Holoprotein expression in four biliary cast syndrome patients after liver transplantation★

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Abstract

BACKGROUND: The formation mechanism of biliary cast syndrome following liver transplantation has not been thoroughly illuminated, and it is unclear that whether some proteins correlated to the formation mechanism of biliary cast or prewarning to the formation of biliary cast.

OBJECTIVE: To investigate the holoprotein expression in biliary cast syndrome patients following liver transplantation.

METHODS: Four patients underwent liver transplantation at Liver Transplantation Institute, General Hospital of Chinese People's Armed Police Force. Three months later, 10 g biliary cast was harvested. Four kinds of biliary cast specimens at different colors and textures were preserved at deep hypothermia, followed by protein abstraction and restriction enzyme digestion, the total protein abstraction solution of biliary cast were analyzed by high definition mass spectrometry and query on MASCOT database. All protein name of biliary cast were list, the conjunct protein was found by comparing 4 specimens.

RESULTS AND CONCLUSION: There were totally 208 proteins in 4 biliary cast specimens, 82, 44, 56 and 65, respectively. By comparison, 5 proteins were found to overlay in 2 biliary cast specimens, 7 proteins in 3 specimens and 13 proteins in 4 specimens. Among the latter 13 proteins, 5 unnamed-proteins, as well as 8 named-proteins (termed alpha-fibrinogen precursor, beta-fibrinogen precursor, fibrinogen gamma chain, proapolipoprotein, Chain A of Human Cathepsin G, S100 calcium-binding protein A9, lactoferrin) were included. The proteins exists in biliary cast, the common proteins of 4 biliary cast specimens imply a correlation between the formation of biliary cast and the exudative inflammation following the damage of biliary tract epithelium; Some proteins might be considered as a marker of prewarning the presence of biliary cast syndrome, judging the inflammation severity following the damage of biliary tract epithelium and the prognosis of biliary cast syndrome.

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INTRODUCTION

Studies on human tissue and body fluids, as well as secretion proteomics have already been carried out extensively at home and abroad, and play different indicative effects on the pathogenesis, diagnosis and treatment of various diseases[1-3]. This technology also has ever been used in the field of organ transplants, mostly for the blood, urine and other specimens of patients[4-5], however, no reports are regarding this technology in the analysis of biliary cast and study of biliary cast syndrome (BCS) following liver transplantation. BCS following liver transplantation is a serious surgical complication affecting survival rates and quality of life in liver transplantation patients, accounting for 4%–18% incidence rate[6]. The biliary cast formation mechanism of BCS has not yet been completely clarified. We collected four typical specimens of biliary cast, performed whole protein analysis, and investigated the protein expression.

MATERIALS AND METHODS

Design

Prospective basic research.

Time and setting

Performed from November 29th 2007 to March 20th 2008 at the National Center of Biomedical Analysis, Academy of Military Medical Sciences.

Materials

The general information of following included patients is shown in Table 1.

Table 1 Clinical data of four patients with biliary cast syndrome

Item	Case 1	Case 2	Case 3	Case 4
Gender	Male	Male	Male	Male
Age (yr)	66	26	35	61
Date of liver transplantation	2006-12-28	2007-02-07	2007-02-06	2007-11-12
Surgical approach	Cadaveric liver transplantation	Cadaveric liver transplantation	Cadaveric liver transplantation	Cadaveric liver transplantation
Preoperative diagnosis	Primary hepatic carcinoma, decompensation cirrhosis post viral hepatitis B	Decompensation cirrhosis post viral hepatitis B	Primary hepatic carcinoma	Decompensation cirrhosis post viral hepatitis B, chronic hepatitis gravis
Previous history	Antitoxin tetanus injection after trauma	Rabies antitoxin injection after dog bite injury	None	None
Time of diagnosis	Post-operative 2 weeks	Post-operative 2 weeks	Post-operative 3 months	Post-operative 3 months
Biliary cast color	Brown	Buffy	Dark brown	Black
Biliary cast texture	Moderate soft	Moderate	Moderate hard	Hard
Biliary cast shape	Dead branch	Dead branch	Antler	Antler
Necrosis in intrahepatic bile duct	Severe	Severe	Moderate	Mild
Bile bacterial culture	Positive	Positive	Positive	Negative

Four patients underwent liver transplantation at Liver Transplantation Institute, General Hospital of Chinese People's Armed Police Force between December 2006 and November 2007, 3–4 months later biliary cast was harvested when the patients were treated by fiberoptic choledochoscopy *via* T-tube sinus tract. Intrahepatic bile duct necrosis was divided into mild, moderate and severe according to necrotic range, mild: common hepatic duct local biliary epithelial necrosis; moderate: common hepatic duct, left or right hepatic duct necrosis; severe: common hepatic duct, left and right hepatic duct necrosis as shown in Table 1.

Specimen preservation: At 3 months following liver transplantation, biliary cast was harvested when all patients were treated by fiberoptic choledochoscopy *via* T-tube sinus tract, 10 g specimens were preserved in sterile glass bottle at –80 ℃ deep freeze refrigerator. The patients gave informed consents to the experiment.

The main drugs and reagents used are as follows:

Drug and reagent	Source
Cocktail protease inhibitor, bovine serum albumin, CHAPS	Sigma, USA
DNA, RNA enzyme	Sino-American Biotechnology Company
Dithiothreitol, Tris(hydroxymethyl)aminomethane	Promega
Ultrasonic processor	Sanyo, Japan
Refrigerated centrifuge	Mikro 22R, Hettich, Germany
Common centrifuge	Eppendorff, minispin
Oscillator	QL-901, Haimen City Qilin Medical Equipment Factory, China
High definition mass spectrometry	Waters Micromass, type Synapt HDMS

Methods

Biliary cast protein extraction methods

Biliary cast whole protein extraction and restriction enzyme digestion: –80 ℃ preserve specimens, take out before use; adding 500 μL lysis buffer at 1: 10 volume ratio, while adding 10 μL cocktail protease inhibitor at the proportion of 50: 1; lysis buffer composition: 40 mmol/L Tris-Hcl, 7 mol/L urea, 2 mol/L thiourea, 4% CHAPS, 1% DTT, 1 mmol/L EDTA; ultrasonic processors of biliary cast, each 5 seconds at an interval of 15 seconds, until the sample completely dissolved and turned to be transparent and clarified; adding 10 g/L DNA, RNA enzymes 5 μL; ice bath 20 minutes; 4 ℃ 14 000 r/min high-speed centrifuge 20 minutes; the supernatant was removed and subpackaged.

Protein identification

High definition mass spectrometry was purchased from Waters Micromass Inc., Synapt HDMS. The supernatant 4.8 μL obtained by the above-mentioned steps were automatically subjected into the analysis of proteins.

Design, enforcement and evaluation

The experiment was designed and evaluated by the first author, and implemented by the fourth, fifth authors.

Statistical analysis

Mass spectrometry data acquisition software MassLynx 4.1, and data analysis software PLGS v2.3, were both provided by Waters.

RESULTS

Total protein solution was successfully extracted from the biliary cast, by use of high definition mass spectrometry, totally 208 kinds of proteins were identified out of whole protein solution of 4 biliary cast specimens, 82 ones in case 1, 44 in case 2, 56 in case 3, and 65 ones in case 4. By comparison and analysis, 13 kinds of proteins overlapped in 4 protein samples (including 8 named proteins and 5 non-named proteins), in addition, 7 kinds of proteins overlapped in 3 samples of protein (including 6 named proteins and 1 non-named protein), 5 kinds of proteins overlapped in 2 samples of protein (Table 2).

Table 2 Overlapped proteins in biliary cast specimens of four patients

Protein No.	Serial accession No.	Protein name
Overlapping 4 specimens		
1	gi|38154680	lactoferrin [Homo sapiens]
2	gi|34719	unnamed protein product [Homo sapiens]
3	gi|29446	unnamed protein product [Homo sapiens]
4	gi|4506773	S100 calcium-binding protein A9 [Homo sapiens]
5	gi|29888	unnamed protein product [Homo sapiens]
6	gi|178775	proapolipoprotein
7	gi|2392230	Chain A, Human Cathepsin G
8	gi|182430	beta-fibrinogen precursor
9	gi|31077	unnamed protein product [Homo sapiens]
10	gi|34810822	Chain B, Non-Covalent Complex Between Alpha-1-Pi-Pittsburgh And S195a Trypsin
11	gi|35193	unnamed protein product [Homo sapiens]
12	gi|182424	alpha-fibrinogen precursor
13	gi|182439	fibrinogen gamma chain [Homo sapiens]
Overlapping 3 specimens		
1	gi|1942187	Chain, H253m N Terminal Lobe Of Human Lactoferrin
2	gi|182051	neutrophil elastase precursor
3	gi|122920512	unnamed protein product [Homo sapiens]
4	gi|229751	Chain A, Alpha-Ferrous-Carbonmonoxy, Beta-Cobaltous-Deoxy Hemoglobin (T State)
5	gi|1620909	ceruloplasmin [Homo sapiens]
6	gi|28977	azurocidin [Homo sapiens]
7	gi|75765819	Chain A, Crystal Structure Of Human Neutrophil Peptide 2, Hnp-2 (Variant Gly16-> D-Ala)
Overlapping 2 specimens		
1	gi|75766355	Chain X, Structure Of Recombinant Human Lactoferrin Produced In The Milk Of Transgenic Cows
2	gi|300181	neutrophil gelatinase-associated lipocalin, NGAL [human, neutrophils, Peptide, 178 aa]
3	gi|13489087	serine (or cysteine) proteinase inhibitor, clade B (ovalbumin), member 1 [Homo sapiens]
4	gi|28336	mutant beta-actin (beta'-actin) [Homo sapiens]
5	gi|179619	plasma protease (C1) inhibitor precursor

DISCUSSION

After liver transplantation, BCS is a serious complication threatening patients, at present the mechanism is not completely clear. The naming of the biliary cast is in a variety, such as biliary sludge, gallstones and bile duct epithelial shedding. The exudative inflammation after bile duct epithelial damage (large leakage of fibrinogen and then formation of cross-linked fibrin) leading to the formation of biliary cast, is a persuasive ratiocination recently raised by the author[7-8], some

of the previous biochemical analysis have confirmed the compositions of biliary cast include bilirubin, bile salts and proteins[9], and it is also confirmed in a view of electron microscopy and histological slices that fibrin exists in the biliary cast[10]. So, whether massive proteins bio-information exist in biliary cast, whether the new ratiocination can be verified or a prewarning marker can be found all deserve further investigation.

There is no report addressing the protein analysis of biliary cast at home and abroad, the difficulty of this experiment is also in the handling of specimens. In preliminary experiments, the authors have used 10% HCl solution and 10% NaOH solution to boil biliary cast, respectively, but no dissolution of biliary cast was found. In this experiment, during the procedure of ultrasonic processors, some non-broken fibers were still seen and not easily dissolved, the specific reasons remain un-known yet. Thus the whole protein obtained in this experiment may not be the whole. In the high definition mass spectrometry analysis on biliary cast protein, the authors found that some samples contained special proteins: case 1 containing anti-tetanus toxoid Ig, case 2 containing anti-rabies virus Ig. The accuracy of this experiment has been confirmed through the return visit cases. The type of whole protein is specific in each people body fluids or tissues. To make clear of the reasons for the casting formation, we should find common features. In this study, a common protein is reliable and accurate in the biliary cast through the observation of the whole protein overlapped in 4 specimens, also showing that biliary cast common protein exhibits a very important value on revealing the biliary cast formation mechanism and expanding the following study.

The discovered common protein includes some proteins which are not yet named in the world, its exact function is not clear and this article will not mention. From 4 specimens of common protein finger printing, we found that there are three kinds of fiber proteins (α-fibrinogen precursor, β-fibrinogen precursor, fibrinogen γ-chain), fully explaining a correlation of biliary cast formation with fibrin exudation. The cathepsin G, calcium-binding protein A9 and lactoferrin has been extensively studied in the medical field at recent years, greatly associated with inflammatory reaction in various systems and tissues, the existence of these proteins in the biliary cast also indicates an inflammation of bile duct wall following bile duct epithelial damage, which is consistent with the biliary cast formation mechanism.

Usually cathepsin G refers to the activated lysosomal protease in the acidic environment, belonging to a papain. Cathepsin G plays an important role in the protein degradation, in addition to lysosomes, according to cell type and cell micro-environment, cathepsin G may distributes widely and acts various functions. Beside matrix degradation, it is also involved in growth factor, vascular proliferation regulation and assisting other cytokines regulation, and contributes to cell migration, proliferation and apoptosis. Because of the specificity, cathepsin substrate cab modify and process many elements, leading to their activation and inactivation, plays an important role. Cathepsin G is of great importance on the regulation of stromal vascular proliferation[11-13].

Calcium-binding protein A9 (also S100A9) at relatively small molecular weight (13×10^3), its expression has a strict specificity, under normal circumstances only granulocytes and monocytes express at the early stages of cell differentiation and in the cycle state in bone marrow, while the macrophages settled in tissues don't express, under certain conditions such as early stage of inflammation, exudative inflammatory cells express, most of which exhibit S100A9/S100A8 complex. S100A9 is mainly localized in the cytoplasm, also turns to the cytoskeleton and plasma membrane so as to facilitate the accumulation of intracellular calcium[14]. It is suspected that S100A9 is related to wound healing, and its possible mechanism is involved in S100A9 chemotaxis on keratin cytoskeleton reconstruction in epithelial wound and (or) on the inflammatory cells[15-19]. In the cerebral infarction, trauma or cardiac surgery, the serum S100 A9 protein concentration also increases, and it is considered as serum biochemical marker of severe brain injury, plays a certain extent predictive value on minor brain damage[20-21]. Some studies have shown a positive correlation between the rejection reaction intensity and the concentration of S100A9 in serum following kidney transplantation[22].

Lactoferrin is an iron-binding glycoprotein, belonging to transferrin protein family. Lactoferrin can be found in milk and animal body fluids, is a secretion of neutrophils. Recently, many studies have revealed the physiological and biological functions of lactoferrin. Its biological activity includes ion-transfer function; anti-microbial function; anti-fungal activity; anti-viral activity; toxin binding activity; promoting the activity of some animal cells; platelet binding activity; immunomodulatory activity, involved in local secretion immunization together with immune globulin and other protective factors, reducing damage and promoting wound healing[23-30].

Further studies should focus on whether these proteins are expressed in patient's bile following liver transplantation, and used as a standard for determining the BCS and the inflammatory response after bile duct epithelial damage.

In some cases of severe bile duct necrosis, the matrix metalloproteinases, neutrophil elastase precursor, neutrophil gelatinase-associated lipocalin, Chain A, Crystal Structure of Human Neutrophil Peptide 2, Hnp-2 (Variant Gly16 -> D-Ala) (trypsin-like serine protease) and the Human Cathepsin G expression may be associated with scar formation after biliary epithelial necrosis. Previous studies have confirmed that these enzymes (specific proteins) are involved in the tissue reconstruction following acute inflammation[11]. Therefore these proteins are expected to become a marker of long-term prognosis of BCS.

The proteins exist in biliary cast; the common protein of 4 biliary cast specimens reveals a correlation of biliary cast formation with bile exudative inflammation (fibrin) after bile epithelial damage; some proteins may be used as an marker of prewarning BCS emergence, determining the bile inflammation following bile epithelial damage and the BCS prognosis.

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肝移植后胆道铸型 4 例全蛋白质的表达*

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摘要

背景：肝移植后胆道铸型综合征的胆道铸型形成机制尚未彻底被阐明，因此胆道铸型中是否存在一些和其形成有关或对铸型形成有预警作用的蛋白质还不清楚。

目的：了解肝移植后胆道铸型综合征患者胆道铸型中全蛋白质表达情况，总结其规律。

方法：武警总医院肝移植研究所实施肝移植患者 4 例，于移植后 3 个月经 T 管窦道行纤维胆道镜检查治疗时取出胆道铸型，将 4 种不同颜色质地的胆道铸型深低温保存，经过蛋白质提取、酶切，最后经高解析离子淌度质谱仪鉴定并经 MASCOT 数据库查询，得出每份标本的全蛋白质名称。比较 4 份标本的差异，找出共同的蛋白质。

结果与结论：通过检测及查询 4 份标本分别包含 82、44、56 及 65 种蛋白质，经比对分析，重叠 4 份标本的共同蛋白质 13 种，除此外，重叠 3 份标本的蛋白质 7 种、重叠 2 份标本的蛋白质 5 种。重叠 4 份标本共同蛋白质中已命名蛋白质 8 种，未命名蛋白质 5 种，命名蛋白质包括：α-纤维蛋白原前体、β-纤维蛋白原前体、纤维蛋白原 γ 链、载脂蛋白 A 链、人组织蛋白酶 G、钙结合蛋白 A9 和乳铁蛋白等。证实胆道铸型中确实存在蛋白质，4 例胆道铸型的共同蛋白质揭示了胆道铸型的形成与胆道上皮受损后的胆道渗出性炎症(纤维蛋白渗出)有关；一些蛋白质有可能作为预警胆道铸型综合征的出现、判定胆道上皮受损后胆道炎症程度及胆道铸型综合征预后的标记物。

关键词：胆道铸型；肝移植；蛋白分析；全蛋白质

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