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RESEARCH PAPER

Extra-Hepatic Cancer Represses Hepatic Drug Metabolism *Via* Interleukin (IL)-6 Signalling

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ABSTRACT

Purpose In many cancer patients, the malignancy causes reduced hepatic drug clearance leading to potentially serious complications from the use of anticancer drugs. The mechanisms underlying this phenomenon are poorly understood. We aimed to identify tumor-associated inflammatory pathways that alter drug response and enhance chemotherapy-associated toxicity.

Methods We studied inflammatory pathways involved in extra-hepatic tumor mediated repression of CYP3A, a major hepatic drug metabolizing cytochrome P450 subfamily, using a murine Engelbreth-Holm-Swarm sarcoma model. Studies in IL-6 knockout mice determined the source of elevated IL-6 in tumor-bearing animals and monoclonal antibodies against IL-6 were used to intervene in this inflammatory pathway.

Results Our studies confirm elevated plasma IL-6 levels and reveal activation of Jak/Stat and Mapk signalling pathways and acute phase proteins in livers of tumor-bearing mice. Circulating IL-6 was predominantly produced by the tumor xenograft, rather than being host derived. Anti IL-6 antibody intervention partially reversed tumor-mediated inflammation and *Cyp3a* gene repression.

Conclusions IL-6 is an important player in cancer-related repression of CYP3A-mediated drug metabolism and activation of the acute phase response. Targeting IL-6 in cancer patients may prove an effective approach to alleviating cancer-related phenomena, such as adverse drug-related outcomes commonly associated with cancer chemotherapy.

KEY WORDS cancer · cancer chemotherapy · CYP3A · drug metabolism · inflammation · interleukin-6

ABBREVIATIONS

CRP	C-reactive protein
CYP3A4	Cytochrome P450 3A4
EHS	Engelbreth-Holm-Swarm Sarcoma
ERK	extracellular-signal-regulated kinases
GAPDH	glyceraldehyde 3-phosphate dehydrogenase
gp130	glycoprotein 130
IL-1β	interleukin-1 beta
IL-6	interleukin-6
JAK	Janus kinase
Jnk	c-Jun N-terminal kinases
MAPK	mitogen-activated protein kinase
SAP	serum amyloid P
SAPK	stress-activated protein kinases
STAT	signal transducers and activators of transcription
TNF-α	tumor necrosis factor-alpha

INTRODUCTION

The substantial variability in the clearance of anticancer drugs exhibited by patients with extra-hepatic malignancies is an important contributing factor to the adverse reactions commonly associated with cancer chemotherapy (1, 2). Differential hepatic expression of drug metabolising enzymes is a significant factor in this variability resulting in altered pharmacokinetics. Cytochrome P450 3A4 (CYP3A4) is a key human enzyme in the metabolism of many anticancer drugs, including taxanes, vinca alkaloids and camptothecins (3). It has been previously observed that CYP3A4 activity in patients with

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advanced extra-hepatic cancer may be significantly reduced (4). This reduction in CYP3A4-mediated drug clearance was associated with increased toxicity from docetaxel and vinorelbine and significantly correlated with circulating markers of inflammation, particularly acute phase proteins, including C-reactive protein (CRP) and the pro-inflammatory cytokine interleukin-6 (IL-6) (5).

It is well recognised that cancer is a disease frequently associated with inflammation. A chronic inflammatory state can provide the setting for subsequent development of some tumors (6), while the tumor and its microenvironment may resemble a site of inflammation with release of cytokines, chemokines and growth factors. These inflammatory mediators have local actions that are important in determining tumor behaviour. However, these mediators may also reach the systemic circulation in sufficient quantities to exert distal effects (7). Moreover, systemic inflammation in patients with malignancy is being increasingly recognised as an adverse predictor of outcome (8, 9). Raised levels of acute phase proteins and pro-inflammatory cytokines are associated with a poorer prognosis in a number of tumor types including breast, ovarian, gastric, renal cell and colon cancers (1, 10, 11).

IL-6 is one of several pro-inflammatory cytokines with a well-documented role in cancer. It is involved in tumor growth, invasion and metastasis and is associated with many of the systemic features of cancer, including fevers, weight loss and fatigue (12, 13). IL-6 has recently been incorporated into the consensus clinical definition of cachexia in cancer and other diseases (14). IL-6 is also a principal regulator of acute phase protein synthesis and is regarded as being an integral cytokine in the hepatic response to inflammation (15). Moreover, IL-6 plays an important role in regulating expression of hepatic CYP enzymes, including CYP3A subfamily members (16, 17). IL-6 binds to its cognate plasma membrane receptor or circulating soluble IL-6 receptor, which complexes with the common signal transducing receptor chain glycoprotein 130 (gp130). Signal transduction involves the activation of two major pathways, JAK (Janus kinase) tyrosine kinase family members and the MAPK (mitogen-activated protein kinase) cascade. The JAK pathway in IL-6 signalling leads to the activation of transcription factors of the STAT (signal transducers and activators of transcription) family, particularly STAT3 (18, 19). This pathway induces suppressor of cytokine signalling (SOCS) proteins, which act as classical feedback inhibitors of gp130-mediated signal transduction (20, 21).

We have previously demonstrated elevated circulating levels of IL-6 in several mouse cancer models, including the Engelbreth-Holm-Swarm Sarcoma (EHS), breast EO771, colon 38 and melanoma B16 (22, 23). Increased IL-6 levels were accompanied by an acute phase response and associated with repression of hepatic CYP3A expression. Therefore, it has been suggested that the links between tumor-derived inflammatory responses and reduced hepatic drug metabolism may be a common feature of several different malignancies and that IL-6 may play an pivotal role in tumor-mediated repression of hepatic drug metabolism. In this study we demonstrate the presence of an inflammatory response with active downstream cytokine signalling in the livers of extra-hepatic tumor-bearing mice and provide evidence for the involvement of IL-6 in the tumor-mediated repression of CYP3A *in vivo*.

MATERIALS AND METHODS

Animals

All animal experimentation was conducted in accordance with the guidelines of the Australian Council on Animal Care and approved by the Westmead Hospital Animal Ethics Committee. Animals were kept in a temperature-controlled facility with 12-hour light/dark cycles and were fed a standard rodent chow diet with water *ad libitium*. FVB, C57Bl/6 and IL-6 knockout (C57Bl/6 background) mice were bred in-house.

Tumor Transplantation and Mouse Harvest

EHS tumor implantation has been previously described in detail (24). Mouse body, liver and tumor were weighed and the carcass weight was estimated by subtracting the tumor weight from the total body weight. All animals were anaesthetised with ketamine and xylazine (100 mg/kg and 50 mg/kg respectively) prior to cardiac puncture for the collection of blood. The liver was immediately harvested, snap frozen in liquid nitrogen then stored at –80C. Plasma was prepared from whole blood by centrifugation at 5,000 g for 10 min at 4C, then aliquoted and snap frozen in liquid nitrogen before –80C storage.

Anti IL-6 Antibody Treatment

A monoclonal anti-mouse IL-6 antibody was purchased from R & D Systems (cat. no. MAB406) and diluted in phosphate buffered saline. FVB mice bearing the EHS tumor were injected i.p. with 3 doses of 2 mg/kg over 3 consecutive days prior to sacrifice. This dose was selected following a pilot experiment that showed reduced expression of the IL-6 downstream targets, serum amyloid P (*Sap*) and suppressor of cytokine signalling 3 (*Socs3*) in tumor-bearing animals administered with 3 × 1 mg/kg i.p. injections of the antibody. Vehicle-treated controls received an equal dose of non-specific rat IgG (R & D Systems, cat. no. MAB005).

Inflammatory Signalling Detection

Inflammatory signalling proteins were investigated by Western blot analysis with antibodies against total and phosphorylated Stat3 at Tyrosine 727 (Santa Cruz Biotechnology cat. no. sc-7179 [total protein], Cell Signalling cat. no. 9138 [phospho-protein]), Erk 1 and 2 (Cell Signalling cat no. 9102 [total protein], cat no. 4695 [phospho-protein]) and P38 (Cell Signalling cat. no. 9212 [total protein], Calbiochem cat. no. 50611[phospho-protein]). Extraction and preparation of reduced proteins from liver tissue was performed as previously described (24). Detection of Jnk activity in mouse livers was performed using the Sapk/Jnk assay kit (Cell Signalling cat no. 9810) where liver lysates were prepared as recommended by the manufacturer. In brief, 200 μg of total liver protein was incubated with c-Jun fusion protein bead slurry to immunoprecipitate Jnk. Liver proteins/c-Jun fusion protein mix was then incubated in kinase buffer containing ATP allowing active JNK to phosphorylate c-Jun. Western blot analysis then detected phosphorylated c-Jun, which is proportional to Jnk activity. This assay allows for the simultaneous detection of the many Jnk isoforms that can be activated. Socs3 was investigated by mRNA expression using real-time quantitative PCR (QPCR).

Gene Expression

Total RNA was isolated from snap frozen mouse liver wedges using Trizol reagent (Invitrogen). Prior to cDNA synthesis, RNA was treated with DNAse I (Ambion) according to the manufacturer's protocol. cDNA was synthesised from 5μg of total RNA with SuperScript III cDNA First-Strand Synthesis System, using random hexamer primers and deoxynucleotides. Taqman or SYBR green protocols were used to amplify cDNAs of interest by QPCR using the Rotor-Gene 3000 and 6000 platforms (Corbett Research). mRNA levels were normalized against both GAPDH and 18S ribosomal RNA expression and both housekeeping genes gave comparable results so all results are presented normalized to GAPDH. Graphs of mRNA levels show expression relative to a standard curve representing 5-fold dilutions of stock cDNA and are not true concentrations. Primers used include: *Cyp3a11* Fwd TGCTCCTAGCAATCAGCTTGG, Rev GTGCCTAAAAATGGCAGAGGTT, probe FAM-CCTCTACCGATATGGGACTCGTAAACATGAACTT-TAMRA; *Sap* Fwd CAAGGCGGCAGAGTTCAC, Rev GTGGCAGCTCCCCCTCCCCTCAG; *Socs 3* Fwd GGCCACCCTCCAGCATCTTTGTCG, Rev GTGGCAGCTCCCCCTCCCCTCAG; *Gapdh* Fwd GTCGTGGATCTGACGTGCC, Rev TGCCTGCTTCACCACCTTCT, probe VIC-CCTGGAGAAACCTGCCAAGTATGATGACAT-TAMRA; *18S* pre-developed TaqMan assay (Applied Biosystems, part no. 4319413E)

Circulating IL-6 Detection

Circulating IL-6 levels in plasma of tumor bearing and control mice were measured using the Quantikine high sensitivity mouse IL-6 immunoassay as per the manufacturer's instructions (R & D Systems). Each assay used 50 μl of undiluted plasma.

Midazolam sleep Time Assay

In vivo Cyp3a enzyme function was assessed using the midazolam sleep test (25). Hepatic Cyp3a-mediated hydroxylation is a major pathway of midazolam clearance mice (26). Therefore, the length of sedation following treatment with midazolam is indicative of CYP3A activity. Mice were administered 60 mg/kg of midazolam i.p. and were deemed to be asleep when loss of the righting reflex was observed. The sleeping time was measured from the initiation of sleep to awakening, taken as time when the righting reflex returned.

Data Analysis and Statistics

Quantitative data are expressed as mean ± standard error of the mean (SEM). Statistical analyses comparing control and tumor groups was performed using a Student's unpaired *t*-test. Significance was set at $p \leq 0.05$.

RESULTS

Cytokine Signalling is Activated in Livers of Tumor-Bearing Mice

To determine if tumor-associated cytokines were impacting on hepatic gene regulation, cytokine signalling pathways were examined within livers of tumor-bearing animals and compared to controls. Specifically, components of the IL-6 downstream signalling pathway were investigated; including molecules linked with the Jak/Stat and Mapk pathways, such as Stat3, Erk1, Erk2, c-Jun, and P38. The phosphorylated (p) or activated state of these molecules as determined by Western blot analysis using phospho-specific antibodies, was much higher in tumor-bearing mouse livers compared with controls (Fig. 1). Indeed, phosphorylated Stat3 and activated JNK were observed in extracts from tumor bearing mouse livers only (Fig. 1a and d). Similarly, increased hepatic Erk 1 and 2 phosphorylation was observed in tumor-bearing mice (Fig. 1b) and while phosphorylation of P38 was detected, densitometric analysis did not attain statistical significance Fig. 1cii. For all signalling molecules, only the phosphorylation state was altered while total protein was unchanged, consistent with their known mechanism of activation (27, 28). Another important signalling molecule

in the IL-6 triggered Jak/Stat cascade is Socs3. Socs3 acts as a feedback inhibitor of the Jak/Stat pathway (29, 30) and is induced by IL-6 (20, 21). In livers of tumor-bearing mice *Socs3* mRNA levels were increased up to 14-fold (Fig. 1e), confirming activation of Jak/Stat signalling.

Oxidative stress was assessed by thiobarbituric acid reactive substances (TBARS) in liver homogenates, a well-accepted technique to assay the burden of oxidative insult. TBARS did not differ between groups, indicating absence of inflammation-induced oxidative stress (data not shown).

Cancer Cells are the Major Source of Circulating IL-6

To determine if circulating IL-6 in EHS-bearing mice is tumor- or host-derived, we employed IL-$6^{-/-}$ mice inoculated with tumor. The xenograft grew in these mice at the same rate as in wild-type controls. As expected, circulating IL-6 as determined by an ELISA assay was not detectable in the non-xenografted IL-$6^{-/-}$ mice, but was elevated in EHS tumor-bearing IL-$6^{-/-}$ mice (Fig. 2a), with IL-6 levels comparable to those observed in wild-type tumor-bearing mice.

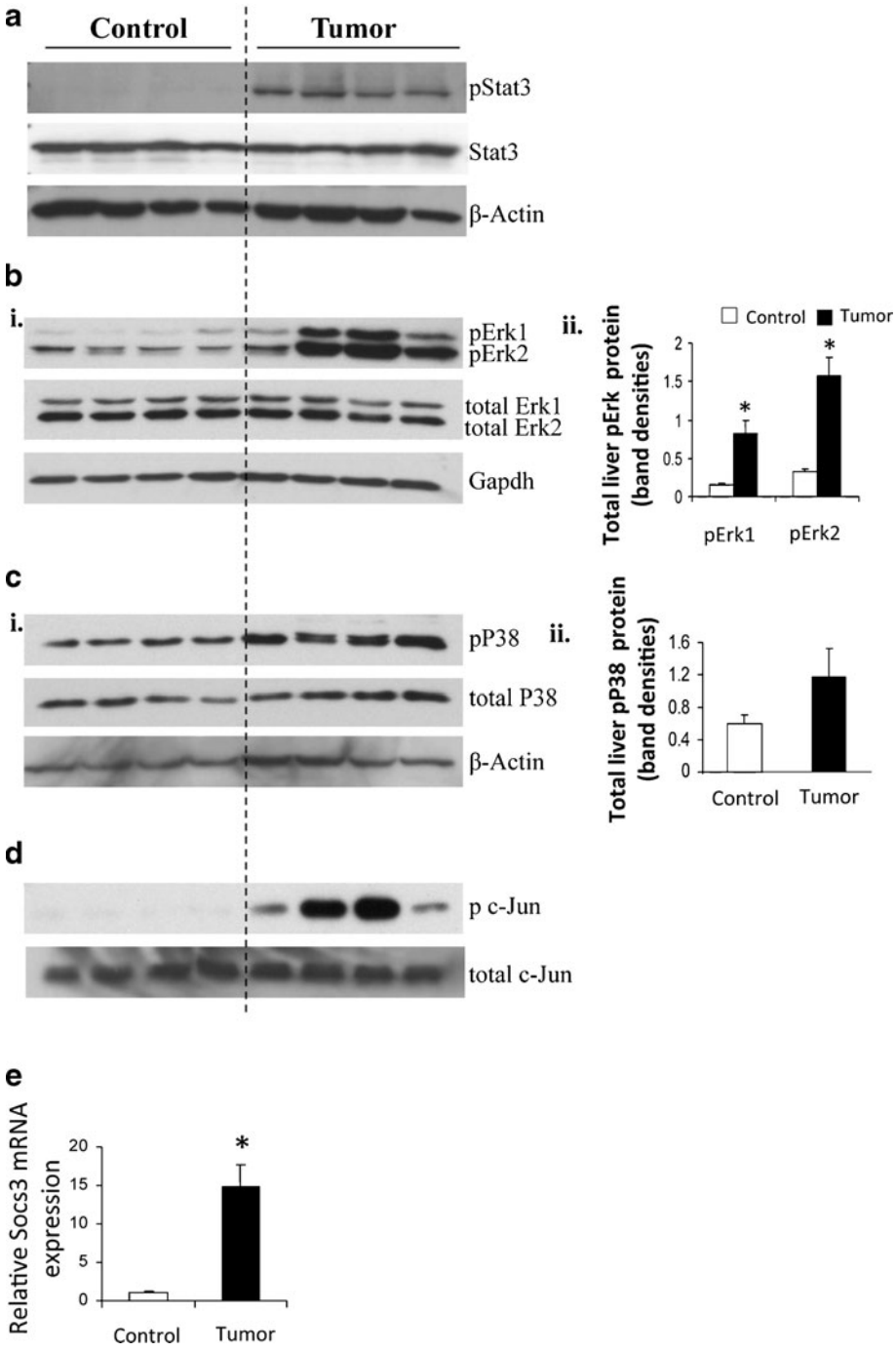

Fig. 1 Hepatic cytokine signalling in tumor-bearing mice. Phosphorylation of hepatic (**a**) Stat3**,** (**b**) Erk1/2, (**c**) P38 and (**d**) c-Jun in the presence of extra-hepatic cancer in FVB mice. Figures show representative blots ($n = 7$–8 per group per treatment). c-Jun *blots* represents an indirect *in vitro* measure for the activity of isolated JNK using a pull down approach (see Materials and Methods). Densitometric analysis was performed for ERK1/2 (**b** ii) and P38 (**c** ii) to quantitate phosphorylation states, p = phosphorylated. (**e**) Relative mRNA expression of Socs3 in livers of tumor-bearing mice compared to controls ($n = 5$ per group,*$p < 0.05$).

This demonstrates that the tumor xenograft is the predominant source of IL-6 as opposed to a host-derived reaction to the implanted cancer. In addition, tumor-bearing IL-6 KO mice retained an acute phase response as measured by hepatic Sap mRNA levels (Fig. 2b) and exhibited a similar degree of *Cyp3a11* gene repression to that observed in wild-type mice (Fig. 2c). Interestingly, even in the absence of tumor the IL-$6^{-/-}$ mice exhibited an exaggerated expression of Sap mRNA, suggesting a degree of dysregulation of this gene in the knockout mice. This is in keeping with previous observations that inflammatory mediators other than IL-6, such as IL-1β, are capable of regulating this gene (31).

Anti-IL-6 Antibody Treatment Reduces Tumor-Associated Inflammation and Hepatic Cyp3a Repression

To determine if tumor-associated inflammation and reduced Cyp3a-mediated drug metabolism could be ameliorated by targeting IL-6, an anti-IL-6 antibody was administered daily for 3 days to tumor-bearing mice while control mice were injected with non-specific IgG. Physical characteristics of these mice including body, tumor and liver weights are listed in Table I. Tumor-bearing mice exhibited a lower tumor-adjusted carcass weight (body weight minus tumor weight) and increased liver weights when compared to mice without cancer. The increased liver weight is consistent with the known role of IL-6 in liver growth and regeneration (32). Mice treated with anti-IL-6 antibody exhibited a reduction of liver weight that more closely resembled the body weight to liver ratio of non-cancer animals (Table I). Anti-IL-6 antibody therapy had no impact on growth of the implanted EHS tumor and had no discernible impact on non-cancer bearing mice.

As we have previously observed, (22, 23) circulating IL-6 levels were elevated in tumor-bearing mice (Fig. 3a) along with increased expression of Sap, a known IL-6 target gene (Fig. 3b), with no significant changes in circulating TNFα and IL-1β (data not shown). Following antibody administration, there was a strong trend towards reduced circulating IL-6 levels, which just failed to reach statistical significance (Fig. 3a) due to a highly variable response to this treatment. However, hepatic expression of Sap was significantly reduced in tumor-bearing mice receiving the anti-IL-6 antibody (Fig. 3b) and was paralleled by reduced hepatic expression of the IL-6 target gene *Socs3* (Fig. 3c). Furthermore, western blot analysis of activated Stat3 showed a reduction in phosphorylation following anti-IL-6 treatment (Fig. 3d). These results demonstrate that the anti-IL-6 antibody treatment does interfere with cancer associated IL-6 signalling in the liver.

In accord with our previous findings, EHS tumor-bearing mice used in these studies also exhibited a reduction in both hepatic Cyp3a11 mRNA expression and Cyp3a-mediated drug metabolism, as determined by midazolam sleep times (Fig. 4). Importantly, tumor-induced repression of *Cyp3a11* mRNA was significantly abrogated by the administration of the anti-IL-6 antibody (Fig. 4a). Moreover, this intervention was able to significantly recover Cyp3a function compared to non-specific IgG treated tumor-bearing mice, as indicated by the midazolam sleep test (Fig. 4b). This provides strong evidence for a direct link between IL-6 and tumor-induced repression of Cyp3a-mediated drug metabolism. Due to the high cost of the antibody, more intensive dosing regimes were not explored, so it is unknown if this approach can completely normalize Cyp3a-mediated drug metabolism in the murine model of extra-hepatic cancer used.

DISCUSSION

Our studies indicate that cancer distant from the liver can secrete inflammatory mediators that activate hepatic inflammatory pathways and compromise hepatic drug metabolism. Earlier observations in cancer patients identified a potential

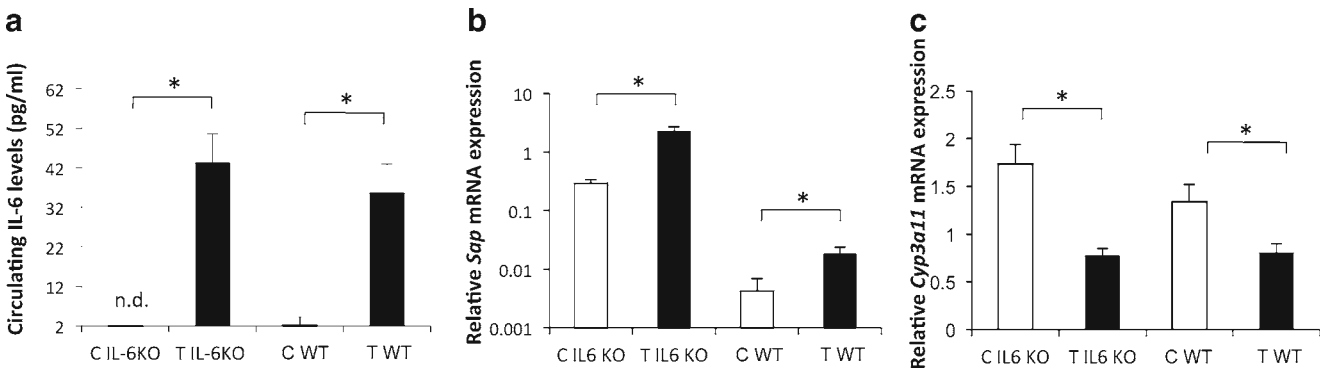

Fig. 2 Inflammatory response and Cyp3a expression in IL-6 KO mice bearing EHS tumor. Wild-type (WT) FVB mice and IL-6 knockout (KO) on a C57Bl/6 background strain were injected with EHS tumor (tumor-bearing) or control vehicle (control) and probed for (**a**) Circulating IL-6 levels using an ELISA, (**b**) relative mouse hepatic Sap and (**c**) Cyp3a11 mRNA levels using real time QPCR normalized against Gapdh. ELISA detection limit of IL-6 was 2 pg/ml. (*$p < 0.05$, $n = 8–10$ mice per group, n.d.-not detected).

Table I Characteristics of Control (no tumor) and EHS Tumor-Bearing Mice Following Anti-IL-6 Antibody (IL-6 Ab) Treatment Compared to Non-Specific IgG Treated Controls

	Control		Tumor-bearing		*p* value Tumor/Tumor+Ab
	IgG	IL-6 Ab	IgG	IL-6 Ab	
Body Weight	28.20 ± 0.80	28.02 ± 0.44	29.33 ± 0.92	31.90 ± 0.79	0.07
Tumor weight			3.02 ± 0.35	3.08 ± 0.43	0.93
Adjusted body weight	28.20 ± 0.80	28.02 ± 0.44	27.18 ± 0.44	28.96 ± 0.84	0.15
Liver weight	1.39 ± 0.05	1.28 ± 0.04	1.64 ± 0.07#	1.47 ± 0.03	0.05*

antibody (Ab). Error margins represent SEM, $n = 6$–8 per group. * denotes significance of $p \leq 0.05$. # significant increase in liver weight of tumour-bearing compared to control IgG treated mice

association between decreased hepatic drug clearance and inflammatory mediators, such as IL-6, and an inflammatory response reflected by an elevation of CRP (4). These findings have been supported by observations in animal cancer models (22, 23). The studies presented herein establish tumor-derived IL-6 as an important mediator of reduced hepatic CYP3A-mediated drug metabolism in an extra-hepatic cancer model, thus linking IL-6 to perturbed hepatic function and providing a mechanistic explanation for the excessive chemotherapeutic drug toxicity experienced by some patients with advanced malignancy receiving anti-caner drugs metabolised by CYP3A enzymes.

In clinical studies it has been reported that elevated levels of circulating IL-6 are observed in many types of cancer and that high levels are predictive of poor outcome (reviewed in 13). Circulating IL-6 was increased in our mouse model of extra-hepatic malignancy and similar findings have been observed in other tumor-bearing mouse models tested in our laboratory, including melanoma B16, colon 38 and breast EO771 (22). Observations of raised circulating IL-6 in *Il-6*$^{-/-}$ mice implanted with EHS tumor imply that the source of the high circulating IL-6 levels is almost entirely due to tumor cell secretion rather than a host response to the tumor. Hepatocytes express several cytokine receptors, including IL-6R, TNF-R1 and IL-1R, and are capable of

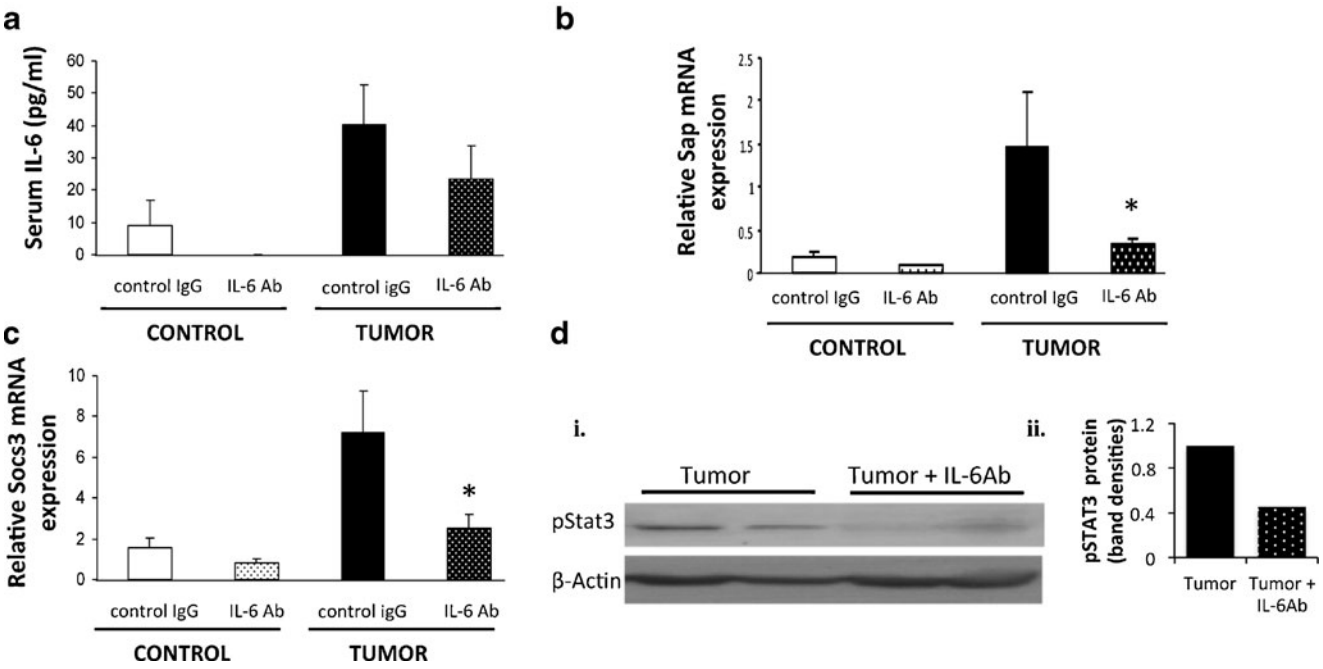

Fig. 3 Use of an anti-IL-6 antibody to neutralize circulating IL-6. The effect of anti-IL-6 antibody administered i.p. to mice daily for 3 days was determined by: (**a**) circulating IL-6 concentrations; expression of IL-6 target genes, (**b**) *Sap* and (**c**) *Socs3*, and (**d**) (i) phosphorylation of Stat3 protein with (ii) corresponding band densities as determined by western blot. Circulating IL-6 was measured using an ELISA assay ($n = 5$ mice per group). Relative hepatic Socs3 and Sap mRNA expression was measured using real time QPCR analysis and normalized against Gapdh ($n = 6$–8 mice per group). Anti IL-6 Ab treated mice were compared to control mice receiving the vehicle IgG in the same manner as the IL-6 specific antibody. All values represent the mean ± S.E.M. (*$p < 0.05$).

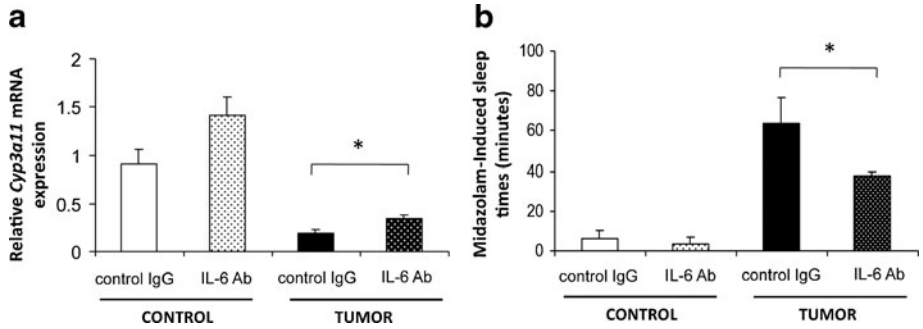

Fig. 4 The effect of IL-6 neutralization on Cyp3a expression and activity. Mice were treated with an anti-IL-6 antibody i.p. daily for 3 days. (**a**) Relative expression of hepatic Cyp3a11 mRNA determined by real-time QPCR and normalized to Gapdh ($n = 6–8$ per group). (**b**) CYP3A-mediated metabolism of midazolam as determined functionally by midazolam sleeping times. Mice received 60 mg/kg midazolam i.p. and the length of sedation was measured in minutes ($n = 3–5$ per group). Values represent mean ± SEM (* $p < 0.05$).

responding to multiple pro-inflammatory mediators (33). In addition, inflammatory stimuli activate Kupffer cells, the resident liver macrophage, which can further amplify the inflammatory signal through local cytokine and chemokine production (34). In the EHS model, circulating tumor-associated IL-6 corresponded well with increased downstream cytokine signalling in tumor mouse livers as demonstrated by the activation of Mapk and Jak/Stat signalling pathways, both downstream components of IL-6 receptor activation. Furthermore, previous studies of IL-6 both *in vivo* and *in vitro* models have shown that it can directly repress human *CYP3A4* gene expression (35). *In vitro* studies particularly show IL-6 repressed CYP3A4 *via* translational induction of the inhibitory CYP3A transcription factor, C/EBPβ LIP (36). However, IL-6 mediated changes in CYP3A expression under conditions that have a chronic inflammatory component, such as in cancer, have not been well studied, despite the fact that IL-6 is the major stimulus for the hepatic secretion of most of acute phase proteins and these proteins are frequently elevated in patients with advanced malignancy (37)

Based on the recurring high circulating IL-6 levels in both clinical studies (4, 38–40) and tumor mouse models (22) and on the existing evidence that IL-6 can impact on hepatic *CYP3A* gene expression (17, 36) an IL-6 targeted intervention was a logical approach to attempt to reverse the effects of extra-hepatic cancer on the liver. Anti-IL-6 antibody treatment attenuated *CYP3A* repression, improved drug metabolism and reduced acute phase protein expression in tumor-bearing mice. Furthermore, this targeted intervention reduced liver weight, counteracting the pro-regenerative effects of IL-6 on hepatocytes. Anti-IL-6 monoclonal antibody therapy has been examined in clinical trials, particularly in patients with advanced multiple myeloma (41, 42). Although antibodies against both IL-6 and the IL-6 receptor are presently in clinical trials for several classical chronic inflammatory diseases such as rheumatoid arthritis (43, 44), to our knowledge there have been few studies of these agents in patients with advanced solid malignancies. It has also been proposed that increased efficacy of IL-6 signal blocking can be achieved by administration of a cocktail of monoclonal antibodies that target different epitopes of the IL-6 cytokine (45, 46). Other IL-6 interventions have explored the targeting of IL-6 trans-signalling through the IL-6/sIL-6R complex (47), as well as downstream mediators of the IL-6 signal such as STAT3 and SOCS3, shown in our studies to be differentially regulated by the presence of cancer. Importantly, targeted anti-IL-6 therapy has potential to normalize drug disposition in individuals with cancer that exhibit an inflammatory phenotype and may also prevent tumor-mediated alterations in other important metabolic functions in which the liver plays a crucial role, especially energy homeostasis.

CONCLUSION

Toxicity in normal tissues is an intrinsic problem in traditional cytotoxic cancer chemotherapy. Wide variability in individual response to anti-cancer drugs, with some cancer patients experiencing extreme toxicity, highlights the need for better strategies designed to reduce unwanted side effects, while maximizing therapeutic impact. Our findings demonstrate that IL-6 is an important player in cancer-related repression of CYP3A-mediated drug metabolism, as well as the cancer-associated activation of the acute phase response. Thus, targeting IL-6 in cancer patients could prove effective in alleviating cancer-related symptoms such as chemotherapeutic tolerance and perhaps cachexia. Furthermore, our studies support the use of monoclonal antibodies, particularly against IL-6, as an intervention strategy aimed at reducing the impact of cancer-related inflammation. The practicality of such an approach requires further investigation in animal models, both to optimize dosing regimens as well as to explore a more diverse range of cancer models, prior to intervention studies in the clinic.

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