Gene Expression Profiling Provides Insights into Pathways of Oxaliplatin-Related Sinusoidal Obstruction Syndrome in Humans

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Introduction

Chemotherapy-related hepatic sinusoidal obstruction syndrome (SOS, previously named veno-occlusive disease or VOD) is one of the limiting factors in the otherwise highly effective use of oxaliplatin for patients with colorectal liver metastases (CRLM; refs. 1–3). Its pathogenesis, preoperative diagnosis, and prevention are thus the subject of intense investigation. In fact, since our initial report (1), several groups have confirmed the existence of oxaliplatin-related SOS in 25% to 36% of treated patients. This has led to concerns that oxaliplatin-associated hepatotoxicity may decrease the chances of curative liver surgery by increasing morbidity through preoperative hemorrhage, postoperative liver failure, delayed regeneration, and portal hypertension (4–13). Rare fatal cases have been reported, inducing a group of experts to publish a cautionary note on the use of chemotherapy before surgical liver resection (14).

SOS is morphologically characterized by centrilobular sinusoidal congestive dilatation and perisinusoidal hemorrhage, occasionally associated with perisinusoidal fibrosis and/or centrilobular hepatic vein fibrotic obstruction, nodular regenerative hyperplasia, or peliosis (15–17). A rat model, based on gavage with monocrotaline (a pyrrolizidine alkaloid), has made an important contribution to understanding SOS pathogenesis, both at the morphologic and biochemical levels. Thus, this model had shown that the major injury occurs in the hepatic sinusoids and that centrilobular vein involvement is not essential, leading to the replacement of the term VOD (18). Toxic injury to sinusoidal endothelial cells (SEC) is the key initiating event, followed by alterations of the

Abstract

Sinusoidal obstruction syndrome (SOS; formerly veno-occlusive disease) is a well-established complication of hematopoietic stem cell transplantation, pyrrolizidine alkaloid intoxication, and widely used chemotherapeutic agents such as oxaliplatin. It is associated with substantial morbidity and mortality. Pathogenesis of SOS in humans is poorly understood. To explore its molecular mechanisms, we used Affymetrix U133 Plus 2.0 microarrays to investigate the gene expression profile of 11 human livers with oxaliplatin-related SOS and compared it to 12 matched controls. Hierarchical clustering analysis showed that profiles from SOS and controls formed distinct clusters. To identify functional networks and gene ontologies, data were analyzed by the Ingenuity Pathway Analysis Tool. A total of 913 genes were differentially expressed in SOS: 613 being upregulated and 300 downregulated. Reverse transcriptase-PCR results showed excellent concordance with microarray data. Pathway analysis showed major gene upregulation in six pathways in SOS compared with controls: acute phase response (notably interleukin 6), coagulation system (Serpine1, THBD, and VWF), hepatic fibrosis/hepatic stellate cell activation (COL3a1, COL3a2, PDGF-A, TIMP1, and MMP2), and oxidative stress. Angiogenic factors (VEGF-C) and hypoxic factors (HIF1A) were upregulated. The most significant increase was seen in CCL20 mRNA. In conclusion, oxaliplatin-related SOS can be readily distinguished according to morphologic characteristics but also by a molecular signature. Global gene analysis provides new insights into mechanisms underlying chemotherapy-related hepatotoxicity in humans and potential targets relating to its diagnosis, prevention, and treatment. Activation of VEGF and coagulation (vWF) pathways could partially explain at a molecular level the clinical observations that bevacizumab and aspirin have a preventive effect in SOS. Mol Cancer Ther; 10(4); 687–96. ©2011 AACR.
perisinusoidal space. SECs initially round up and detach, allowing erythrocytes to penetrate the perisinusoidal space with further dissection of the sinusoidal lining. Sloughed SECs and Kupffer cells intermingled with erythrocytes subsequently embolize downstream within the sinusoidal lumen toward the centrilobular vein (19). Microcirculation plugging causes sinusoidal obstruction, a reduction of blood flow in the sinusoids, increasing portal pressure (20), leading to liver metabolic dysfunction, and affecting the viability of parenchymal cells through hypoxia (15–17). In humans, morphologic studies have confirmed that the sinusoids are the main site of injury.

The aim of this study was to gain further insight into the pathogenesis of SOS in humans by using a molecular approach (global gene analysis with Affymetrix microarrays) to identify key genes through alterations in their mRNA levels. The clinical impact and the availability of human surgical liver specimen led us to study SOS lesions in CRLM surgical resection treated preoperatively by oxaliplatin-based chemotherapy. We compared livers with severe oxaliplatin-related SOS to livers treated with oxaliplatin without SOS, and to histologically normal livers.

Materials and Methods

Patients and liver specimen

From the files of the Department of Pathology of University Hospitals of Geneva, Switzerland and of Cochin Hospital of Paris, France, 3 groups of patients with CRLM were established, matched for sex and age. Group 1 (n = 20) was composed of patients treated with preoperative oxaliplatin-based chemotherapy with histologically confirmed severe SOS (Fig. 1), based on our previous studies (1, 2). Group 2 (n = 20) was composed of patients treated by oxaliplatin-based chemotherapy but without SOS. Group 3 (n = 20) was composed of cases treated by surgery alone, and without histologic lesions. For groups 1 and 2, the protocol used was exclusively oxaliplatin in combination with 5-fluorouracil and leucovorin with an equivalent number of cycles and a similar delay between the end of chemotherapy and surgery. No portal embolization was done before surgery. The use of clinical and pathologic records for our research was in agreement with Swiss and French laws and ethical guidelines related to the protection of the patient.

Microarray analysis

All snap-frozen liver specimens from the selected cases were obtained from the biobanks of Cochin and Geneva Hospitals and reviewed by frozen section to confirm the presence (for group 1) or the absence (for groups 2 and 3) of SOS in the frozen samples. Total RNA was extracted from 25 μm sections of surgical specimen by using TRIzol (Invitrogen). RNA quality was assessed by an Agilent 2100 Bioanalyzer with an RNA 6000 Nano LabChip kit. There was no obvious difference in RNA quality between the specimens from patients treated at the 2 centers. An RNA integrity number was calculated for each sample of RNA and only high-quality samples were used for microarray hybridization, corresponding to intact RNA (n = 23 samples). We generated a hybridization mixture containing 15 μg of double-stranded biotinylated cDNA and hybridized it to GeneChip HG U133 Plus 2.0 (Affymetrix). The data were robust multiarray array normalized (21)

As a first quality control of the dataset we did a 1-way ANOVA (tested factor: group) and we visualized the result by hierarchical clustering in the Partek Genomics Suite (Partek) by using the Pearson correlation similarity
measure and average linkage algorithm (Fig. 2). Following this analysis, samples from groups 2 and 3 were merged.

To assess the difference in gene-expression values between cases (group 1) and controls (groups 2 and 3), we did a Welch \( t \) test in Partek Genomics Suite. \( P \) values were corrected for multiple testing by use of the false-discovery rate (FDR) method of Benjamini and Hochberg (22). We applied a conservative significance threshold of 5% FDR associated with fold change value of 1.5 or more.

The gene expression data can be found in ArrayExpress (http://www.ebi.ac.uk/microarray-as/ae) accession no. E-MTAB-503.

**Network and gene ontology analyses**

Pathway analysis of the genes, which were identified as differentially expressed by microarray experiment was undertaken by using the Ingenuity Pathway Analysis software (http://www.ingenuity.com) as previously described (23). All \( P \) values are calculated by the right-tailed Fisher exact test.

**Real-time quantitative PCR analysis**

To validate our microarray results and further clarify the difference in the expression of the selected genes, we carried out a real-time reverse transcriptase (RT)-PCR on additional samples. cDNA was synthesized from 1 \( \mu \)g of total RNA by using random hexamers and Supercrypt III reverse transcriptase (Invitrogen) following the supplier’s instructions. Amplicons were designed by the software Primer Express v 2.0 (Applied Biosystems) with default parameters. Amplicons sequences were aligned against the human genome by BLAST to ensure that they were specific for the gene being tested. Oligonucleotides were obtained from Invitrogen. The efficiency of each design was tested with serial dilutions of cDNA. Oligonucleotides, amplicons, sequences, and efficiencies can be obtained on request.

**Figure 2.** A, hierarchical clustering (Pearson distance–average linkage) on the robust multiarray average normalized expression values by using the genes that vary across all samples according their group (as selected by ANOVA). Samples showing similar expression profiles are clustered together. Following this analysis, samples from groups 2 and 3 were merged OX-oxaliplatin. B, heat map representation of genes differentially expressed between cases (group 1) and controls (groups 2 and 3) according to a FDR of \( P < 0.05 \) and a fold change value of 1.5 or less.
contained diluted cDNA, 2× Power SYBR Green Master Mix (Applied Biosystems), 300 nmol/L of forward and reverse primers. PCR was done on a SDS 7900 HT instrument (Applied Biosystems) with the following parameters: 50°C for 2 minutes, 95°C for 10 minutes, and 45 cycles of 95°C for 15 seconds or 60°C for 1 minute. Each reaction was done in 3 replicates on 384-well plate. Raw Cq values obtained with SDS 2.2 (Applied Biosystems) were imported into Excel and normalization factor and fold changes were calculated by the GeNorm method. The results were presented as box-plot analyses, using StatView Software (SAS Institute Inc.).

Immunostaining
Specimens showing representative sinusoidal lesions and control hepatectomy cases from colorectal metastasis without lesions were selected for immunohistochemical studies. For immunostaining, additional serial, 4-μm thick liver sections were deparaffinized in xylol and rehydrated in descending ethanol series. The epitopes were recovered by heating slides 30 seconds at 125°C in a buffer containing 0.01 mol/L Tris, 1 mmol/L EDTA (pH 9). Mouse monoclonal α-smooth muscle (αSM) actin was purchased from DakoCytomation and used at 1:400 dilution from Dako (S2022). After blocking endogenous peroxidases with H2O2/methanol, primary antibodies were incubated for 1 hour at room temperature. For αSM actin, microwave pretreatment was used. Sections were incubated for 1 hour at room temperature with the diluted primary antibodies, which were then revealed by ENVISION (DakoCytomation). For anti CCL20 staining, rabbit anti-goat antibodies labeled with HRP (sc-2768; Santa-Cruz Biotechnology) were used as secondary antibodies at 40 μg/mL final concentration and were incubated for 30 minutes at room temperature. The staining reaction was done by the DAB substrate chromogen system from Dako (K3468). A negative control was done with unspecific rabbit immunoglobulin G. Sections were weakly counterstained with Mayer’s hematoxylin and mounted in Eukitt (Kindler GmbH). Negative controls were prepared by omitting the first antibodies.

Results
Microarray analysis
To gain insights into the pathogenesis of SOS, we compared expression profiles of 1 group of 11 human liver tissues with oxaliplatin-related SOS with 2 control groups of histologically normal livers, one having received preoperative oxaliplatin chemotherapy but with no hepatic toxic lesions (n = 7), the other without preoperative chemotherapy (n = 5).

A hierarchical clustering of the 3 groups on the basis of similarity in the expression pattern of genes selected by ANOVA yielded 2 major clusters that separated samples with histologically severe SOS (group 1) from histologically normal livers (groups 2 and 3; Fig. 2A). This result underlines the fact that SOS status has a greater impact on the expression profile than the presence or absence of oxaliplatin-based chemotherapy. On the basis of this observation, groups 2 and 3 were pooled together for further analysis.

These analyses produced a list of 913 genes that were differentially expressed between SOS and controls (FDR-adjusted P ≤ 0.05), 613 statistically upregulated (Supplementary Table S1) and 300 statistically downregulated (Supplementary Table S2) by more than 1.5-fold in SOS relative to histologic normal liver tissue and a FDR-adjusted P ≤ 0.05 (Fig. 2B). Ingenuity Pathway Analysis tool was used to examine functional associations between genes and revealed that several pathways implicated with high significance in human SOS.

Biological pathway analysis
IPA revealed significant upregulation of expression in SOS compared with controls in genes involved in acute phase response pathway (P = 0.00002; Supplementary Table S3), notably affecting the interleukin 6 (IL-6) pathway (IL-6, IL6ST, LBP, STAT3). The relative overexpression of STAT3 and IL-6 mRNA was confirmed by quantitative RT-PCR experiments that compared the expression levels of samples from group 1 (oxaliplatin-related SOS n = 20) with those observed group 2 (treated by oxaliplatin-based chemotherapy but without SOS, n = 20) and group 3 (treated by surgery alone, and without histologic lesions, n = 20; P < 0.001; Fig. 3).

IPA revealed other biological pathways implicated in SOS with the coagulation system reaching high signifi-

![Figure 3. Box-plot analysis of STAT3 (A) and IL-6 (B) expression by real-time quantitative RT-PCR. OX-related SOS (n = 20) is compared with liver treated with OX without SOS (n = 20) and histologic normal livers (n = 10). Student’s t test was used to calculate P values (*, P ≤ 0.05; **, P ≤ 0.01). Mean and SE are indicated OX-oxaliplatin.](Image 365x170 to 450x338)

![Image 472x170 to 556x338]
cance ($P = 0.0001$), notably with upregulation of genes such as SERPINE1, THBD, F3, PLAU, and VWF (Supplementary Table S4) and the oxidative stress pathways ($P = 0.006$) with upregulation of genes such as JUN, SOD2. RT-PCR confirmed overexpression of SERPINE1, VWF, and SOD2 (Fig. 4) and was concordant with the microarray data.

IPA analysis also showed activation of the hepatic fibrosis/hepatic stellate cell activation pathway ($P = 0.0002$; Supplementary Table S5). Most of the activated genes encoded for extracellular matrix proteins, associated molecules, or profibrogenic cytokines (COL15A1, COL1A2, COL1A1, COL4A1, TIMP1, MMP2, CCL2, IFNGR1, LBP, PDGF-A, THBS1, THBS2). RT-PCR confirmed TIMP1 and MMP-2 overexpression in group1, compared with group 2 and group 3 (Fig. 5). The overexpression of a number of genes involved in hepatic fibrosis was confirmed by Masson’s trichrome staining on histologic section of SOS where centrilobular perisinusoidal fibrosis was present (Fig. 1). Hepatic stellate cell activation was illustrated by diffuse ßSM cells expression on immunohistochemistry (Fig. 5).

In SOS, several cytokine and chemokine mRNAs were upregulated (Supplementary Table S6); the highest fold change ($10.97 \times$) was observed in CCL 20 gene expression. Real-time quantitative RT-PCR revealed considerable overexpression of CCL20 in SOS ($n = 20$), relative to histologically normal liver (groups 2 and 3; Fig. 6A). Immunohistochemistry for CCL20 localized expression in portal and sinusoidal cells aggregates, morphology identified as macrophages and Kupffer cells, respectively (Fig. 6B and C).

Several genes involved in angiogenesis and hypoxia were also significantly overexpressed. HIF1A and VEGF-C were upregulated in SOS (Supplementary Table S1), whereas VEGF-A and -B, ANGPT1 and -2, and NOS3 showed no significant changes. RT-PCR was concordant with the microarray data, notably for the increased HIF1a mRNA in SOS and the significant increase in VEGF-C RNA in both groups 1 and 2 compared with group 3 (Fig. 7). VEGF-A mRNA was present in the 3 groups, with no significant increase in SOS (Fig. 7).

Several cytochrome p450 enzyme mRNAs were downregulated (Supplementary Table S7). RT-PCR for CYP7A1 showed excellent concordance with the microarray data (data not shown).

Discussion

To our knowledge, this is the first study to investigate the molecular mechanism of oxaliplatin-related hepatic toxicity in humans by using Affymetrix microarrays to evaluate quantitative gene expression profiles. The investigation provides new insights into the biological and cellular mechanisms involved in chemotherapy-related SOS in humans.

We identified 913 genes differentially expressed in oxaliplatin-related SOS compared with 2 control groups with histologically normal livers. Interestingly, the 2 latter groups, one composed of patients who had received preoperative oxaliplatin for CRLM but who did not develop toxic liver injury and the other composed of patients who had been treated by surgery alone, without chemotherapy, did not segregate on hierarchical clustering. Thus, SOS can readily be distinguished from normal liver not only according to its morphologic characteristics but also to its molecular configuration.
To pinpoint important functional networks and ontologies, genes over- and underexpressed in SOS were analyzed by the Ingenuity Pathway Analysis tool. The canonical pathways that were primarily implicated were acute phase response signaling, coagulation system, hepatic fibrosis/hepatic stellate cell activation, and oxidative stress. On additional samples, we validated 14 of the main deregulated genes by RT-PCR, all showing excellent concordance with the microarray data. In addition, overexpression of VEGF revealed the upregulation of angiogenic factors in SOS and that of HIF1 was indicative of presence of hypoxia in this condition.

Upregulation of acute phase response signaling genes in SOS concerned, in particular the IL-6 pathway. Although inflammation is one of the main initiators of the acute phase reaction, this is unlikely to be the case in SOS, given that no significant inflammation is observed in human SOS (1, 2) and studies on the rat model have shown that polymorphonuclear and Kupffer cells are not critical mediators of monocrotaline hepatotoxicity (24). Interestingly, the IL-6 pathway may also be activated in response to toxic damage, where it plays a critical role in hepatic regeneration and hepatoprotection, or to ischemic injury. Both of these effects seem to be mediated through the actions of STAT3 that blocks apoptosis, reduces oxidative injury (25), and maintains capillary integrity (26). An equivalent role could occur in SOS where the oxidative stress pathway is activated and ischemia is present. Interestingly, the STAT1 and STAT2 genes were also both upregulated in SOS. STAT1 contributes to liver inflammation and injury and to suppression of liver regeneration (25). Further studies on animal models are needed to understand better STAT function in SOS pathogenesis, both at level of apoptosis and of liver regeneration impairment.

Interestingly, the highest mRNA upregulation in SOS was observed for the chemokine CCL20. Interactions of CCL20 and its receptor CCR6, expressed in colorectal cancer, may play a role in development of metastasis by promoting cancer cell proliferation and migration (27, 28) and increased expression of CCL20 has been reported in livers of patients with CRLM (29). These studies, however, did not address the effect of preoperative chemotherapy on this system. In our study, hepatic CCL20 expression could not be explained exclusively by the presence of CRLM, its level being higher in patients with...
SOS than in patients with CRLM alone. Immunohistochemistry showed CCL20 expression in macrophages but not in endothelial cells (30). In monocytes/macrophages, CCL20 is a hypoxia-inducible gene as illustrated by ischemic/hypoxic transcriptome studies (31, 32), in which it constitutes an important mechanism to promote recruitment of specific leukocyte subsets at pathologic sites. Thus, in SOS, hypoxia possibly triggers CCL20 expression. Upregulation of genes involved in the acute phase reaction could result in changes in serum concentrations of specific plasma acute phase proteins. Inflammatory mediators produced in SOS such as CCL20 could circulate in the blood. Further studies are needed to evaluate whether such proteins or cytokines could be used as serum diagnostic markers of severe SOS.

Interestingly, CCL20 and IL-6 signaling molecules have been reported to be upregulated in inflammatory hepatocellular adenoma (33), a tumor characterized by inflammation and sinusoidal dilatation. IL-6 pathway activation in inflammatory adenoma has been related

Figure 6. A, box-plot analysis of CCL-20 expression by real-time quantitative RT-PCR. OX-related SOS (n = 20) is compared with liver treated with OX without SOS (n = 20) and histologic normal livers (n = 10). Student’s t test was used to calculate P values (*, P < 0.05; **, P < 0.01). Mean and SE are indicated OX-oxaliplatin. B and C, expression of CCL20 by immunohistochemistry. B, representative view of a portal tract shows cytoplasmic staining several portal macrophages. No staining is observed in endothelium. C, representative view of IHC reveals Kupffer cells in the lobules in OX-related SOS.

Figure 7. Box-plot analysis of VEGF-C (A), VEGF-A (B), and HIF-1 (C) expression by real-time quantitative RT-PCR. OX-related SOS (n = 20) is compared with liver treated with OX without SOS (n = 20) and histologic normal livers (n = 10). Student’s t test was used to calculate P values (*, P < 0.05; **, P < 0.01). Mean and SE are indicated OX-oxaliplatin.
to GP130 mutation. Similar levels of overexpression of CCL20 and STAT3 mRNA were observed in SOS compared with 6 inflammatory adenomas (data not shown).

IPA analysis showed activation of coagulation pathways, underlining their role in human SOS. The role of clotting abnormalities in the experimental SOS model (34) and in humans is matter of debate. Injury to SEC creates a procoagulant condition in the sinusoids and overexpression of MMPs could be associated with increased platelet adhesion as is observed following cold preservation of liver (35). However, ultrastructural studies of livers from individuals with bush tea–related SOS revealed no evidence of clotting abnormalities (36) and immunohistochemical studies of autopsy livers did not detect platelets, although fibrinogen and factor VIII were detected in the hepatic veins (37). Conversely, thrombocytopenia has recently been shown as being associated with severe oxaliplatin-related SOS in humans (38). Because of the role of platelets in liver regeneration through a serotonin-mediated mechanism (35), alteration in platelet function could play a role in postoperative liver insufficiency that may occur following severe SOS lesions. Our results underline the role of coagulation in SOS and open the possibility of therapeutic approaches to prevent oxaliplatin-associated liver injury, such as aspirin that has been associated with reduced risk for sinusoidal lesions (13). Treatment with antiagglutinants such as heparin and defibrotide, prostaglandin E1, and plasminogen activator inhibitor I, have been examined for their ability to prevent hematopoietic stem cell transplantation–related SOS. They have to be yet evaluated in oxaliplatin-related hepatotoxicity.

Several drugs such as oxaliplatin and other platinum compounds lead to the production of reactive oxygen species and glutathione depletion in SEC, resulting in SEC injury in vitro (30). Oxidative stress also contributes to SEC injury through monocrotaline induced depletion of cellular glutathione and the augmentation of reactive oxygen species production in vitro and in vivo (39). Our findings show an activated reactive oxygen species pathway in human tissue.

In SOS, genes involved in hepatic fibrosis/HSC activation pathways were also upregulated. This correlates directly with the histologic features of human SOS where a significant proportion of patients develop centrolobular perisinusoidal and vein occlusive fibrosis (1, 2, 4, 15, 40). In the animal model deposition of collagen in the sinusoids also occurs, albeit at late event (18), when activated, HSC acquire a myofibroblastic phenotype and are essential actors in hepatic fibrosis (41) as underlined by the diffuse perisinusoidal αSM actin expression (41).

The animal model has shown that MMPs (extracellular matrix remodeling proteins) play an essential role in SOS, where they contribute to SECs detachment and sinusoidal lining denudation (42). Drugs such as cisplatin may cause upregulation of MMP activity in vitro (43). We show here that MMPs upregulation also occurs in human hepatic tissue, underlining its role in oxaliplatin-SOS pathogenesis.

VEGF-C and HIF1α mRNA were significantly upregulated in oxaliplatin-related SOS. Hepatic VEGF mRNA expression is significantly increased in the rat model in parallel with sinusoidal damage (44) and serum VEGF increase correlates with the development of SOS in patients after hematopoietic stem cell transplantation (45). VEGF plays a major role in maintaining SEC differentiation (46–48). The increased expression of VEGF could therefore be a response to endothelial barrier disruption or to cellular hypoxia following SOS. In fact, microcirculatory disturbances lead to insufficient energy supply and reduced hepatic tissue oxygenation (46). The increased HIF1α mRNA levels that we detected underline the presence of hepatic hypoxia in SOS and could contribute to VEGF induction.

Bevacizumab is a monoclonal anti-VEGF antibody that is used in combination with oxaliplatin to increase response rates in patients with stage IV colorectal cancer and thus improve progression free survival. Bevacizu- mab treatment has been shown to have a protective effect against oxaliplatin-induced sinusoidal injury (2, 49, 50). Our molecular observation could partially explain this clinical observation. VEGF blockade by bevacizumab could lead to downregulation of MMP expression by SEC (41, 46), and thus attenuate sinusoidal lesions. VEGF-C mRNA was increased in SOS whereas VEGF-A remained at the same level as in controls.

Finally, the few data that exist regarding the interaction of platinum compounds with the human liver microso- mal cytochrome P450 system mainly come from in vitro studies. Our results on human liver tissue documents the cytochromes that are altered in oxaliplatin induced hepatotoxicity.

In conclusion, global gene analysis of oxaliplatin-related SOS provides new insights into the mechanisms underlying SOS and opens new opportunities for diagnosis and therapeutic interventions.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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