API5 Confers Tumoral Immune Escape through FGF2-Dependent Cell Survival Pathway

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Abstract

Identifying immune escape mechanisms used by tumors may define strategies to sensitize them to immunotherapies to which they are otherwise resistant. In this study, we show that the antiapoptotic gene API5 acts as an immune escape gene in tumors by rendering them resistant to apoptosis triggered by tumor antigen-specific T cells. Its RNAi-mediated silencing in tumor cells expressing high levels of API5 restored antigen-specific immune sensitivity. Conversely, introducing API5 into API5low cells conferred immune resistance. Mechanistic investigations revealed that API5 mediated resistance by upregulating FGF2 signaling through a FGFR1/PKCδ/ERK effector pathway that triggered degradation of the proapoptotic molecule BIM. Blockade of FGF2, PKCδ, or ERK phenocopied the effect of API5 silencing in tumor cells expressing high levels of API5 to either murine or human antigen-specific T cells. Our results identify a novel mechanism of immune escape that can be inhibited to potentiate the efficacy of targeted active immunotherapies. Cancer Res; 74(13); 3556–66. ©2014 AACR.

Introduction

Despite the presence of a competent immune system, tumor cells may elude detection from host immune surveillance through a process of cancer immune editing. In this process, elimination of tumor cells sensitive to host immune attack leads to the selection and survival of immune-resistant cancer cells. For this reason, immune-based strategies can engender an initial response, but recurrences are common as immune-resistant tumor cell variants develop under immunoselective pressure. Extrinsic mechanisms associated with upregulation of immunosuppressive cytokines such as TGFβ and IL10 and the accumulation of regulatory cells (1–4) can exacerbate the immune inhibitory milieu, whereas intrinsic genetic instability can generate cells resistant to immune eradication (5). Therefore, successful anticancer therapies depend on the control of tumor cell growth and their microenvironment along with strategies to overcome immune tolerance in patients. However, the current understanding of molecular mechanisms and signaling pathways underlying tumor immune evasion remains nascent and calls for the identification of master factors governing immune escape.

In an effort to elucidate potential targetable pathways of immune resistance and restore immune sensitivity, we dissected the immune resistance phenotype with the prospect of identifying a master gene regulating tumor immune escape. Our studies in the murine model utilized a highly immune-resistant cervical tumor cell subline, TC-1/P3/A17, generated by serial in vivo selection of its immune-susceptible parental cell line TC-1/P0 expressing the CTL target antigen, HPV16/E7 (6). This model allowed us to use E7-specific CTL to assess immune sensitivity both in vitro and in vivo tumor models. Comparative microarray analysis revealed selective overexpression of an antiapoptotic gene, apoptosis inhibitor 5 (API5), in the immune-resistant phenotype. Through a series of in vitro and in vivo assays assessing immune sensitivity, we found that API5 plays a critical role as a master regulator of tumor immune escape in mouse. We also validate the role of API5 as an immune escape factor in human cancer cells by using a CTL clone generated from patients with melanoma that recognizes an endogenous tumor-associated antigen, MART-1. Furthermore, we define a new pathway involved in API5-induced immune resistance that is dependent on the secretion of FGF2 and downstream FGFR1 receptor signaling, which...
triggers specific degradation of the proapoptotic molecule, BIM, by PKCδ-dependent ERK activation. Therefore, our data uncover a major axis of tumor immune resistance regulated by API5 and underline the necessity for combinatorial strategies that include targeting API5 to circumvent tumor immune resistance in patients with cancer.

Materials and Methods

Chemical kinase inhibitors

LY294002 (Calbiochem Corp) for PI3K, API-2 (Calbiochem Corp) for AKT, SB203580 (Calbiochem Corp) for p38, PD98059 (Stressgen) for ERK, and rottlerin for PKCδ were used to specifically suppress the activity of indicated kinases.

Flow-cytometric analysis and CTL assays

For in vitro CTL assays, 1 × 10⁴ E7-expressing or MART-1-expressing/HLA-A2–restricted M27 peptide pulsed tumor target cells were incubated with murine E7–specific CD8⁺ T cells or MART-1–specific human CD8⁺ T cells, respectively, at 1:1 ratio for 4 hours. The percentages of active caspase-3⁺ tumor cells were measured by flow cytometry to determine the level of apoptotic cell death. All analysis was performed using a Becton Dickinson FACScan with CELLQuest software (BD Biosciences).

Inhibition of BIM degradation

To measure the stability of BIM, MG132 (Calbiochem) was dissolved in DMSO and then added to a 0.1% FBS containing medium for 48 hours at 37°C. Because the resistance of Api5-expressing TC-1/P0 cells to CTLs could simply be due to inhibition of apoptosis or increased cell survival, the expression of pro- and antiapoptotic molecules was assessed by Western blot analysis (Fig. 2A). The protein levels of Xiap, Bcl-2, and Bcl-XL antiapoptotic molecules and Bad, Bak, Bax, and Bid proapoptotic molecules were comparable between TC-1/P0/Api5 and TC-1/P0/no insert cells. However, the expression of Bim, a proapoptotic protein, was substantially diminished in TC-1/P0/Api5 cells. Exposure to the proteasome inhibitor, MG 132, restored Bim levels in TC-1/P0/Api5 cells (Fig. 2B), indicating that Bim was undergoing restricted M27 peptide pulsed tumor expressing/HLA-A2–restricted tumor cells were measured by flow cytometry to determine the level of apoptotic cell death. All analysis was performed using a Becton Dickinson FACScan with CELLQuest software (BD Biosciences).

Inhibition of BIM degradation

To measure the stability of BIM, MG132 (Calbiochem) was dissolved in DMSO and then added to a final concentration of 25 μmol/L for 3 hours to inhibit proteasome activity.

Real-time quantitative RT-PCR

The total RNAs of the cells were isolated using TRIzol reagent (Invitrogen). First-strand synthesis were performed by using RT&Go Mastermix (MP Biomedicals) and real-time reagent (Invitrogen). First-strand synthesis were performed followed by adoptive transfer of E7-speciﬁc CTLs (Fig. 1B). Api5 was also overexpressed in murine cancer cells of skin and colorectal origin (B16 and CT26, respectively; Supplementary Fig. S2A). Downregulation of Api5 led to enhanced CTL-mediated killing, whereas forced expression in Api5-negative targets (EL-4) led to immune resistance to antigen-speciﬁc lysis (Supplementary Fig. S2B and S2C).

To confirm the role of Api5 as an immune escape factor in vivo, C57BL/6 mice were inoculated subcutaneously with A17 cells and administered either siApi5– or siGFP–loaded chitosan nanoparticles (CNP) starting 7 days after initial tumor challenge followed by adoptive transfer of E7–specific CD8⁺ T cells (Fig. 1C). As expected, mice receiving E7–specific CTL demonstrated poor control of tumor growth; however, combination with siApi5 restored the immune sensitivity, resulting in significantly lower tumor volumes (P < 0.05). Conversely, forced expression of Api5 in parental TC-1/P0 cells led to immune resistance and unchecked tumor growth in the presence of antigen-specific CTL (Fig. 1D). These results demonstrate that Api5 directly controls immune resistance in tumor cells both in vitro and in vivo.

FGF2 assessment of medium supernatants

The cells were grown in 6-well plates and incubated with 0.1% FBS containing medium for 48 hours at 37°C in a 5% CO2 incubator. Supernatants were collected and centrifuged to remove cell debris. FGF2 levels in the supernatants were determined by following the eBioscience FlowCytomix detection kit instructions. For Western blot analysis, supernatants were further concentrated in the 10 × by Centricon Plus-70 centrifugal Filter Units-10 kDa (Millipore).

Statistical analysis

All data are representative of at least three separate experiments. Nonparametric one-way or two-way ANOVA was performed with SPSS version 12.0 software (SPSS), depending on the data. Comparisons between individual data points were analyzed by Student t test. Where P value was less than 0.05, the result was considered significant.
posttranscriptional degradation. Furthermore, silencing Bim using siBim in TC-1/P0/no insert cells conferred resistance to CTL-mediated lysis (Fig. 2C). Because phosphorylation of Bim by MAPKs has been shown to be critical in the degradation of Bim via proteasomal pathway (7), we next investigated whether Bim and other members of MAPKs were activated in TC-1/P0/Api5 cells. Expression of the active form of Erk, Thr202/Tyr204-pErk, was found to be highly elevated in TC-1/P0/Api5 cells. Expression of human API5 (hAPI5) was investigated in several human tumor cell lines arising from various tissue types challenged with TC-1/P0/Api5 cells and intratumorally injected with PD98059-loaded chitosan hydrogel along with E7-specific CTL. Delivery of PD98059 almost completely restored immune sensitivity of TC-1/P0/Api5 to E7-specific CTL (Fig. 2G). Notably, PD98059 alone seemed to slightly reduce the tumor volume, but was not found to be statistically significant (P < 0.12). Taken together, these data corroborate the essential role of Erk in the degradation of Bim and the development of immune resistance in vivo.

**API5 regulates immune resistance in human tumor cells**

To explore the physiologic relevance of API5 in the development of immune resistance in patients with cancer, the expression of human API5 (hAPI5) was investigated in several human tumor cell lines arising from various tissue types.
API5 Is a Novel Tumor Immune Escape Factor

Figure 2. Identification of BIM as a proapoptotic molecule downregulated by API5. A, Western blot analysis characterizing the expression of pro- and antiapoptotic molecules in TC-1/P0/no insert and TC-1/P0/Api5 cells. B, proteasomal degradation of Bim in TC-1/P0/no insert and TC-1/P0/Api5 cells was assessed by Western blot analysis in cells treated with or without MG132. C, TC-1/P0 cells were transfected with siGFP or siBim and exposed to E7-specific CTL. Fractions of apoptotic tumor cells induced by CTL killing are represented by the percentage of activated caspase-3. D, putative MEK kinase intermediates upstream of Bim were analyzed by Western blot analysis. Expression of pAkt, Akt pp38 MAP kinase, p38 MAP kinase, pErk, Erk, and β-actin was analyzed by Western blot analyses. E, TC-1/P0/Api5 tumor cells were incubated with either DMSO or PD98059 for 12 hours and the level of pErk, total Erk, Bim, and β-actin was analyzed by Western blot analyses. F, TC-1/P0/Api5 tumor cells were incubated with DMSO, SB203580, API-2, LY294002, or PD98059 for 18 hours and the level of pErk, total Erk, Bim, and β-actin were analyzed by Western blot analyses. G, TC-1/P0/Api5 tumor cells were incubated with either DMSO, CH-MPD98059, CH-PD98059, E7-specific CTL, or E7-specific CTL w/o PD98059 for 12 hours and the level of pErk. Bar graphs represent tumor volumes at day 18 from TC-1/P0/Api5-challenged mice treated with or without PD98059-loaded chitosan hydrogel in the presence or absence of E7 CTL. The data are representative of three separate experiments and bar graphs represent the tumor volume of 5 mice in each group (mean ± SD).

(Fig. 3A). Among those tested, API5 was found to be markedly elevated in HeLa, PC-3, MCF-7, HCT116, and 526mel, while the expression of API5 in other tumor lines was comparable with that of nontumorigenic HEK293 cells (Fig. 3A). When the expression of hAPI5 was silenced in HeLa, PC-3, MCF-7, HCT116, and 526mel cells using siAPI5-loaded CNP (Fig. 3B), pERK level was significantly reduced with concomitant elevation of cellular BIM, confirming the role of API5 in regulating the activity of ERK and BIM degradation in human cancer cells. To further examine the immune sensitivity of API5-silenced human cancer cells, we chose two API5-expressing tumor lines: HeLa cells and 526mel. HeLa cells, expressing the highest levels of API5, were engineered to express single-chain trimer (SCT) of MHC class I (H-2D^d) linked to an HPV-16 E7 immunodominant CTL epitope (aa 49–57; HeLa/SCT-E7) for recognition by murine E7-specific CTL (Fig. 3C; ref. 8). The human melanoma cell line 526mel was chosen for high endogenous expression of the tumor-associated antigen, MART-1, and presentation of its HLA-A2–restricted epitope for recognition by MART-1-specific CTL (clone KKM; Supplementary Fig. S3). When HeLa/SCT-E7 and 526mel cells were transfected with siAPI5, enhanced killing by E7-specific and MART-1-specific CTL was observed as compared with siGFP controls (Fig. 3C). Similar enhancement was noted when the cellular activity of
ERK was suppressed by treatment with PD98059 (Fig. 3D). Thus, inhibition of ERK activity led to reduced BIM degradation and restored immune sensitivity to antigen-specific CTL in human.

To further demonstrate the role of hAPI5 in immune resistance, API5-negative HEK293DΔ cells and A375 melanoma cells were retrovirally transduced with hAPI5 and their immune sensitivity monitored. As expected, overexpression of API5 in both cell types caused elevation of pERK (>4-fold), and down-regulation of BIM (~80% reduction) compared with no-insert controls (Fig. 3E). Furthermore, expression of API5 in HEK293DΔ cells pulsed with E7-peptides or A375 melanoma cells pulsed with MART-1-peptides mounted resistance to apoptotic killing by their cognate antigen-specific CTL (Fig. 3F), whereas inhibition of ERK by PD98059 restored immune sensitivity against API5+ target cells (Fig. 3G). The immune resistance by API5 overexpression was neither due to the defect in antigen processing through the MHC class I pathway and activation of T cells nor triggering of T-cell death (Supplementary Fig. S4). Taken together, our data indicate that API5 represents a shared immune escape factor in human cancer cells and endogenous overexpression of API5 confers immune resistance through an ERK-dependent mechanism while gene silencing of API5 restores immune sensitivity to antigen-specific CTL.

**API5 activates ERK via the FGF2/FGFR1 pathway**

As a transcription factor, the ability of API5 to deliver an activation signal to ERK is not well defined. Because multiple receptor tyrosine kinases (RTK) can mediate ERK signaling in tumor cells, an antiphosphotyrosine receptor antibody array was performed to identify an upstream RTK, which might have been involved in API5-mediated ERK activation (Supplementary Fig. S5A). These arrays detected increased...
phosphorylation of FGFR1 and EGFR in HEK293/hAPI5 cells compared with HEK293/no insert cells. Because both API5 and FGFR2 have been found to be upregulated in some malignancies (Supplementary Fig. S5B; ref. 9), we postulated that the FGFR2/FGFR1 signaling pathway may be involved in delivering API5 signals downstream to ERK and initiating the subsequent antiapoptotic cascade by transcriptionally regulating FGFR2 production. As expected, HEK293/hAPI5 cells expressed higher levels of phosphorylated FGFR1 (4.2-fold) and accompanying downstream signals (p-PKCδ, p-ERK) compared with HEK293/no insert cells (Fig. 4A; refs. 10, 11). We also found that both mRNA and protein levels of FGFR2 were elevated among API5-overexpressing cells (Fig. 4B–D). Knockdown or neutralization of secretable 18 kDa FGFR2 by its specific siRNA (Fig. 4E) or mAbs (10 μg/mL of anti-FGFR2; Fig. 4F), respectively, led to a significant decrease in phosphorylated FGFR1 and downstream phosphorylation intermediates (p-PKCδ, p-ERK) with concomitant elevation of cellular BIM, suggesting a direct role for FGFR2 in the API5-induced antiapoptotic axis (9, 12). Functionally, anti-FGF2mAb treatment of HEK293/hAPI5 cells led to increased sensitization to immune-mediated apoptosis when exposed to antigen-specific CTL (Fig. 4G).

To further validate the significance of FGFR2 in API5-mediated immune resistance, we assessed for a correlation in protein expression levels between FGFR2 and API5 in various tumor cell lines (Fig. 4H). A highly significant near 1:1 correlation was observed between API5 and FGFR2 level, suggesting close relationship between these two proteins in all cell lines tested (Fig. 4H). Consistent with these findings, we observed increased mRNA and protein levels of FGFR2 among the A375 cells engineered to express hAPI5, and decreased levels of FGFR2 when API5-overexpressing tumor cells (HeLa and 526mel) were treated with siAPI5 (Fig. 4I–K). Furthermore, antibody blockade of FGFR2 led to a decrease in p-FGFR1, p-PKCδ, and pERK, and reciprocal increase in BIM expression in API5-positive A375/hAPI5, HeLa, and 526mel cells (Fig. 4L). These intracellular signaling events, occurring in the presence of neutralizing anti-FGFR2 Abs, were accompanied by increased sensitization of API5+ tumor targets to antigen-specific CTL-mediated lysis (Fig. 4L). Taken together, these results provide strong evidence for FGFR2 in mediating API5-induced immune resistance and degradation of BIM via the FGFR1/PKCδ/ERK axis.

Silencing of PKCδ leads to reconstitution of immune sensitivity in API5-expressing tumor cells

We next determined whether silencing of PKCδ, a downstream molecule of FGFR1 signaling proximal to the ERK/MAPK (13), was sufficient to inhibit API5-induced tumor immune resistance. Exposure of HeLa/SCT-E7 and 526mel to rottlerin, an inhibitor of PKCδ, resulted in a dose-dependent decrease in pERK levels and accompanying increase in BIM expression (Fig. 5A). Furthermore, rottlerin treatment restored immune sensitivity of HeLa/SCT-E7 or 526mel cells to antigen-specific CTLs in vitro (Fig. 5B). No effect of rottlerin was observed on API5+/hAPI5-transfected HeLa/SCT-E7 or 526mel cells treated with siAPI5 (Fig. 5B). To exclude potential off-target effects of rottlerin, we performed the same experiment using siRNA targeting PKCδ and observed similar results (left panels, Fig. 5C and D). Consistent with this result, siPKCδ-treated HeLa/SCT/E7 cells and 526mel cells were more susceptible to CTL-mediated killing (right panels, Fig. 5C and D). Likewise, the in vivo tumor growth of 526mel-bearing NOD/SCID mice, in vivo siPKCδ treatment using CNP before the adoptive transfer of MART-1–specific CD8+ T cells (Fig. 5E), demonstrated significantly lower tumor volume compared with those receiving control siGFP treatment (Fig. 5F). Together, these data reveal that the activation of PKCδ by FGFR2/FGFR1 pathways in API5-overexpressing human tumor cells can lead to ERK activation and BIM degradation, hence controlling API5-mediated immune resistance both in vitro and in vivo.

Silencing of hAPI5 renders the tumor susceptible to immune-mediated control in a preclinical human melanoma model

To demonstrate the potential translational relevance of API5-targeting and its downstream FGFR2/FGFR1 signaling pathways in human tumor immunity, the efficacy of antigen-specific CTL recognizing MART-1 was tested in NOD/SCID mice bearing established API5+ human tumors. Mice receiving MART-1–specific CTL together with siAPI5, according to the schedule described in Fig. 6A, experienced significantly lower tumor burden at 49 days after tumor challenge compared with siAP5 alone or CTL with control siRNA (Fig. 6B). Tumors excised on day 49 were also substantially smaller by weight and size among mice receiving both MART-1–specific CTL and siAPI5 compared with either treatment alone (Fig. 6C). Western blot analysis of ex vivo isolated tumors at day 49 after challenge demonstrated decreased FGFR2, pFGFR1, pPKCδ, and pERK and a concurrent increase in BIM proteins among those mice receiving siAPI5 treatment (Fig. 6D), demonstrating that in vivo delivery of siAPI5 to the tumor and modulation of the tumor immune resistance pathway was successfully achieved. Treatment with siAPI5 resulted in an increased percentage of apoptotic tumor cells (Fig. 6F), not as a result of increased CTL infiltration at the tumor site (Fig. 6E), but rather due to enhanced lytic capacity of infiltrating CTL. Taken together, our data demonstrate that targeting and silencing of API5 or any of its downstream elements represents an attractive strategy for restoring immune sensitivity to resistant tumor cells.

Discussion

In this study, we identify API5 as a novel shared immune escape gene that plays a significant role in controlling immune resistance to antigen-specific T cells both in mouse and human cancer cells. Using murine TC-1/P3 (A17) lung cancer and human 526mel tumor cells that endogenously overexpressed API5, the role of API5 in controlling immune resistance was validated both in vitro and in vivo tumor models receiving their antigen-specific T-cell adoptive transfer. Specific knockdown of API5 in API5-positive tumor cells restored antigen-specific immune sensitivity, whereas the introduction of API5 into

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Cancer Res; 74(13) July 1, 2014 3561
**API5 Is a Novel Tumor Immune Escape Factor**

API5-null tumor cells rendered tumors resistant to immune-mediated cytotoxicity. At the molecular level, we report, for the first time, that the tumor immune resistance conferred by API5 is attributable to upregulation of FGF2 and activation of a downstream pathway involving FGRF1/PKCδ/ERK, ultimately leading to the ubiquitin-dependent degradation of the pro-apoptotic molecule BIM (Fig. 7).

API5 has previously been shown to be expressed in multiple cancers and contribute to tumor invasion and metastases (14, 15); however, its precise molecular mechanism of action remained unclear. Recent studies have shown that API5 caused suppression of apoptosis by inhibiting caspase-3–mediated DNA fragmentation (16) and in an E2F-dependent manner (17). Depletion of API5 was shown

**Figure 5.** Identification of PKCδ as an immediate target gene for API5 controlling CTL resistance. A, the protein expression in HeLa/SCT-E7 or 526mel tumor cells was analyzed in the treatment of 0, 10, 100, or 1,000 nmol/L of rottlerin. B, the percentage of caspase-3⁺ apoptotic cells in siGFP- or siAPI5-transfected HeLa/SCT-E7 (top) and 526mel cells (bottom) following exposure to antigen-specific CTL was shown in the presence of increasing doses of rottlerin. C, left, protein expression was assessed in HeLa/SCT-E7 cells silenced with siGFP or siPKCδ. Right, levels of caspase-3⁺ cells in HeLa/SCT-E7 cells silenced with siGFP or siPKCδ following exposure to E7-CTL. D, left, protein expression was assessed in 526mel cells silenced with siGFP or siPKCδ following exposure to MART-1–specific CD8⁺ T cells. E, schematic representation illustrating in vivo xenogeneic challenge of 526mel tumors and subsequent treatment protocol. F, tumor volume was analyzed at day 31. The data are representative of three separate experiments.

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**Figure 4.** API5 activates ERK through the FGF2/FGFR1 pathway. A, FGF2 signaling following API5 expression is evaluated by Western blot analysis of pFGFR1, pERK, PKCδ, PKCζ, and ERK expression in HEK293D/α insert and HEK293D/β insertion cells. B, mRNA expression analysis of FGF2. C, the protein expression of API5, internal FGF2, and secreted FGF2 in the HEK293D/α insertion cells versus HEK293D/β insertion D, the amount of FGF2 secreted into the media was measured by flow cytometry. E, Western blot results were shown in siGFP- or siFGF2-transfected HEK293D/α insertion cells. F, Western blot analysis of expression in IgG isotype controls or FGF2 antibody-treated HEK293D/α insertion cells. G, IgG antibody– or FGF2 antibody-treated HEK293D/α insertion cells were subjected to CTL assays with E7-CTL. H, scatter plot graph shows the linear relationship between expressing API5 (y-axis) and FGF2 (x-axis) in all tumor cell lines tested in Fig. 3A. I–K, mRNA expression of FGF2 (β) protein expression of API5 and internal FGF2 (as surrogates for all FGF2); J, and secretion of FGF2 were monitored in A375 cells transfected with no insert or API5 as well as HeLa and 526mel tumor cells silenced with either siGFP- or siAPI5 (K). L, the top, the percent killing of A375/API5, HeLa, or 526mel cells, treated with either IgG antibody or FGF2 antibody, was measured in CTL assays. Bottom, Western blot results in IgG or FGF2 antibody-treated A375/526mel cells are shown.

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to enhance the cytotoxic effect of chemotherapeutic drugs (18), presumably by facilitating apoptosis of tumor cells in vivo. Notably, the proapoptotic factor, BIM, which can bind not only antiapoptotic BCL-2 family members, such as BCL-XL and BCL-2, but also BAK and BAX, was shown to be critical for paclitaxel-mediated cell death (19). These
observations, together with our findings presented here, suggest that BIM is likely a key mediator of cell death induced not only by chemotherapeutic agents, but also by antigen-specific T cells. Thus, controlling the cellular level of BIM by API5 seems to be an efficient means of conferring immune resistance in tumors.

The impact of API5 overexpression in tumor immune evasion has significant therapeutic implications. Although several clinical trials demonstrated tumor regression following antigen-specific vaccination or adoptive cellular therapy, a substantial proportion of patients experience partial responses and subsequent relapse (20, 21). Altered expression of apoptosis-regulating molecules, such as BIM, represents one possible mechanism of immune resistance, which may be exacerbated by prior treatment with chemotherapy or irradiation (22–24), both of which can induce upregulation of API5 and inhibition of apoptotic death pathways in tumor cells. The increasing availability of clinic-ready pharmacologic and biologic reagents that target and silence API5 or downstream elements including anti-FGF2, FGFR, ERK, and PKCθ provides a rich opportunity for developing broadly applicable combinational strategies designed to control immune-resistant and recurrent human malignancies.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References


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