Regulation of Survivin by ErbB2 Signaling: Therapeutic Implications for ErbB2-Overexpressing Breast Cancers

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Abstract

In breast cancer, overexpression of ErbB2 or aberrant regulation of survivin, a member of the inhibitor of apoptosis family, is associated with resistance to chemo/hormone therapy and predicts for a poor clinical outcome. A functional link between the two predictive factors has not been previously shown. Here, using genetic and pharmacologic approaches to block ErbB2 signaling, we show that ErbB2 regulates survivin protein expression in ErbB2-overexpressing breast cancer cells. Selective knockdown of ErbB2 using small interfering RNA markedly reduced survivin protein, resulting in apoptosis of ErbB2-overexpressing breast cancer cell lines such as BT474. Alternatively, inhibition of ErbB2 signaling using lapatinib (GW572016), a reversible small-molecule inhibitor of ErbB1/ErbB2 tyrosine kinases, at pharmacologically relevant concentrations, leads to marked inhibition of survivin protein with subsequent apoptosis. The effect of lapatinib on survivin seems to be predominantly posttranslational, mediated by ubiquitin-proteosome degradation as lactacystin, a proteosome inhibitor, reverses these effects. Furthermore, lapatinib down-regulated the expression of Hs-tagged survivin, which was under the transcriptional control of a heterologous promoter, providing additional evidence supporting a posttranslational mechanism of regulation. In contrast, trastuzumab and gefitinib failed to down-regulate survivin in ErbB2-overexpressing breast cancer cells. Importantly, the clinical relevance of these findings was illustrated in patients with ErbB2-overexpressing breast cancer whose clinical response to lapatinib was associated with marked inhibition of survivin in their tumors. These findings shed new light on the mechanism by which ErbB2 overexpression protects against apoptotic stimuli in breast cancer and identifies therapeutic interventions to improve clinical outcomes in these aggressive tumors. (Cancer Res 2006; 66(3): 1640-7)

Introduction

Aberrant expression of survival factors protects tumors from cell death following activation of intrinsic or extrinsic apoptotic pathways. Among the major gene families regulating cell survival are the inhibitor of apoptosis proteins (IAP), which consists of eight family members (1). Members of the IAP family protect against apoptosis by either directly or indirectly inhibiting activation of effector caspases (1–4). Included among the most common transcripts selectively expressed in tumors, but not in normal tissue, is survivin, the smallest IAP family member (5, 6). Expression of survivin in tumors correlates with a poor clinical outcome in a variety of malignancies including breast cancer (5, 7, 8).

In nonmalignant proliferating cells, expression of survivin protein is regulated in a cell cycle–dependent manner, transiently up-regulated during G2-M, followed by its rapid down-regulation on entry into G1 phase (9–11). Survivin regulates two critical activities during G2-M. First, it enables cell cycle progression by associating with and stabilizing components of the mitotic spindle apparatus (12–15). And second, by maintaining the integrity of the mitotic spindle, survivin protects against apoptosis triggered by activation of the mitotic spindle checkpoint (16). Induction of survivin during G2-M is primarily transcriptionally regulated (9) whereas its down-regulation on entry into G1 is both transcriptional and posttranslational, the latter mediated by the ubiquitin-proteosome pathway (17). Increased survivin protein in tumors does not seem to be solely cell cycle dependent as it occurs in tumor cells that are not actively cycling (18).

Members of the ErbB family of transmembrane tyrosine kinase receptors promote tumor cell growth and survival. Overexpression or gene amplification of ErbB2 (Her-2/neu), which occurs in 20% to 30% of breast cancers, predicts for a poor clinical outcome and resistance to chemo- and hormonal therapies (19, 20). On binding a cognate ligand, ErbB receptors undergo homodimerization or heterodimerization and autophosphorylate cytoplasmic tyrosine residues that serve as binding sites for proteins containing Src homology 2 and phosphotyrosine-binding domains, which in turn link activated ErbB receptors to downstream proliferation [e.g., mitogen-activated protein kinase (MAPK)-extracellular signal-regulated kinase (Erk) 1/2] and survival [e.g., phosphatidylinositol 3-kinase (PI3K)-Akt] pathways (21). ErbB2, which lacks an exogenous ligand, is the preferred partner for other ErbB receptors amplifying the biological signal emanating from ErbB2-containing heterodimers (22, 23). Although the exact mechanism(s) is unknown by which ErbB2 overexpression protects tumors against chemotherapy, it has largely been attributed to activation of the PI3K-Akt survival pathway, which is concomitantly up-regulated in ErbB2-overexpressing breast cancer cells (24–27). Furthermore, ErbB2 heterodimerizes with ErbB3, the latter lacking intrinsic autokinase activity and requiring transactivation through interactions with its ErbB partner (28). ErbB3 contains six PI3K binding sites, making ErbB2/ErbB3 heterodimers among the most potent activators of the PI3K-Akt pathway (29–32).
Here we show that survivin is regulated by ErbB2 and ErbB3, but not by ErbB1. Interrupting ErbB2/ErbB3 heterodimer signaling using RNA interference or lapatinib (GW572016; ref. 33), a potent small-molecule inhibitor of ErbB1 and ErbB2 tyrosine kinases, down-regulates survivin and induces apoptosis in ErbB2-overexpressing breast cancer cell lines and in primary tumors. Moreover, down-regulation of survivin by lapatinib is largely mediated by proteosome-dependent degradation. Our results provide insight into the mechanism(s) by which ErbB2 overexpression protects breast cancers from apoptosis and identifies therapeutic strategies to improve clinical outcomes in these aggressive tumors.

Materials and Methods

Cell culture and reagents. BT474, SKBR3, and AU565 cells were from the American Tissue Culture Collection (Manassas, VA). BT474, SKBR3, and AU565 cells were maintained in RPMI 1640 supplemented with 10% fetal bovine serum and 1-glucose. The LICR-LON-HNS (HNS) cell line (kindly provided by Helmut Modjtahedi at the Institute of Cancer Research, Surrey, United Kingdom) were maintained in DMEM with high glucose and 10% FCS. Cells were maintained in a humidified atmosphere of 5% CO2 at 37°C. The following antibodies were purchased for Western blot: survivin from R&D Systems (Minneapolis, MN); phosphotyrosine and actin from Sigma-Aldrich (St. Louis, MO); ErbB1 (Ab-12) and ErbB2 (Ab-11) from LabVision (Fremont, CA); p-Akt (Ser473) from Cell Signaling Technology (Beverly, MA); and Akt, p-Erk1/2, Erk1/2, and p-Erk1/2 from Santa Cruz Biotechnology (Santa Cruz, CA). Terminal deoxynucleotidyl transferase–mediated dUTP nick end labeling (TUNEL) assay from Roche Diagnostics (Indianapolis, IN) was done according to the instructions of the manufacturer. Lapatinib or N-[3-chloro-4-[(3-fluorobenzyl)oxy]phenyl]-6-[5-([2-(methylsulfonyl)ethyl]amino)methyl]-2-furyl]-4-quinazolinamine was synthesized as previously described (33). Lapatinib for cell culture work was dissolved in DMSO (34). Lactacystin was purchased from BioSource (Camarillo, CA); LY294002 and PD98059 were purchased from Calbiochem (La Jolla, CA).

siRNA preparation and transfection. Twenty-one-nucleotide small interfering RNAs (siRNA) targeting survivin (accession no. NM_0011681) and its appropriate nonsilencing control were synthesized by Qiagen (Valencia, CA). Both siRNAs were synthesized using 2'-OM-phosphoramide chemistry, deprotected, and high protein purity purified. The survivin targeting sequence (5'-GCAUUCGUCGGUGGCGCU-3') corresponds with position 286, relative to the first nucleotide of the start codon. The nonsilencing control (5'-UUCUCGGAACGUGACCUAG-3') is a random sequence with 16-base overlap to Thermotoga maritima, and no other matches, siRNA SMARTpools generated using 2'-ACE chemistry targeting ErbB2 (accession no. AF077350), ErbB3 (accession no. NM_002288), and ErbB1 (accession no. NM_002288), along with the siControl, were purchased from Pharmacia Research (Fremont, CA). RNAi liposomes were generated using Lipofectamine 2000 from Gibco/Invitrogen (Carlsbad, CA) complexed with Dharmacon Research (Lafayette, CO). RNAi liposomes were generated using Lipofectamine 2000 from Gibco/Invitrogen and transferred to polyvinylidene difluoride membranes. Blots were blocked for 1 hour in 10% milk in PBS-T [PBS-calcium magnesium-free (PBS-CMF)/0.1% Tween 20], then incubated for 16 hours at 4°C in primary antibody in blocking buffer. After four washes in PBS-T, the blots were incubated in horseradish peroxidase–conjugated secondary antibody or antirabbit from Jackson ImmunoResearch Labs (West Grove, PA) at a 1:2,000 dilution for 1 hour. Blots were again washed four times and signals were detected using enhanced chemiluminescence from Amersham Biosciences (Piscataway, NJ).

Results

Modulation of survivin in response to inhibition of ErbB2 signaling in breast cancer cells. Although the effects of ErbB2 on growth and survival pathways have been extensively studied in breast cancer cells, the exact mechanism(s) by which overexpression of ErbB2 protects against apoptosis is not completely understood. Both ErbB2 overexpression and deregulation of survivin predict a poor clinical outcome in breast cancer, making it tempting to speculate that the two are related. To address this possibility, we used two strategies. First, we genetically depleted survivin using its siRNA construct (Sur286) that reduced levels of survivin protein by 90% in ErbB2-overexpressing BT474 breast cancer cells compared with a control siRNA construct (NSC; Fig. 1A). Treatment with Sur286 resulted in a 3-fold increase in apoptosis (<2N DNA content) compared with NSC-treated cells (Fig. 1B). Exposure to Sur286 also increased the percentage of cells in G2-M phase as well as those exhibiting polyplody (>4N; Fig. 1B). The selectivity of Sur286 was shown by its lack of effect on other cellular proteins (e.g., Erk1/2; Fig. 1A). In addition, nonspecific induction of IFN, which has been associated with survivin, was not observed with our siRNA constructs (data not shown). Thus, in contrast to other tumor cell lines that primarily undergo cell cycle arrest (12, 36), depleting survivin in ErbB2-overexpressing breast cancer cells induced apoptosis.
If survivin is regulated by ErbB2, then blocking ErbB2 signaling might modulate expression of survivin and affect cell survival. Selective ErbB2 depletion using siRNA not only down-regulated survivin (Fig. 1C) but also increased apoptosis in BT474 cells in a time-dependent manner (Fig. 1D), establishing a functional link between ErbB2, survivin, and cell survival. Cells exposed to a control pool of siRNA (siPool) served as controls.

ErbB2 is one of four ErbB receptor family members (ErbB1-4; ref. 21). ErbB3, which lacks intrinsic autokinase activity, heterodimerizes with ErbB2, forming a receptor complex that potently activates the PI3K survival pathway (29–32). Similar to ErbB2, selective depletion of ErbB3 using ErbB3 siRNA (Fig. 1C) enhanced apoptosis of BT474 cells in a time-dependent manner (Fig. 1D). As a consequence of depleting ErbB3, steady-state survivin and p-Akt protein levels were markedly reduced (Fig. 1C), implicating both ErbB2 and ErbB3, possibly through ErbB2/ErbB3 heterodimers, in the regulation of survivin.

ErbB1 (epidermal growth factor receptor) is highly homologous to ErbB2 and frequently expressed in epithelial tumors (21). To determine whether ErbB1 also regulates survivin, we genetically depleted survivin in HN5 cells, a head and neck carcinoma line that predominantly expresses ErbB1 and relatively less ErbB2 and ErbB3 (34). In contrast to BT474, exposing HN5 cells to Sur286 did not increase apoptosis but instead triggered a 6-fold increase in the percentage of cells exhibiting polyploidy and a concomitant increase in the percentage of cells arrested in G2-M compared with cells exposed to a control siRNA (siPool; Fig. 2A). Moreover, siRNA depletion of ErbB1 did not affect survivin or HN5 cell survival (Fig. 2A and B), suggesting that ErbB1 might not play a significant role in regulating survivin or cell survival in these cells.

To examine the potential clinical relevance of the association between survivin and ErbB receptors, expression of survivin was analyzed by immunohistochemistry in 202 breast cancer biopsies with varying degrees of ErbB1, ErbB2, and ErbB3 protein expression. Expressions of survivin, ErbB1, ErbB2, and ErbB3 proteins were scored according to the intensity of staining (e.g., 0, 1, 2/3+) and analyzed for statistical correlation. No association was found between survivin and ErbB1 protein expression ($P = 0.2678$;
Supplementary Table S1). In contrast, increased survivin protein expression (e.g., 2/3+) correlated with increased ErbB2 and ErbB3 protein expression with P values of 0.0528 and 0.0039, respectively (Supplementary Figs. S1-3 and Table S1). Thus, the relationship between ErbB2 and ErbB3 overexpression, but not ErbB1, and increased survivin in ErbB2-overexpressing tumor cell lines was also relevant in primary breast cancers.

An ErbB2 tyrosine kinase inhibitor down-regulates survivin, inducing apoptosis. The second strategy to study the relationship between ErbB2 and survivin was a pharmacologic one. We previously showed that inhibition of ErbB receptor signaling using lapatinib (GW572016), a reversible inhibitor of ErbB1 and ErbB2 tyrosine kinases, induced apoptosis of ErbB2-overexpressing breast cancer cell lines and primary tumors (34, 35, 37). The effects of lapatinib on survivin were shown by Western blot analysis wherein survivin steady-state protein levels were inhibited in a concentration- and time-dependent manner in two ErbB2-overexpressing breast cancer cell lines and primary tumors (34, 35, 37). The effects of lapatinib on survivin were shown by Western blot analysis wherein survivin steady-state protein levels were inhibited in a concentration- and time-dependent manner in two ErbB2-overexpressing breast cancer cell lines and primary tumors (34, 35, 37). The effects of lapatinib on survivin were shown by Western blot analysis wherein survivin steady-state protein levels were inhibited in a concentration- and time-dependent manner in two ErbB2-overexpressing breast cancer cell lines and primary tumors (34, 35, 37). The effects of lapatinib on survivin were shown by Western blot analysis wherein survivin steady-state protein levels were inhibited in a concentration- and time-dependent manner in two ErbB2-overexpressing breast cancer cell lines and primary tumors (34, 35, 37).

To determine whether these observations were generalized to other ErbB-targeted therapies, we next assessed the effects of two ErbB2-targeted therapies on survivin. The first, trastuzumab, is a humanized anti-ErbB2 monoclonal antibody approved for treating patients whose tumors overexpress ErbB2 or exhibit ErbB2 gene amplification (38). Trastuzumab had little effect on cell survival or steady-state survivin protein levels in BT474 cells (Fig. 3A). The second, gefitinib, a small-molecule inhibitor of ErbB1 tyrosine kinase activity with reported antiproliferative activity in BT474 cells (39), did not significantly affect survivin in BT474 cells compared with lapatinib (Fig. 3C).

Regulation of survivin by lapatinib is dependent on the proteosome. If the down-regulation of survivin plays a role in lapatinib-induced apoptosis, then overexpressing survivin might protect cells from the antitumor activity of lapatinib. Moreover, if the regulation of survivin by lapatinib is solely transcriptionally mediated, then lapatinib would not be expected to reduce His-tagged survivin protein, which is under the transcription control of a heterologous promoter. To this end, we established stably transfected SKBR3 cell lines expressing His-tagged survivin under the transcriptional control of a heterologous CMV promoter. As shown, induction of apoptosis by lapatinib was unaffected by the expression of His-tagged survivin (Fig. 4A and B). Protein levels of His-tagged (dotted line) and endogenous (solid line) survivin were equally down-regulated in response to lapatinib (Fig. 4B), implicating the posttranscriptional mechanism by which lapatinib regulates survivin.

The ubiquitin-proteosome pathway plays an important role in regulating apoptosis (40). ErbB2 regulates CXCR4, p53, and the androgen receptor through proteosome-dependent proteolysis (13, 25, 41), making it tempting to speculate that lapatinib regulation of survivin might also be dependent on the ubiquitin-proteosome pathway. Lactacystin, a specific proteosome inhibitor, reversed lapatinib-mediated down-regulation of survivin (Fig. 5, lane 5), suggesting that the effects of ErbB2/ErbB3 signaling on survivin are in part dependent on proteosome degradation.

The role of PI3K in mediating the effects of lapatinib on survivin. In hematopoietic and endothelial cells, regulation of survivin has been linked to MAPK-Erk and PI3K-Akt signaling pathways (42, 43). Blocking ErbB2 signaling using either siRNA or lapatinib abrogates downstream MAPK-Erk1/2 and PI3K-Akt signaling (34, 37). To determine the downstream pathways involved in the regulation of survivin by ErbB2, we used specific MAPK/Erk kinase (MEK) and PI3K inhibitors or combinations thereof. Steady-state survivin protein levels were reduced in BT474 cells treated with the PI3K inhibitor LY294002 (10 μmol/L), similar to that achieved using lapatinib alone (Fig. 6). In contrast, the MEK1 inhibitor PD98059 (10 μmol/L) had relatively little effect on survivin (Fig. 6). Based on these results, we propose that lapatinib regulates survivin primarily through its inhibition of PI3K signaling rather than MAPK. However, siRNA knockdown of Akt (simultaneous knockdown of Akt1, Akt2, and Akt3) in BT474 cells did not affect survivin protein levels (Supplementary Fig. S4). These findings suggest that the regulation of survivin by lapatinib seems to be PI3K dependent but primarily Akt independent.

Because ErbB2/ErbB3 heterodimers potently activate the PI3K pathway (29–32), we next examined the effect of ablating ErbB2 kinase activity on the activation state of ErbB3. Steady-state protein levels of activated p-ErbB3 were markedly reduced following ErbB2-targeted siRNA, resulting in the inhibition of PI3K signaling as reflected by a reduction in p-Akt expression (Fig. 1C).

Inhibition of survivin in primary tumors correlates with clinical response to lapatinib. To determine if the regulation of survivin by ErbB2 occurs in primary tumor tissue, we did quantitative immunohistochemical analysis on tumor biopsies
obtained from patients with metastatic tumors overexpressing ErbB2 and/or expressing ErbB1, who were treated with lapatinib as part of a phase I clinical trial, the results of which were recently described (35). Fresh tumor biopsies were obtained before and after 21 days of lapatinib therapy. Stained tissue sections were computer analyzed and a mean absorbance score representative of the intensity of staining was assigned to each biopsy. Decreased survivin protein expression at day 21 correlated with tumor regression and clinical response to lapatinib. Figure 7 shows the effects of lapatinib therapy on survivin and TUNEL in one of the patients—all of whom had ErbB2-overexpressing breast cancers—who responded by achieving a partial remission (35). The effects of lapatinib on survivin were representative of the effects of lapatinib in the other four responders (Supplementary Table S2). As shown, survivin was reduced by 90% compared with pretreated biopsies after only 21 days of lapatinib therapy, with a concomitant increase in tumor cell apoptosis (TUNEL-positive cells; Fig. 7). The effects of lapatinib on survivin were examined in an additional four nonresponders and shown to be essentially unchanged, along with an absence of tumor cell apoptosis (data not shown).

Discussion

Breast cancers that overexpress ErbB2 or exhibit deregulation of survivin protein have a poor clinical outcome (8, 19, 20). To date, a functional link between these two key prosurvival factors has not been shown. The underlying mechanism(s) responsible for the ant apoptotic effects of ErbB2 overexpression has largely been attributed to the concomitant up-regulation of the PI3K-Akt survival pathway (24–27). We now show that ErbB2 regulates survivin protein in ErbB2-overexpressing breast cancer cells, providing protection against apoptotic stimuli.

Inhibition of ErbB2 kinase using genetic (siRNA) or pharmacologic (lapatinib) interventions triggered apoptosis in ErbB2-overexpressing breast cancer cells (Figs. 1 and 3). Growth and survival signals elicited by activated ErbB2 are largely mediated via PI3K-Akt and Ras-MAPK signaling pathways. Using specific PI3K inhibitors, we have shown that inhibition of ErbB2 kinase reduces survivin expression and induces apoptosis in ErbB2-overexpressing breast cancer cells (Figs. 1 and 3). These findings provide a potential rationale for the use of ErbB2 kinase inhibitors in the treatment of breast cancer patients with ErbB2-overexpressing tumors.
and MEK inhibitors, we were able to show that PI3K signaling, rather than MAPK-MEK, reproduces the effects of lapatinib on survivin, suggesting that the effect of lapatinib on survivin is likely to be mediated in part through PI3K inhibition as a consequence of ErbB2 inactivation. Because ablation of ErbB3 also down-regulated survivin and induced apoptosis, we propose that ErbB2/ErbB3 heterodimers, through their potent activation of PI3K signaling, modulate survivin protein expression in ErbB2-overexpressing breast cancer cells. The exact role of Akt in this process remains to be determined. However, it seems that down-regulation of survivin and tumor cell apoptosis may occur without affecting p-Akt expression (35, 44). Possible PI3K-dependent, but Akt-independent, mechanisms by which lapatinib might regulate survivin include effects on serum- and glucocorticoid-induced kinases (SGK), which are serine/threonine kinases that are highly homologous to Akt and also regulated by PI3K (45–47). Although the effects of SGK on survivin have not been studied, SGK regulates cell survival (47) and may therefore be a candidate for regulating survivin protein expression. In addition, PI3K affects cell survival through a protein kinase C–dependent pathway that is mediated by phospholipase Cγ activity (48). Thus, it is possible that lapatinib regulates survivin in part through PI3K-dependent effects on SGK or phospholipase Cγ. This might provide an explanation about why survivin was down-regulated and tumor cell apoptosis increased in some patients who responded clinically to lapatinib without a change in p-Akt expression (35).

Using His-tagged survivin under the control of a heterologous CMV promoter, we were able to show that the regulation of survivin by lapatinib was in large part posttranscriptional. Down-regulation of survivin on entry to G1 is dependent on the ubiquitin–proteosome pathway (17). Moreover, ErbB2 regulates a number of key molecules involved in tumor metastasis, growth, and survival through ubiquitination and proteosome-dependent degradation (13, 25). Reversal of lapatinib-induced down-regulation of survivin by lactacystin, a selective inhibitor of the proteosome, is consistent with ErbB2 regulation of survivin through the ubiquitin–proteosome pathway. Elucidating the role of the proteosome in mediating the effects of ErbB2 on survivin and identifying the E3-ligase responsible for survivin ubiquitination could provide novel therapeutic strategies to more effectively treat patients with ErbB2-overexpressing tumors.

Deregulated expression of survivin occurs in tumors other than ErbB2 overexpressing breast cancers (5, 6). Lapatinib is
equally effective in inhibiting ErbB2 and ErbB1 tyrosine kinases. However, we were unable to establish the role of ErbB1 in regulating survivin or the role of survivin in regulating cell survival in ErbB1-dependent tumor lines. With the exception of tumors that express gain-of-function ErbB1 mutations (e.g., glioblastoma multiforme and non–small cell lung cancer with bronchioalveolar carcinoma features), the role of ErbB1 in regulating tumor cell survival, including breast cancer, has been questioned. The relevance of ErbB2, and in particular ErbB2/ErbB3 heterodimers, rather than ErbB1 in promoting tumor cell survival seems to be a common theme in a variety of epithelial carcinomas (41). The absence of an apparent link between ErbB1, survivin, and cell survival provides a possible explanation about why the majority of breast cancers do not seem to be dependent on ErbB1 signaling for survival and why inhibitors with predominant activity against ErbB1 have thus far lacked significant clinical activity in breast cancer (49).

In a phase Ib clinical trial, the four responding patients to lapatinib monotherapy all had ErbB2-overexpressing breast cancers (35). We had sufficient tumor tissue to assess the effects of lapatinib on survivin in the four responders where marked inhibition of survivin protein expression correlated with the induction of tumor cell apoptosis and clinical response. Although intriguing, these findings are based on a small sample and will require confirmation in subsequent clinical trials with larger numbers of tissue samples.

In summary, aberrant regulation of survivin in ErbB2-overexpressing breast cancer cell lines and primary tumors is reversible using a small-molecule kinase inhibitor like lapatinib. In certain situations, down-regulation of survivin alone will be sufficient to induce spontaneous tumor cell apoptosis. In others, it might be sufficient to sensitize tumors to the killing effects of additional anticancer cytotoxic agents. The ability of ErbB-targeted therapies to modulate survivin should be taken into consideration when selecting targeted therapies to combine with anticancer cytotoxic agents because not all ErbB-targeted therapies down-regulate survivin. This is particularly relevant to combination therapies wherein many anticancer cytotoxic agents increase survivin in tumors, potentially contributing to the development of resistance (50, 51). Elucidating the regulation and role of survivin in ErbB2 and ErbB3 signaling pathways will hopefully lead to improved treatment options for patients whose tumors are dependent on these pathways for their survival.

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