Nuclear ErbB2 Enhances Translation and Cell Growth by Activating Transcription of Ribosomal RNA Genes

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Abstract

Aberrant regulation of rRNA synthesis and translation control can facilitate tumorigenesis. The ErbB2 growth factor receptor is overexpressed in many human tumors and has been detected in the nucleus, but the role of nuclear ErbB2 is obscure. In this study, we defined a novel function of nuclear ErbB2 in enhancing rRNA gene transcription by RNA polymerase-I (RNA Pol I). Nuclear ErbB2 physically associates with β-actin and RNA Pol I, coinciding with active RNA Pol I transcription sites in nucleoli. RNA interference–mediated knockdown of ErbB2 reduced pre-rRNA and protein synthesis. In contrast, wild-type ErbB2 augmented pre-rRNA level, protein production, and cell size/cell growth, but not by an ErbB2 mutant that is defective in nuclear translocation. Chromatin immunoprecipitation assays revealed that ErbB2 enhances binding of RNA Pol I to rDNA. In addition, ErbB2 associated with rDNA, RNA Pol I, and β-actin, suggesting how it could stimulate rRNA production, protein synthesis, and increased cell size and cell growth. Finally, ErbB2-potentiated RNA Pol I transcription could be stimulated by ligand and was not substantially repressed by inhibition of PI3-K and MEK/ERK (extracellular signal regulated kinase), the main ErbB2 effector signaling pathways. Together, our findings indicate that nuclear ErbB2 functions as a regulator of rRNA synthesis and cellular translation, which may contribute to tumor development and progression. Cancer Res; 71(12); 4269–79. ©2011 AACR.
transcriptional regulation, DNA repair, and DNA replication (12–16, 20, 26–32), the biological significance and functions of the nuclear RTKs, including ErbB2, is still far from clear. Our study described herein identified a novel function of nuclear ErbB2 in enhancing cellular translation, and thereby cell growth, which may contribute to tumorigenesis.

Materials and Methods

Cells, antibodies, and chemicals

Cell lines were grown in Dulbecco modified Eagle medium (DMEM)-F-12 containing 10% fetal calf serum. MCF-7, SKBR3, and MDA-MB-231 cells were purchased from ATCC in 2007. Liquid nitrogen stocks were done on receipt. Cells were used for no more than 4 months after being thawed. The antibodies and chemicals used were: anti-ErbB2 (Calbiochem, Thermo Scientific); anti-β-actin, anti-α-tubulin, and mouse immunoglobulin (Ig) G (mIgG; Sigma); anti-RPA194 (Santa Cruz); anti-lamin B (Calbiochem); anti-BrDU (Molecular Probes, Abcam); anti-Akt, anti-phospho (p)-Akt, anti-ERK (extracellular signal regulated kinase), anti-p-ERK, and U0126 (Cell Signaling); BrUTP, α-amanitin, and actinomycin D (Act. D; Sigma); LY294002 (Promega); and Heregulin (HRG; Thermo Scientific). Secondary antibodies were purchased from Santa Cruz Biotechnology and Jackson ImmunoResearch. siRNAs were from Dharmaco (control siRNA and ErbB2 siRNA) and Bio-Rad (β-actin siRNA).

Cellular fractionation and immunoprecipitation

Nuclear and cytoplasmic fractions, single immunoprecipitation (IP), and sequential double IP assays were carried out as described (26, 33). Cellular fractionation was examined with α-tubulin and lamin B antibodies.

Chromatin IPs

The chromatin IPs (ChIP) assay was done by the EZ-ChIP Kit (Millipore) according to the manufacturer's instructions. The immunoprecipitated DNA was extracted and purified for PCR by using primers (rDNA promoter, 5'-GGTA-TATCTTTTCGCTCCGAG-3' and 5'-AGCGACAGGTCGCCAGAGGA-3'; 28S rRNA, 5'-CGACGCCCATTTGGCAAGCTCT3'- and 5'-CTCTCCGGAATCGACCCCGA-3'; ref. 34). PCR products were examined on ethidium-bromide-stained agarose gel. For the sequential double ChIP, the first ChIP products were eluted in 10 mmol/L DTT buffer (30 minutes, 37 °C), diluted with 40-fold ChIP lysis buffer, and subjected to a second IP as described before by using indicated antibodies.

Real-time quantitative PCR analysis of pre-rRNA synthesis

Cellular RNA was isolated with Trizol reagent (Invitrogen) and purified by the RNasy Mini Kit (Qiagen), cDNA was generated from total isolated RNA by random primed reverse transcription (RT) and subjected to real-time quantitative PCR (qPCR) performed in triplicate by SYBR Green and LightCycler 480 System (Roche) with 45S pre-rRNA primers (5'-CTCTCCGTTATGTGAGCGCTC-3' and 5'-CGAGAACCTCT- GTTCTCTC-3'; ref. 34). The RAGAPDH (human glyceroldehydes 3-phosphate dehydrogenase) and β-2-microglobulin primers were used to normalize the loaded amount of RNA.

Protein synthesis analysis

Equal numbers of cells were incubated in methionine-free DMEM ( Gibco/BRL) medium (30 minutes) and 30 μCi of 35S-methionine (Perkin Elmer) was added to the cells (30 minutes). Cells were lysed in equal amount of lysis buffer as described previously (33) and frozen at −70 °C. One micro-liter of thawed lysate was spotted onto a filter and analyzed by liquid scintillation counting. For analysis of total protein level, equal numbers of cells were lysed in lysis buffer and protein concentration determined by the Bradford method (6).

Flow cytometry and measurement of cell size

Cells were washed, trypsinized, resuspended in 1 mL of PBS, and fixed by adding 4 mL of 99% ethanol (80% final) overnight or stored at −20 °C until the time of analysis. The fixed cells were then centrifuged, washed, and incubated (37 °C, 30 minutes) in propidium iodide/RNase A solution (10 μg/mL propidium iodide in 0.76 mmol/L sodium citrate at pH 7.0; 250 μg/mL RNAse A in 10 mmol/L Tris-HCl and 15 mmol/L NaCl at pH 7.5). To detect the relative cell size, the mean forward scatter height (FSC-H) of the cells was determined by the FACsCaliber machine (Becton Dickinson). Data were then analyzed by using CellQuest software (Becton Dickinson) and WinMDI 2.8 software.

Results

ErbB2 associates with β-actin

In an attempt to understand the functionality of nuclear ErbB2, we set to identify potential nuclear proteins that associate with nuclear ErbB2 in the nucleus. By using proteomic assays, monoclonal ErbB2 antibody–precipitated nuclear lysates were subjected to SDS gel electrophoresis and analyzed by mass spectrometry. Interestingly, β-actin, which has also been shown to localize in the nucleus to modulate gene transcription (34–37), was reproducibly detected, suggesting β-actin might be an ErbB2 associating protein. Indeed, association of ErbB2 with β-actin was detected in multiple ErbB2–expressing breast cancer cell lines by using co-IP assays (Fig. 1A and Supplementary Fig. S1A). Moreover, ErbB2 associated with β-actin both in the cytoplasm and the nucleus (Fig. 1A and Supplementary Fig. S1B). The ErbB2/β-actin colocalization was further supported by the yellow spots in the confocal microscopy data (Fig. 1C). Insets 1 and 2 further show the colocalization in the nucleus. Consecutive confocal planes of the nuclei were also examined to show the nuclear colocalization of ErbB2 and β-actin in another cell line (Fig. 1D and Supplementary Fig. S1C). The merged (yellow) signals of ErbB2 (green) and β-actin (red) were detected in plane 18 (arrows). The β-actin (but not ErbB2) signal was still detected in the nucleus in plane 24 and neither was detected in the nucleus of plane 10. Planes 10 to 24 all cover the nucleus [as evident by 4', 6 diamidino 2 phenylindole (DAPI) staining], indicating that ErbB2 and β-actin colocalize in the nucleus. Together, the results suggest
that ErbB2 can associate with β-actin in both the cytoplasm and the nucleus.

**ErbB2 forms a complex with β-actin and RNA Pol I**

Although nuclear β-actin has been known to be associated with RNA Pol I and is required for RNA Pol I transcription (34) and the nuclear ErbB2 complex was also found to be associated with DNA binding ability and RNA Pol II transcriptional activity (29, 38), we then asked whether ErbB2 might associate with RNA Pol I and be involved in RNA Pol I transcription. Co-IP experiments showed that ErbB2 binds to RNA Pol I in multiple breast cancer cell lines (Fig. 2A and Supplementary Fig. S2A). Association between ErbB2 and RNA Pol I only occurred in the nucleus as revealed by co-IP analyses (Figure 2A, right, and Supplementary Fig. S2B). The colocalization of ErbB2 and Pol I in the nucleus was further supported by confocal microscope data (Fig. 2B, left, and Supplementary Fig. S2C) and sequential confocal image sections (Supplementary Fig. S2D). ErbB2 staining (red) was clearly seen both outside and inside the nucleus (DAPI staining, blue) and RNA Pol I (green) was detected only in the nucleus. In the merged images, the yellow spots indicate the colocalization of ErbB2 (green) and β-actin (red) complexes whose colocalization is indicated by white arrows in the merged images. Scale bar, 5 μm.
detected gold particles. It should be mentioned that the ErbB2 and RNA Pol I complex was colocalized in the nucleoli (Fig. 2B, see discussion later). To further explore whether ErbB2, β-actin, and RNA Pol I form a complex, we performed sequential IP assays and showed ErbB2 and RNA Pol I complex with β-actin (Fig. 2C, top), which was further shown by immuno-EM. We used the primary antibodies mouse anti-ErbB2, goat anti-RNA Pol I, and rabbit anti-β-actin followed by
secondary antibodies with gold particles labeling ErbB2 (donkey anti-mlgG, 25 nm), RNA Pol I (donkey anti-goat IgG, 6 nm), and β-actin (donkey anti-rabbit, 10 nm). ErbB2, Pol I, and β-actin were detectable and colocalized in the nucleus as evident from 3 different sized gold particles, which seemed only when primary antibodies against ErbB2, Pol I, and β-actin were applied (Fig. 2C, bottom, inset 1), but did not seem in the negative control without treatment of primary antibodies.
notably, knockdown of β-actin using siRNA impaired the association between ErbB2 and RNA Pol I, indicating that β-actin was required for the association of ErbB2 with RNA Pol I (Fig. 2D). However, siRNA-mediated knockdown of ErbB2 exerted no impact on the association between β-actin and RNA Pol I (Fig. 2E). Taken together, our data show that ErbB2 forms a complex with β-actin and RNA Pol I in the nucleus, raising an interesting question about whether nuclear ErbB2 may involve in RNA Pol I transcription.

Nuclear ErbB2 increases RNA Pol I transcription in vivo

To address whether nuclear ErbB2 plays a role in RNA Pol I transcription in vivo, pre-rRNA synthesis was assessed by RT-qPCR. Strikingly, siRNA-mediated knockdown of ErbB2 resulted in attenuated synthesis of 45S pre-rRNA in 2 different cell lines (Fig. 3A and Supplementary Fig. S3). Consistently, in situ run-on transcription assays also showed that BrU-labeled nascent nucleolar RNA levels were reduced in ErbB2 siRNA-treated cells compared with control cells (Fig. 3B). BrU-trPC and ErbB2 were also shown to be colocalized in the nucleus (Fig. 3B, inset 1). It should be mentioned that nuclear ErbB2 localized in the nucleoli, where RNA Pol I transcription occurs (Fig. 2B, insets 1 and 2). This was further supported by the colocalization of ErbB2 and the nucleoli-specific marker, fibrillarin (Supplementary Fig. S4). To distinguish ErbB2-mediated RNA Pol I transcription from RNA Pol II and
on pre-rRNA synthesis (Fig. 3E, lanes 3 and 6). The results were exhibited impaired RNA Pol I binding and less enhancement of mutant, which is known defect in nuclear translocation (33), nuclear localization signal (NLS) was mutated, ErbB2 synthesis (Fig. 3E, lanes 2 and 5). However, ErbB2 whose with RNA Pol I binding ability greatly enhanced pre-rRNA synthesis caused by increasing amounts of sites and may play a novel role in modulation of RNA Pol I transcription activity. 

ErbB2 may be involved in the complex binding to rDNA; indeed, RNA Pol I to rDNA. Since ErbB2 associates with rDNA promoter and the 28S rRNA transcribed region (34), which are required for the rRNA gene transcription.

To investigate the mechanism underlying ErbB2-mediated augmentation of RNA Pol I transcription, we performed ChIP or quantitative ChIP (qChIP) assays and found that increasing level of ErbB2 caused an enhanced association of RNA Pol I with rDNA promoter and the 28S rRNA transcribed region (Fig. 4A, left). However, knocking down ErbB2 resulted in diminished occupancy of RNA Pol I at rDNA gene (Fig. 4A, right). These data indicate that ErbB2 enhances the binding of RNA Pol I to rDNA. Since ErbB2 associates with β-actin and RNA Pol I in vivo (Fig. 1 and Fig. 2), raising the possibility that ErbB2 may be involved in the complex binding to rDNA; indeed, ChIP assays showed that ErbB2, similar to β-actin and RNA Pol I, associated with the 5′-terminal part of rDNA containing promoter and the 28S rRNA transcribed region in multiple ErbB2–expressing breast cancer cell lines (Fig. 4B). These results are in line with colocalization of ErbB2 with the active

Figure 5. Nuclear ErbB2 increases protein synthesis and cell size. A, left, total protein contents from equal cell numbers of MCF-7 and HER18 cells were determined by the Bradford method. Right, 35S-methionine labeling of protein synthesis in equal cell numbers of MCF-7 and HER18 cells was measured by scintillation counting. B, knockdown of ErbB2 by using siRNA results in decreased protein biosynthesis. Cells transfected with ErbB2 or NS siRNAs were monitored for total protein concentration (left, top) and 35S-methionine incorporation (right, top) as analyzed in (A). ErbB2 protein knockdown was confirmed by Western blotting (bottom). C and D, total protein level and cell size are increased in WT ErbB2 expressing cells but not in cells expressing ErbB2ΔNLS mutant. MCF-7 and MDA-MB-231 cells expressing WT ErbB2. ErbB2ΔNLS mutant, or vector control were assayed for total protein synthesis (C, top) and ErbB2 protein expression (C, bottom) as in (B). Cells were also analyzed by flow cytometry to detect DNA content and cell size of G1-, S-, and G2-M phase cells by using the parameter mean FSC-H, which is a measure of relative cell size (D). P value was analyzed by Student’s t test.

Pol III transcription, α-amanitin, a specific inhibitor of RNA Pol II and III transcription was used to treat cells while performing the in situ run-on transcription assays. The results showed reduced BrU-labeled nascent nuclear RNA level in the presence of α-amanitin (Fig. 3C); however, the residual BrU-labeled nascent nuclear RNA, which represented Pol I transcribed RNA and is known to be localized in the nucleoli, was still detectable. Overlapping imaging also showed BrUTP and ErbB2 colocalization in the nucleoli, strongly revealing that nuclear ErbB2 resides in the active RNA Pol I transcription sites and may play a novel role in modulation of RNA Pol I transcription apart from its RNA Pol II–associated function (29). In support of this notion, increased expression of ErbB2 also augmented pre-rRNA synthesis (Fig. 3D, left) and BrU-labeled newly synthesized RNA levels (Fig. 3D, middle) compared with cells that express basal levels of ErbB2. Note that HER18 is an ErbB2 stable transfecant of MCF-7 cells. These results were further supported by a dose–dependent enhancement in pre-rRNA synthesis caused by increasing amounts of ErbB2 (Fig. 3D, right). Furthermore, wild-type (WT) ErbB2 with RNA Pol I binding ability greatly enhanced pre-rRNA synthesis (Fig. 3E, lanes 2 and 5). However, ErbB2 whose nuclear localization signal (NLS) was mutated, ErbB2ΔNLS mutant, which is known defect in nuclear translocation (33), exhibited impaired RNA Pol I binding and less enhancement on pre-rRNA synthesis (Fig. 3E, lanes 3 and 6). The results were consistent in all 3 cell lines tested. Together, the results suggest that ErbB2 localizes in the nucleoli and increases RNA Pol I transcription in vivo.

ErbB2 enhances binding of RNA Pol I to rDNA and associates with rDNA during RNA Pol I transcription in vivo

Recent studies have shown that β-actin and RNA Pol I are associated with the promoter and the coding region of the rDNA (34), which are required for the rRNA gene transcription. To investigate the mechanism underlying ErbB2-mediated augmentation of RNA Pol I transcription, we performed ChIP or quantitative ChIP (qChIP) assays and found that increasing level of ErbB2 caused an enhanced association of RNA Pol I with rDNA promoter and the 28S rRNA transcribed region (Fig. 4A, left). However, knocking down ErbB2 resulted in diminished occupancy of RNA Pol I at rDNA gene (Fig. 4A, right). These data indicate that ErbB2 enhances the binding of RNA Pol I to rDNA. Since ErbB2 associates with β-actin and RNA Pol I in vivo (Fig. 1 and Fig. 2), raising the possibility that ErbB2 may be involved in the complex binding to rDNA; indeed, ChIP assays showed that ErbB2, similar to β-actin and RNA Pol I, associated with the 5′-terminal part of rDNA containing promoter and the 28S rRNA transcribed region in multiple ErbB2–expressing breast cancer cell lines (Fig. 4B). These results are in line with colocalization of ErbB2 with the active...
RNA Pol I transcription sites within nucleoli (Fig. 3B and C). To further elucidate whether ErbB2 occupies rDNA together with β-actin and RNA Pol I, the sequential ChIP experiments using ErbB2 or control mIgG antibodies for first ChIP followed by antibodies against ErbB2 or control mIgG antibodies for second ChIP with antibodies against RNA Pol I transcription sites within nucleoli (Fig. 3B and C). To further elucidate whether ErbB2 occupies rDNA together with RNA Pol I transcription sites within nucleoli (Fig. 3B and C). To further elucidate whether ErbB2 occupies rDNA together with RNA Pol I transcription sites within nucleoli (Fig. 3B and C).

**Nuclear ErbB2 enhances protein synthesis and cell size**

It is known that regulation of rRNA transcription by RNA Pol I is an essential cellular process for ribosome biogenesis. The extent of rRNA gene transcription reflects the cellular need for protein synthesis demanded by cell growth. Hence, it is a fundamental step in controlling the capability of protein synthesis, and thereby cell growth (1–5). To validate the biological significance of ErbB2-enhancing RNA Pol I-mediated rRNA synthesis, we therefore analyzed total protein content and protein biosynthetic rate. Total protein level was dependent on active transcription. Taken together, these results reveal that ErbB2 enhances binding of RNA Pol I to rDNA and associates with rDNA concomitantly with β-actin and RNA Pol I in vivo, which is relied on the proceeding transcription. These data support our finding that nuclear ErbB2 increases rDNA transcription by RNA Pol I (Fig. 3).
ErbB2 Enhances rRNA Transcription and Translation

results that pre-rRNA synthesis was visibly increased in WT ErbB2 expressing cells but not in cells expressing ErbB2ΔNLS mutant (Fig. 3E). Together, these results indicate that nuclear ErbB2 enhances total protein synthesis and cell size, suggesting that nuclear ErbB2 may power cell growth advantage and tumorigenesis by increasing rRNA and protein synthesis.

**ErbB2-potentiated RNA Pol I transcription can be stimulated by ligand and is independent of PI3-K and ERK pathways**

To further address whether the observed ErbB2-mediated pre-rRNA synthesis is physiologically relevant, we examined the 45S pre-rRNA synthesis in cells that were stimulated by a ligand able to induce ErbB2 nuclear localization (Fig. 6E). Indeed, elevation of ErbB2 nuclear translocation by HRG (refs. 39, 40; Fig. 6A), an ErbB2 activator that induces ErbB2 nuclear translocation–enhanced pre-rRNA synthesis in multiple ErbB2–expressing breast cancer cell lines (Fig. 6B and C, left). Remarkably, 45S pre-rRNA levels were not significantly reduced by inactivation of PI3-K and MEK/ERK, the major ErbB2 downstream signaling cascades. Consistently, total protein content was apparently increased in cells treated with HRG compared with cells without HRG treatment, and was not inhibited by PI3-K inhibitor LY294002 and MEK inhibitor U0126 (Fig. 6B and C, middle). In addition, as shown in Figures 3D and 5A, increased expression of ErbB2 augmented pre-rRNA and total protein synthesis (Figs. 3D, left and 5A), similarly, U0126 and LY294002 also do not affect the over-expressed ErbB2-induced increase in pre-rRNA synthesis and total protein production (Supplementary Fig. S5). Collectively, these results indicate that nuclear ErbB2–augmented RNA Pol I transcription can be stimulated by ligand and is independent of its downstream PI3-K and ERK signaling pathways.

**Discussion**

Deregulation of translational control can promote cellular transformation. Protein synthesis and the expression of components of the translation machinery are elevated in cancers and contribute to tumorigenesis (1–5, 7). Here, we show that nuclear ErbB2 promotes binding of RNA Pol I to rDNA, co-occupies the rRNA gene with β-actin and RNA Pol I, and stimulates rRNA production and protein translation independently of traditional ErbB2 downstream PI3-K and ERK signalings, suggesting that nuclear ErbB2 may contribute to oncogenesis by upregulating total cellular translation. rRNA synthesis by RNA Pol I plays a critical role in production of mature ribosomes that are central protein synthesis machinery of the cells. Perturbation of RNA Pol I activity as well as rRNA and protein biosynthesis (i.e., translation control) by oncoproteins such as Myc or tumor suppressors p53, RB, and ADP ribosylation factor has been reported to be associated with tumor development (1, 2, 7–10). The capability of Myc to increase protein synthesis is necessary for its oncogenic activity (7). In support of this notion, our findings also manifest the importance of nuclear ErbB2–coordinated rRNA and protein synthesis to tumor biology. In addition, although ErbB2 is known to activate both the MAPK and PI3-K pathways and inhibitors of both pathways (such as AZD6244 and MK2206) have been tested in clinical trials, our current report shows that nuclear ErbB2–potentiated RNA Pol I transcription was not suppressed by inhibition of PI3-K and MEK/ERK, increasing the interesting possibility of whether ErbB2-mediated rRNA transcription might contribute to acquired resistance to clinically used inhibitors of the MAPK and PI3-K pathways.

It is worth mentioning that β-actin, which is originally considered as a cytoplasm protein, also exists in the nucleus and has been shown to be involved in diverse nuclear activities including RNA Pol I transcription (34). Our results show that knocking down β-actin by using siRNA impairs association between ErbB2/RNA Pol I and reduces the level of ErbB2 binding to rRNA gene. Whereas inhibition of RNA Pol I transcription using Act. D, which impedes Pol I transcription by reduced binding of Pol I to DNA, decreases the rRNA gene occupancy of ErbB2 and RNA Pol I, but exerts no impact on β-actin binding to rDNA (Fig. 4E), which is consistent with a previous study, showing that association of β-actin with rDNA does not require ongoing transcription (41). These findings suggest that β-actin is necessary but not sufficient for rDNA association of ErbB2, which also depends on active RNA Pol I transcription. Furthermore, ErbB2, similar to RNA Pol I and β-actin (34), occupies both the rDNA promoter and 28S rDNA coding region, implying that ErbB2 may play a role both in early and later stages (likely elongation) of transcription. It should be mentioned that ErbB2 is a tyrosine kinase and the β-actin/rDNA Pol I complex contains multiple proteins, it will be interesting to further pursue whether ErbB2 might phosphorylate some components of the β-actin/ RNA Pol I complex to affect RNA Pol I transcriptional activity.

Thus, on the basis of our results, we propose a model (Fig. 7), hypothesizing that ErbB2 enhances binding of RNA Pol I to rDNA and co-occupies rDNA together with β-actin and RNA Pol I, progressing along with these factors in early and elongation steps of transcription, expediting rRNA synthesis and protein translation, and thereby promoting cell growth and tumorigenesis. To the best of our knowledge, our discovery for the first time links the nuclear ErbB2 to a novel function in
regulating cellular translation and provides insights into the possible mechanism by which nuclear ErbB2 modulates tumor development through enhancing protein translation.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

We thank S.A. Miller for editing the manuscript.

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Grant Support

This work was supported by grants from NSC95-2311-B-039-002-NHRI-EX99-9603B, DOH99-TD-I-111-TM026, NSC99-3111-B-039-001-L-Y Li, NIH RO1 CA109311, DOD COE W81XWH-06-2-0033 (M.-C. Hung), and NSC98-3111-B-039-DOH100-TD-C-111-005, and NSC98-3652-B-039-001-MT3 (M.-C. Hung and L.-Y. Li).

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Received September 27, 2010; revised April 12, 2011; accepted April 21, 2011; published OnlineFirst May 9, 2011.
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Cancer Res 2011;71:4269-4279. Published OnlineFirst May 9, 2011.

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