ABSTRACT

Interleukin-6 (IL-6) is a pleiotropic cytokine with diverse biological effects. IL-6 has been implicated in autocrine signaling pathways promoting tumor progression and chemoresistance in some human tumors. However, the mechanism by which IL-6 modulates these responses is unknown. Aberrant apoptosis has been implicated as a fundamental mechanism of chemotherapeutic resistance. Thus, we investigated whether IL-6 alters the expression of apoptosis regulatory proteins as a mechanism of drug resistance. We provide evidence that IL-6 rapidly phosphorylates the translation initiation factor eukaryotic initiation factor-4E and triggers antiapoptotic responses in cholangiocarcinoma cells. Reduction of cellular eukaryotic initiation factor-4E by RNA interference decreases IL-6-induced effects on cytototoxic drug-induced caspase activation and apoptosis. Furthermore, IL-6 increases expression of the endogenous X-linked inhibitor of apoptosis protein expression by translation at an internal ribosome entry site. Our findings suggest that IL-6 transcriptionally regulates X-linked inhibitor of apoptosis protein expression and thereby targets the expression of apoptosis regulatory proteins as a mechanism of drug resistance. We provide evidence that IL-6 rapidly phosphorylates the translation initiation factor eukaryotic initiation factor-4E and triggers antiapoptotic responses in cholangiocarcinoma cells. Reduction of cellular eukaryotic initiation factor-4E by RNA interference decreases IL-6-induced effects on cytototoxic drug-induced caspase activation and apoptosis. Furthermore, IL-6 increases expression of the endogenous X-linked inhibitor of apoptosis protein expression by translation at an internal ribosome entry site. Our findings suggest that IL-6 transcriptionally regulates X-linked inhibitor of apoptosis protein expression and thereby targets the expression of apoptosis regulatory proteins as a mechanism of drug resistance. We provide evidence that IL-6 rapidly phosphorylates the translation initiation factor eukaryotic initiation factor-4E and triggers antiapoptotic responses in cholangiocarcinoma cells. Reduction of cellular eukaryotic initiation factor-4E by RNA interference decreases IL-6-induced effects on cytotoxic drug-induced caspase activation and apoptosis. Furthermore, IL-6 increases expression of the endogenous X-linked inhibitor of apoptosis protein expression by translation at an internal ribosome entry site. Our findings suggest that IL-6 transcriptionally regulates X-linked inhibitor of apoptosis protein expression and thereby targets the expression of apoptosis regulatory proteins as a mechanism of drug resistance. We provide evidence that IL-6 rapidly phosphorylates the translation initiation factor eukaryotic initiation factor-4E and triggers antiapoptotic responses in cholangiocarcinoma cells. Reduction of cellular eukaryotic initiation factor-4E by RNA interference decreases IL-6-induced effects on cytotoxic drug-induced caspase activation and apoptosis. Furthermore, IL-6 increases expression of the endogenous X-linked inhibitor of apoptosis protein expression by translation at an internal ribosome entry site. Our findings suggest that IL-6 transcriptionally regulates X-linked inhibitor of apoptosis protein expression and thereby targets the expression of apoptosis regulatory proteins as a mechanism of drug resistance.
added for 5 min to arrest ribosome movement on polysomes. Cellular cytosolic extracts were obtained by lysing using buffer containing 10 mM Tris-HCl (pH 7.4), 100 mM KCl, 100 mM MgCl₂, 10% NP40, and 30 units/ml RNase inhibitor at 4°C and removal of nuclei by centrifugation. The supernatant was then layered onto a 10-ml linear 10% (w/v) sucrose gradient supplemented with 10 mM Tris-HCl (pH 7.5), 100 mM ammonium chloride, and 2 mM 2-mercaptoethanol and centrifuged in a SW41 rotor without brake (Beckman , Palo Alto, CA) at 35,000 rpm, for 150 min, and at 4°C. Fractions (500 µl) were collected, and absorbance at 260 nm was recorded. The polysome: monosome ratio, an index of translational efficiency, was determined as the ratio of the areas of 2–4mer polysomes (actively translated mRNA) to the areas of 80s monosomes (untranslated or under-translated mRNA) measured using NIH image.

**Immunoblot Analysis.** Cell lysis and immunoblotting were performed as described previously using the respective antihuman primary antibody (1:1000 dilution), and a polyclonal goat antirabbit secondary antibody (1:2000 dilution), and visualized using an enhanced chemiluminescence method (Lumi-GLO; Cell Signaling, Beverly, MA; Ref. 12).

**Double-Stranded RNA Design and Synthesis and Transfection.** RNA interference for gene silencing was performed using small interfering 21-nucleotide double-stranded RNA (siRNA) molecules (16). siRNA molecules were designed, prepared, and evaluated as we have described (13). The mRNA target sequences of siRNA to eukaryotic initiation factor (eIF)-4E were 5'-AAGGTGATTTGAGCCTATG-, whereas the mRNA target of the scrambled nucleotide control was 5'-AAGTGTCAGATTGAGCTAG-. The mRNA target sequence of siRNA to XIAP was 5'-AACTTGCTAATCTCTCT-TGGG, whereas the mRNA target of the corresponding control siRNA was 5’-AATGTGACTTCCGATCGTTG-. siRNA (0.1 µg) was mixed with 6 µl of transfection agent (TransIt TKO; Mirus Corp., Madison, WI) in 1 ml of media and incubated at room temp for 15–20 min before adding to cultured cells grown to 50–60% confluency for 48 h.

**Protein Antibody Microarray.** Cells were transfected with siRNA to eIF-4E or a scrambled nucleotide control as described previously (13). After 48 h, the media were replaced with serum-free media for 6 h. Cells were then incubated with IL-6, 10 ng/ml for 1 h, before extraction of cellular protein and analysis of relative differences in protein expression using the antibody microarray (BD Biosciences Clontech, Palo Alto, CA) as per the manufacturer’s instructions. Image and data acquisition from the antibody microarray slides was performed using an Axon GenePix 4000A laser scanner and the GenePix 4.1 software package (Axon Instruments, Foster City, CA). Internal normalization was performed following the manufacturer’s protocol. A >1.5-fold difference in relative protein expression was considered significant.

**Semi-quantitative reverse transcription-PCR.** Total cellular RNA was extracted from cells using the Ultraspec RNA isolation reagent (Biotec Laboratories, Inc., Houston, TX) and semiquantitative reverse transcription-PCR performed. cDNA was prepared from 2–10 µg of total RNA using Moloney murine leukemia virus reverse transcriptase and random oligonucleotide primers. PCR was then performed using a DNA thermal cycler and reaction mixture containing 2 µl of cDNA and the Taq PCR core kit (Qiagen, Inc., Valencia, CA) with the following primers: human XIAP 5’-GCGCATCT-GAGACACATGCAG-3’ (sense) and 5’-GCATTCATCTAGATCTGCAA-C-3’ (antisense); glyceraldehyde-3-phosphate dehydrogenase 5’-TGGCAGTGATGCTTCC-3’ (sense) and 5’-CACCAGTGGAGAGCC-3’ (antisense). For XIAP, 2 µl of cDNA were incubated at 95°C for 45 s, followed by 35 three-step cycles (95°C, 55°C, and 72°C for 1 min each) and a final step at 72°C for 10 min. For glyceraldehyde-3-phosphate dehydrogenase, 2 µl of cDNA were incubated at 95°C for 2 min, followed by 25 three-step cycles (94°C, 55°C, and 72°C for 1 min each) and a final step at 72°C for 10 min. The products were analyzed using the Agilent 2100 Bioanalyzer, and gene expression of XIAP was normalized against glyceraldehyde-3-phosphate dehydrogenase.

**XIAP Expression.** Cells were seeded at 50% confluency in six-well plates and transiently transfected with 2 µg of the XIAP expression plasmid pCI-IREXIAP (17) or control pCI-IacZ using TransIT LT-1 (6 µg; Mirus Corp.) in serum-free media. The transfection reaction was replaced after 4 h with serum-containing media. After 48 h, XIAP expression levels were assessed by immunoblot analysis using monoclonal antibodies to XIAP. Cells were incubated with camptothecin, and cell viability was assessed after 24 h.

**XIAP Internal Ribosome Entry Site (IRES)-Mediated Translation.** KMCH cells were transiently transfected with the XIAP IRES bicistronic retroviral construct pMD9gal/UTR/chloramphenicol acetyltransferase (CAT) described previously (17). The cells were then treated with IL-6 (10 ng/ml) for varying times ≤24 h. Cell extracts were obtained using the M-PER extraction reagent (Pierce, Rockford, IL). β-galactosidase enzymatic activity was determined in cell extracts by a spectrophotometric assay using chlorophenolred-β-D-galactopyranoside monosodium as we have reported previously (18). CAT activity was assessed using a commercially available ELISA assay (Roche Molecular Biochemicals, Indianapolis, IN) according to the manufacturer’s instructions. IRES-mediated translation was assessed as the relative CAT activity calculated by normalizing CAT activity with β-galactosidase activity and expressed relative to activity in untreated cells which were set as 100%.

**Materials.** Fetal bovine serum and reagents were obtained from Sigma (St. Louis, MO). All other cell culture reagents and media were from Life Technologies, Inc. (Grand Island, NY). Monoclonal antibodies to eIF-4E, XIAP, and actin were from Sigma. All phospho-specific antibodies used were obtained from Cell Signaling. The protease inhibitor cocktail tablets were obtained from Roche. Gemcitabine was provided by Eli Lilly (Indianapolis, IN). All other reagents were of analytical grade from the usual commercial sources.

**Statistical Analysis.** Data are expressed as the mean ± SE from at least three separate experiments performed in triplicate, unless otherwise noted. The differences between groups were analyzed using a double sided Student t test when only two groups were present. Statistical significance was considered as P < 0.05. Statistical analyses were performed with the GB-STAT statistical software program (Dynamic Microsystems, Inc., Silver Spring, MD).

**RESULTS**

**IL-6 Decreases Chemotherapy-Induced Apoptosis in Malignant Cholangiocytes.** IL-6 has been shown to decrease the susceptibility of human cholangiocytes to undergo apoptosis (19). To assess the role of IL-6 in mediating cell survival in malignant cholangiocytes, we began by determining IL-6 receptor expression. All cell lines were shown to express the IL-6 receptor by immunoblot analysis (data not shown). Next, we assessed the effect of IL-6 on chemotherapy-induced apoptosis. KMCH cells were incubated for 48 h with camptothecin, gemcitabine, or 5-fluorouracil in the presence or absence of 10 ng/ml IL-6. Under these conditions, basal apoptosis rates in control untreated cells varied from 0.9 to 2.2%, whereas drug treatment increased apoptosis to 19, 28, and 14%, respectively. Importantly, preincubation with IL-6 decreased chemotherapy-induced apoptosis (Fig. 1A). Similar results were observed for camptothecin and gemcitabine in TFK-1 and Mz-ChA-1 malignant cholangiocytes but not in H69 nonmalignant cholangiocytes (data not shown). Furthermore, preincubation with 10 ng/ml IL-6 decreased caspase-3-like activation by camptothecin (Fig. 1B). Because IL-6 has been implicated as an autocrine factor promoting cholangiocarcinoma growth, these observations suggest that autocrine IL-6-mediated signaling may contribute to chemoresistance by inhibition of cytotoxic drug-induced apoptosis.

**Translational Inhibitors Block the Antiapoptotic Effects of IL-6 and Decrease Tumor Cell Resistance to Chemotherapy-Induced Apoptosis.** We have shown previously that IL-6 aberrantly activates the p38 MAPK signaling pathway and that p38 MAPK signaling mediates diverse tumoral characteristics (8, 11, 13). Furthermore, we have shown that p38 MAPK signaling modulates the initiation of protein translation (13). To assess the role of translational mechanisms during cell death induced by chemotherapy, we first determined the effects of the translation inhibitors cycloheximide or rapamycin on the protective effect of IL-6 on camptothecin-induced apoptosis. Both cycloheximide and rapamycin increased apoptosis during incubation with camptothecin (Fig. 2). Furthermore, both of these inhibitors of translation decreased the antiapoptotic effects of IL-6 (Fig. 2). Col-

**IL-6 REGULATION OF XIAP TRANSLATION**

**IN.) All other reagents were of analytical grade from the usual commercial sources.**
Collectively, these data support the involvement of translationally modulated mechanisms in IL-6 modulation of camptothecin-induced apoptosis.

**IL-6 Increases eIF-4E Phosphorylation and Translation in KMCH Cells.** Translational regulation of gene expression mainly occurs by modulation of the initiation stage of protein translation. The main mechanisms for regulating the initiation of translation involve the formation of active eIF4F and the eIF2-GTP-Met-tRNA ternary complexes. The initiation of translation is highly regulated, and the assembly and functional activity of these initiation complexes can be manipulated by phosphorylation of specific subunits or their interacting proteins. The phosphorylation state of specific translational regulatory factors was assessed in serum-starved KMCH cells incubated with IL-6 for varying periods of time (Fig. 3). Although expression of eIF-4E was not increased, IL-6 markedly increased eIF-4E (Ser209) phosphorylation. Relatively minor changes were seen in the phosphorylation of eIF2A (Ser51), p70 S6 kinase (Thr389), or ribosomal protein S6 (Ser235/236), suggesting a role for direct modulation of eIF4E by IL-6 as a mechanism for translational regulation. eIF-4E is a rate-limiting translation initiation factor that binds to the cap structure at the 5′-end of mRNAs of eukaryotic mRNAs as a component of the cap-binding complex eIF-4F that mediates the recruitment of ribosomes to mRNA. Alterations in initiation will result in altered protein synthesis. 

Fig. 3. Interleukin-6 (IL-6) increases eukaryotic initiation factor (eIF)-4E phosphorylation. KMCH cells were incubated with IL-6 (10 ng/ml) for the indicated times at 37°C. Expression of total (phosphorylation state independent) eIF-4E and phosphorylation state-specific eIF-4E (Ser209), eIF2A (Ser51), p70 S6 kinase (Thr389), or ribosomal protein S6 (Ser235/236) was assessed by immunoblot analysis in cell extracts obtained at the indicated times. IL-6 increased eIF4E phosphorylation but did not alter total eIF-4E expression. A representative immunoblot from four experiments is shown.

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**Fig. 1.** Interleukin-6 (IL-6) inhibits chemotherapy-induced apoptosis. In A, KMCH malignant cholangiocytes (1 × 10⁵) were preincubated with 0 or 10 ng/ml IL-6 for 24 h before incubation with 30 μM camptothecin (CPT), 30 μM gemcitabine (GEM), 10 μM 5-fluorouracil (5FU), or diluent control. After 24 h, the cells were stained with 4,6-diamidino-2-phenylindole, and the number of cells with morphological features of apoptosis was identified by fluorescence microscopy. In B, cells were incubated with 0 or 10 ng/ml IL-6 for 24 h, before incubation with 30 μM camptothecin, or diluent control for 24 h. After 24 h, caspase-3-like activity was assessed as described in “Materials and Methods.” Results represent mean ± SE of four separate determinations. *, P < 0.05 compared with controls.

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**Fig. 2.** Translation inhibitors decrease resistance to chemotherapy. KMCH cells (10⁵/ml) were plated in six-well plates. Cells were pretreated for 30 min with the protein synthesis inhibitors rapamycin (2 μg/ml) or cycloheximide (10 μg/ml) or diluent controls before incubation with interleukin-6 (10 ng/ml) for 24 h. Cells were then incubated with camptothecin (30 μM) for 24 h. Apoptosis was assessed by fluorescence microscopy. Preincubation with the protein synthesis inhibitors increased camptothecin-induced apoptosis and reduced the antiapoptotic effects of interleukin-6 (IL-6). Results represent mean ± SE of three to five studies. *, P < 0.05 compared with controls without IL-6, rapamycin, or cycloheximide; **, P < 0.05 compared with IL-6 alone.
distribution of rRNA between monosome and polysome-associated fractions. Incubation of serum-starved KMCH cells with IL-6 (10 ng/ml) altered global rRNA distribution with an increase in the polysome:monosome ratio to 112 ± 4% of controls after 1 h and 129 ± 7% after 3 h, consistent with an increase in initiation of translation. Collectively, these data support the involvement of eIF-4E in translational regulation by IL-6.

**EIF4E Expression Modulates Camptothecin Sensitivity.** eIF-4E is an important regulator of mRNA translation and protein synthesis and is up-regulated in malignant or proliferating cholangiocytes (20). To directly assess the role of translational regulation in the response to camptothecin, we used siRNA to functionally decrease eIF-4E expression. Translational dysregulation by siRNA to eIF-4E increased camptothecin-induced cell death compared with scrambled nucleotide RNA controls (Fig. 4). Thus, resistance to camptothecin-induced apoptosis is dependent on translationally regulated gene expression.

**IL-6 Increases XIAP Translation in an eIF4E-Dependent Manner.** We next sought to define translationally regulated survival mechanisms downstream of IL-6 receptor activation. Cells were transiently transfected with either siRNA to eIF4E or scrambled nucleotide control before incubation with IL-6 (10 ng/ml) for 60 min. Using a commercial antibody microarray (Clontech antibody microarray), we compared relative changes in expression levels of 378 proteins in cellular extracts between the two groups. Several proteins were identified whose expression was induced or repressed by ≥1.5-fold. This protein-profiling screen revealed alterations in the XIAP, an endogenous inhibitor of apoptosis that has been associated with chemoresistance in other cell types. XIAP expression was reduced in cells transfected with siRNA to eIF-4E compared with controls. This raised the possibility that XIAP may represent an effector of the antiapoptotic effects of IL-6. We first confirmed our antibody microarray data by Western blot analysis using commercial antibodies to XIAP after IL-6 treatment in KMCH cells. An increase in XIAP protein was observed during incubation with IL-6 (Fig. 5). Furthermore, we assessed the effect of IL-6 on mRNA expression by reverse transcription-PCR. No significant changes in XIAP mRNA were detected, suggesting that the observed increase in XIAP protein levels is attributable to translational up-regulation.

**XIAP Mediates Resistance to Camptothecin.** To assess the role of XIAP in mediating resistance to camptothecin, two sets of studies were performed. First, we used siRNA to decrease cellular XIAP expression. Compared with a scrambled nucleotide control, siRNA to XIAP decreased cell viability during incubation with camptothecin (Fig. 6). The reduction in cell viability was, however, less than that observed during incubation with siRNA to eIF-4E or with the translational inhibitors cycloheximide or rapamycin. These results suggest the presence of other translationally regulated mediators of resistance to camptothecin, in addition to XIAP. Next, we assessed the potential functional effects of increased cellular XIAP expression. Cells were transiently transfected with pCl-IRE5-XIAP to increase XIAP. Compared with control cells transfected with pCl-lacZ, there was a decrease in camptothecin cytotoxicity in cells overexpressing XIAP (Fig. 7). In combination, these data suggest that modulation of
XIAP expression can inhibit the effects of IL-6 on sensitivity to camptothecin.

**IL-6 Increases Internal Initiation of XIAP at an IRES Site.** XIAP expression is regulated primarily at the translational level (17, 21, 22). XIAP is one of only a few mRNA whose expression can be translationally regulated by initiation of translation at an IRES site located in the 5′ untranslated region (23). To determine the mechanism of regulation of XIAP expression, we assessed the effect of IL-6 on a bicistronic construct comprising of constructs for β-gal and CAT separated by the XIAP IRES. Cap-dependent translation results in β-gal expression, whereas IRES activation results in increased CAT expression. Because both reporter genes are transcribed on the same mRNA, the relative amounts of cap-dependent versus cap-independent, IRES-mediated translation can be determined by the expression of CAT relative to that of β-gal. IL-6 increased relative CAT activity, and, hence, XIAP IRES activity, in a time-dependent manner (Fig. 8). These results suggest that IL-6 regulation of XIAP expression occurs by increased translation at the XIAP IRES site.

**DISCUSSION**

The principal findings of this study are that human cholangiocarcinoma cells respond to IL-6 by increased IRES-mediated translation of the endogenous apoptosis inhibitor XIAP. Dysregulation of protein synthesis and translation by the inhibitors cycloheximide and rapamycin or siRNA-targeted reduction in expression of the rate-limiting translation initiation factor eIF-4E decrease resistance to apoptosis. These studies thus describe a translationally regulated mechanism by which IL-6 can modulate chemotherapy-induced apoptosis.

Abundant evidence implicates translational dysregulation in promoting tumor growth (14, 24). Aberrant expression of translationally regulated apoptosis regulatory genes could promote cell survival under otherwise detrimental environmental conditions. This could result in the survival of cells with inheritable genetic defects that may have otherwise caused cell death. eIF-4E is overexpressed in several diverse malignancies, including cholangiocarcinoma, and modulation of eIF-4E decreases tumor cell growth (20, 25). Consistent with several other observations, eIF-4E appears to translationally regulate proteins that may be involved in the early cellular response to otherwise detrimental environmental changes. We have extended these observations by demonstrating a role for translational regulation of the response of malignant cholangiocytes to chemotherapy-induced apoptosis.

Suppression of apoptosis is a critical feature in human malignancies. XIAP is a member of a multigene family that suppresses apoptosis, has been implicated in chemoresistance, and is overexpressed in many human cancers (26–28). Indeed, inhibition of XIAP is being explored as a strategy for cancer treatment (29, 30). Our studies have identified XIAP as an IL-6-regulated gene. IL-6-mediated autocrine signaling has been implicated in cholangiocarcinoma growth and progression. Thus, modulation of XIAP expression by autocrine IL-6 signaling may contribute to chemoresistance as well as to the pathogenesis and progression of cholangiocarcinoma. Thus, targeting XIAP expression and the cellular mechanisms involved in IL-6 regulation of XIAP expression are attractive targets for improving chemosensitivity and the treatment of cholangiocarcinoma.

Although IRES-mediated translation was initially described for viral RNAs as a mechanism for translation of uncapped viral RNAs, IRES elements have been described in some eukaryotic mRNAs, such as XIAP (23). The presence of IRES sites allows for a rapid response to environmental changes independent of de novo transcription. Furthermore, these IRES sites may function by allowing cap-independent translation of mRNAs under conditions in which cap-dependent translation is inhibited. An emerging paradigm is that selective translation of mRNAs based on internal initiation IRES sites facilitates translation of stress–response proteins under conditions, such as apoptosis, that are associated with inhibition of cap-dependent protein synthesis (31). Our findings are consistent with this concept and support other

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**Fig. 7.** X-linked inhibitor of apoptosis protein (XIAP) increases chemoresistance in KMCH cells. Cells were transiently transfected with pCI-IRES-XIAP (black bars) or pCI-lacZ (white bars) using TransIT LT-1 as described in “Materials and Methods.” Cells were then incubated with camptothecin for 24 h, and cytotoxicity was assessed using a viable cell assay. An immunoblot of XIAP expression in cells transfected with pCI-IRES-XIAP (XIAP) or pCI-lacZ (control) is shown in the inset. The differences between control and XIAP were significant (P < 0.01) for camptothecin-treated cells.

**Fig. 8.** Interleukin-6 increases X-linked inhibitor of apoptosis protein internal ribosome entry site expression. KMCH cells were transfected with the β-gal/X-linked inhibitor of apoptosis protein internal ribosome entry site/chloramphenicol acetyltransferase (CAT) construct. After 24 h, the media were replaced with serum-free media containing 0 or 10 ng/ml IL-6, and the relative internal ribosome entry site activity was determined at the times indicated as described in “Materials and Methods.” Incubation with interleukin-6 increased relative X-linked inhibitor of apoptosis protein internal ribosome entry site-mediated activity. The data represent mean ± SE of three separate determinations and are expressed relative to untreated controls at each time point. *, P < 0.05 compared with controls.
studies demonstrating IRES-mediated translation of XIAP during cellular stresses, such as exposure to ionizing radiation-induced stress or apoptosis (17, 21).

Translational regulation of survival proteins such as XIAP, that are capable of modulating response to chemotherapy, is significant given the intense interest in using mRNA microarray analysis to identify predictors of chemosensitivity in human cancers. Such strategies will be limited to identifying transcriptionally regulated genes but will fail to identify those genes capable of modulating responses to chemotherapy that are predominantly regulated at a translational level. Complementary proteome profiling may enhance the validity and applicability of these strategies.

In summary, we have shown that chemoresistance of malignant human cholangiocytes can be mediated by a mechanism involving translational regulation of XIAP. Furthermore, increased XIAP expression in response to autocrine IL-6 stimulation may contribute to the refractoriness of human cholangiocarcinoma to conventional chemotherapy. Thus, manipulation of XIAP expression or inhibition of the antiapoptotic effects of XIAP is an attractive strategy to improve cholangiocarcinoma responses to chemotherapy.

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Translational Regulation of X-Linked Inhibitor of Apoptosis Protein by Interleukin-6: A Novel Mechanism of Tumor Cell Survival

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