAPK, resulting in the resistance of FGFR-altered cancer cells to MEK inhibition. Therefore, monitoring of DUSP6 could be more beneficial than that of phospho-ERK.

In summary, measurement of the status of downstream signaling could be used to predict a molecule’s therapeutic efficacy. FGFR likely depends on the MAPK pathway, and ERK signal suppression is associated with sensitivity to FGFR inhibition. Therefore, DUSP6, which functions downstream of the ERK signal, is one of the most reliable pharmacodynamic markers of the efficacy of an FGFR inhibitor. CH5183284/Debio 1347 is currently in phase I clinical trials by Debiopharm International S.A. in patients harboring FGFR alterations (NCT01948297).

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Authors’ Contributions
Conception and design: Y. Nakanishi, Y. Aoki
Development of methodology: Y. Nakanishi, K. Sakata
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): Y. Nakanishi, H. Mizuno, T. Fujii
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): Y. Nakanishi, H. Mizuno, T. Fujii
Writing, review, and/or revision of the manuscript: Y. Nakanishi, H. Mizuno, N. Ishii
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): Y. Nakanishi
Study supervision: Y. Nakanishi, Y. Aoki, M. Aoki, N. Ishii

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