Expression and role of matrix metalloproteinases and tissue inhibitor of metalloproteinases in a rat model of traumatic deep vein thrombosis**☆

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Abstract

BACKGROUND: The molecular mechanism of traumatic deep vein thrombosis is complex. Numerous studies focus on clinical observation and epidemiology, but its molecular mechanism has not been a new breakthrough.

OBJECTIVE: By use of gene array technology, this study was aimed to study the expression changes of matrix metalloproteinases in rat models of traumatic deep vein thrombosis, and to explore the roles of matrix metalloproteinases in traumatic deep venous thrombosis.

METHODS: A total of 150 SD rats, SPF grade, of 8-12 weeks old, body weight of 250-300 g, were divided at random into normal control group (*n*=10) and model group (*n*=140). Rat traumatic deep venous thrombosis models were set up by clamping the femoral vein and fixing the bilateral hind limbs, and the fixation of hip spica with plaster bandage was conducted in each group. Then rats were divided into 7 subgroups: post-traumatic 0.5 hours, post-traumatic 2.5 hours (initial period of thrombosis), post-traumatic 25 hours (thrombogenesis at thrombotic crest-time), post-traumatic 25 hours (non-thrombogenesis at the thrombotic crest-time), post-traumatic 72 hours (thrombus resolution), post-traumatic 72 hours (thrombus insolution) and post-traumatic 168 hours (nonthrombosis). At the corresponding phasess, the femoral vein tissues were incised, and total RNA of femoral vein was extracted using Trizol one-step method. Applying Genechip Rat Genome 430 2. 0 genechips, the gene expressions in femoral vein were detected in different groups. The rate of traumatic deep venous thrombogenesis and non-thrombogenesis, the rate of thrombi solution and insolution were observed; the expressions of matrix metalloproteinases and tissue inhibitor of metalloproteinases at different time phases was detected by gene array data analysis.

RESULTS AND CONCLUSION: Three model rats died and the remaining 147 rats were involved in the final analysis. At the post-traumatic 25 hours, the rate of thrombogenesis was 50.5% and nonthrombogenesis was 49.5%. To the post-traumatic 168 hours, the rate of thrombus solution was 56.7% and thrombus insolution was 43.3%. Both matrix metalloproteinases and tissue inhibitor of metalloproteinases exhibited differential expressions in the course of traumatic deep venous thrombosis. Under the thrombus insolution state, matrix metalloproteinases continued to show a high expression, tissue inhibitor of metalloproteinase expression was down-regulated in the thrombus formation, was significantly inhibited in the thrombus insolution process. In the process of traumatic deep vein thrombosis and insolution, matrix metalloproteinase was closely related to traumatic deep vein thrombosis, the matrix metalloproteinase/tissue inhibitor of metalloproteinases are likely to affect the biological state of thrombosis.

INTRODUCTION

Traumatic deep vein thrombosis (TDVT) refers to deep vein thrombosis resulting from trauma or operation factors, it is a common and multiple complications in peripheral vascular disease. TDVT can not only lead to limb bruise or amputation, but also induce life-threatening pulmonary thromboembolism. It is reported that the incidence of DVT after trauma accounts for 12.4%, among them femoral shaft fractures about 30.6%, hip fractures about 15.8%, knee joint fractures about 14.5%, tibia and fibula fractures about 10.8%[1]. Studies have shown that TDVT is a matter of multi-factor, multi-gene, multi-system disease[2-3]. Among the influencing factors of TDVT, the imbalance of matrix metalloproteinases (MMPs) and tissue inhibitor of metalloproteinases (TIMPs) resulting in excessive degradation of endothelial basement membrane is one of the main reasons of thrombus solution or insolution. At recent years, deep vein thrombosis solution/insolution mechanism has become a hotspot.

MATERIALS AND METHODS

Design

A randomized control animal experiment.

Time and setting

Animal experiments were finished completed from March to October in 2007 in Kunming Medical College Laboratory Animal Center (BSL-3). Total RNA extraction and agarose gel electrophoresis were completed between November and December in 2007 in the Institute of Zoology of Chinese Academy of Sciences (National Key Laboratory). The detection of Genechip Rat Genome 430 2. 0 genechips was accomplished on March in 2008 in Shanghai Biochip Co.Ltd.

Materials

A total of 150 SD rats, SPF grade, of 8-12 weeks old, body weight of 250-300 g, were purchased in the Animal Experiment Center of Kunming Medical College [License: SCXK(Yunnan)2005-0008]. All experimental protocols were in accordance with the

Guidance Suggestions for the Care and Use of Laboratory Animals, formulated by the Ministry of Science and Technology of the People's Republic of China[4].

Methods

Establishment of a TDVT rat model [5]

A total of 150 SD rats were randomly divided into normal control group (group A *n*=10) and model group (*n*=140). The model rats were anesthetized with 3% pentobarbital sodium (1 mL/kg). The bilateral thighs were depilated. Along the longitudinal axis of thigh, an incision about 2 cm long was made on each side to find femoral vein. Each femoral vein was clamped in three different positions within 3 seconds by 12# mosquito forceps. Then the incision was sealed up and fixed with hip spica cast, observing the response of local tissue. After modeling, rats can normally drink water and feed grain, no antibiotics were used.

Grouping

According to different observation phases and the formation of thrombus, the model rats were further subdivided into 7 sub-groups: group B, post-traumatic 0.5 hours; group C, post-traumatic 2.5 hours (initial period of thrombosis); group D, post-traumatic 25 hours (thrombogenesis at thrombotic crest-time); group E, post-traumatic 25 hours (nonthrombogenesis at the thrombotic crest-time); group F, post-traumatic 72 hours (thrombus resolution); group G, post-traumatic 72 hours (thrombus insolution); group H, post-traumatic 168 hours (nonthrombosis). At the corresponding phases, according to gross observation, each 10 rats meeting to different pathological features were selected into corresponding groups (Figure 1).

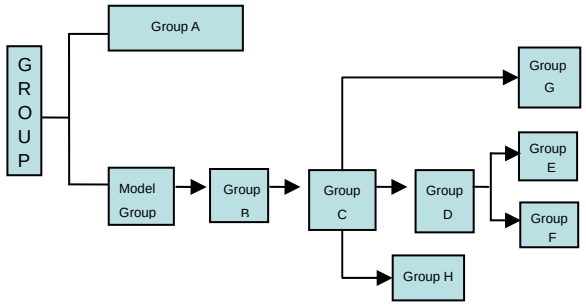


Figure 1 Block diagram of grouping in control and model group

Drawing materials

According to the corresponding time points, bilateral femoral vein vascular tissue (around 2 cm) were cut respectively, with 0.9% normal saline flush to remove blood and intraluminal thrombosis, 30 seconds *in vitro* and placed into frozen pipes, preserved in liquid nitrogen tanks for extraction of total RNA.

Femoral vein gene expression in TDVT

RNA extraction, chip hybridization and scanning: Using Trizol one-step method, the total RNA was acquired. The quality and the total amount if the obtained RNA were preserved in -80 ℃ refrigerator, after using agarose gel electrophoresis and spectrophotometer testing. The valid RNA samples were preserved in dry ice and sent to Shanghai Biochip Co.Ltd within 48 hours, labeled with biotin for hybridization.

Analysis of gene array data: The valid RNA samples were detected again by Lab-on quality determination system. Then they were labeled with biotin and for hybridization. According to the manipulation process of Genechip Rat Genome 430 2.0, genechips were detected through cDNA probe preparation, hybridization, staining and scanning in order. The differential expression genes were classified according to GO classification. The gene array were analyzed by using Affymetrix chip data processing data to read GCOC. The fluorescence intensity was 500. Through genechip data analysis (fold change analysis), we established the selection standards of differentially expressed genes.

Main outcome measures

The rate of thrombogenesis and nonthrombogenesis, the rate of thrombi solution and insolution of TDVT, and the expression of MMP and TIMP.

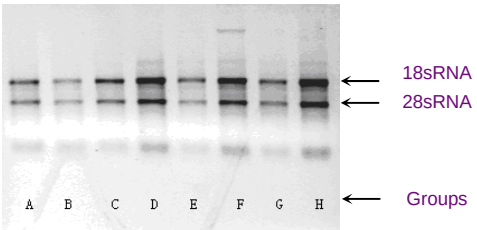
RESULTS

Animal model and grouping

Two of experimental animals died due to excessive bleeding and one died of unknown causes, the remaining rats survived. In this model, femoral vein thrombogenesis started at post-traumatic 2.5 hours. At the post-traurnatic 25 hours, the rate of thrombogenesis was 50.5% and nonthrombogenesis was 49.5%. To the post-traumatic 168 hours, the rate of thrombus solution was 56.7% and thrombus insolution was 43.3%.

Extraction of total RNA samples and electrophoretogram

The total mRNA of femoral vein vascular tissue from each group was extracted with Trizol method. Agarose gel electrophoresis analysis showed that the strip of 28SRNA and 18SRNA was trim. This outcome verified that the RNA samples were well integrity, high quality and no degradation (Figure 2).



A: normal control group; B: post-traumatic 0.5 hours; C: post-traumatic 2.5 hours (initial period of thrombosis); D: post-traumatic 25 hours (thrombogenesis at thrombotic crest-time); E: post-traumatic 25 hours (nonthrombogenesis at the thrombotic crest-time); F: post-traumatic 72 hours (thrombus resolution); G: post-traumatic 72 hours (thrombus insolution); H: post-traumatic 168 hours (nonthrombosis)

Figure 2 The electrophoretogram of RNA sample extracted from each group

MMP expression results

Gene chip test results showed that MMP 2, 3, 7, 8, 9, 10, 11,

12, 13, 14, 16, 17, 23, and 24 had different levels of expression at different critical points in TDVT (Table 1).

Table 1 The expressions of MMPs in traumatic deep vein thrombosis

Gene symbol	Probe set ID	A	B	C	D
MMP 2	1369825_at	181.6	174.1	315.5	272.2
MMP 3	1368657_at	100.7	634.4	1 167.9	2 140.3
MMP 7	1368766_at	7.5	4.4	12.3	16.2
MMP 8	1387735_at	114.0	280.9	547.1	452.6
MMP 9	1369166_at	61.7	92.8	220.8	233.0
MMP 10	1368713_at	14.1	23.4	19.1	34.9
MMP 11	1367858_at	34.4	79.0	95.6	52.8
MMP 12	1368530_at	113.5	116.6	1 398.7	606.0
MMP 13	1388204_at	53.0	48.0	1 363.7	1 545.8
MMP 14	1367860_at	1 313.8	958.8	7 980.9	6 935.8
MMP 16	1368590_at	88.2	47.8	90.9	67.9
MMP 17	1376410_at	1 755.2	1 532.4	364.1	718.8
MMP 23	1368961_at	836.7	748.8	968.6	766.7
MMP 24	1368595_at	109.2	133.5	119.4	149.0

Gene symbol	Probe Set ID	E	F	G	H
MMP 2	1369825_at	112.5	229.1	260.7	123.8
MMP 3	1368657_at	464.8	1087.8	291.0	54.1
MMP 7	1368766_at	9.4	15.9	14.2	4.6
MMP 8	1387735_at	201.3	121.7	93.7	50.6
MMP 9	1369166_at	86.8	88.3	70.4	8.4
MMP 10	1368713_at	17.3	27.3	22.0	10.9
MMP 11	1367858_at	41.4	140.4	29.4	127.3
MMP 12	1368530_at	200.1	480.7	162.2	117.2
MMP 13	1388204_at	355.9	498.7	24.7	12.6
MMP 14	1367860_at	4 486.1	63 26.8	2 968.1	1 076.6
MMP 16	1368590_at	75.8	131.0	117.4	412.6
MMP 17	1376410_at	917.3	913.5	1816.7	156.8
MMP 23	1368961_at	794.1	889.1	855.9	130.0
MMP 24	1368595_at	98.3	102.3	98.1	118.3

MMPs: matrix metalloproteinases; A: normal control group; B: post-traumatic 0.5 hours; C: post-traumatic 2.5 hours (initial period of thrombosis); D: post-traumatic 25 hours (thrombogenesis at thrombotic crest-time); E: post-traumatic 25 hours (nonthrombogenesis at the thrombotic crest-time); F: post-traumatic 72 hours (thrombus resolution); G: post-traumatic 72 hours (thrombus insolution); H: post-traumatic 168 hours (nonthrombosis)

TIMPs expression results

Gene chip test results showed that TIMP 1, 2, 3 had different levels of expression changes at different critical points in TDVT (Table 2).

Table 2 The expressions of TIMPs in traumatic deep vein thrombosis

Gene symbol	Probe set ID	A	B	C	D
TIMP1	1390571_at	39.1	306.0	57.2	88.4
TIMP2	1390573_at	789.6	746.4	805.9	705.8
TIMP3	1390577_at	905.4	504.5	800.5	526.8

Gene symbol	Probe set ID	E	F	G	H
TIMP1	1390571_at	155.4	223.6	41.4	39.1
TIMP2	1390573_at	802.6	642.4	632.1	789.6
TIMP3	1390577_at	533.1	394.4	726.3	905.4

TIMP: tissue inhibitor of metalloproteinases; A: normal control group; B: post-traumatic 0.5 hours; C: post-traumatic 2.5 hours (initial period of thrombosis); D: post-traumatic 25 hours (thrombogenesis at thrombotic crest-time); E: post-traumatic 25 hours (nonthrombogenesis at the thrombotic crest-time); F: post-traumatic 72 hours (thrombus resolution); G: post-traumatic 72 hours (thrombus insolution); H: post-traumatic 168 hou (nonthrombosis)

DISCUSSION

TDVT is one of common complications of clinical orthopedics. It is reported that the incidence of DVT is about 56-160/10 000 000 people each year in America[6], the elderly close to 1%[7]. DVT patients are about 10 000 000 each year in China[8]. The incidence of pulmonary embolism after coronary heart disease and high blood pressure, is the third largest cause of death[8-9]. Some data confirm that only 11%-15% of patients are diagnosed before death as pulmonary embolism[10-11]. Therefore, the study of TDVT mechanism is of great value. Studies have shown that MMPs participates in TDVT[12]. In this experimental study, we found that the expression of MMPs exhibited differential expressions in different time points, indicating the expression of MMPs participates in regulating thrombosis and resolution.

MMPs are a family by the Zn^{2+} dependent endopeptidase family of enzymes, it is the major media of extracellular matrix involving in degradation and remodeling, participating in many physiological and pathological processes in human body[13-14], widely expressed *in vivo*[15]. In 1962, Gross and Lapiere found the MMP (namely MMP-1). The MMPs have been found so far nearly 30 species, and 26 kinds of MMPs have been identified and sequenced[16]. MMPs are divided into five subtypes: collagenase, enzymes matrilysin, gelatinases, membrane proteases and other subtypes, the first three MMPs are located in the cytoplasm, membrane proteases express in the cell membrane[17]. Aa a non-active form of secretion, MMPs can be activated by protein hydrolysis, also be inhibited by some special TIMPs and ethylene diamine tetraacetic acid[18-19]. Through the positive feedback role, the activated MMPs could promote the activation of plasminogen and induce cascade reaction[20].

MMPs which is extracellular activation can degrade all the extracellular matrix components out of polysaccharide involving in growth, development and tissue repair and other physiological processes[21]. The activity of matrix degradation is a marked increasing after the expression of MMPs increased[22]. Study shows that MMP-9 and MMP-2 involve in regulation of vascular wall damage modeling and early repair of the transfer of collagen and matrix[23]. Visse *et al*[24] confirmed that MMP-2 and MMP-9 are closely related into the activities of angiogenesis and proteins, which come from collagen fibers in the thrombolytic process, and their reasons may be due to the u-PA activation of the MMP-2 and MMP-9. In this experiment, the expression of MMPs by gene chip test in the formation of the early and the peak time was significant hightened, indicating their participation in the thrombus formation process, and may serve as a catalyst. In the thrombus resulotion process, the expression of MMPs slightly rose up, in line with foreign research reports[25-27].

TIMPs family are coding proteins secreted by a cell which also secreted metalloproteinases, and they have the synthetic multi-gene family encoding proteins with MMPs and their activation of the zymogen form of combination[28]. TIMPs are the major physiological inhibitor of MMPs, and have already identified four kinds, with a specific inhibition of MMPs[29]. Under normal circumstances, the tissues keeps a balance between MMPs and TIMPs. Their interaction is the decision of

extracellular matrix degradation or aggregation[30]. In this experiment, the expression of TIMPs by gene chip test in the formation of the early and the peak time was different, indicating their participation in the thrombus formation process, and may serve as a catalyst. In the thrombus sulotion process, the expression of TIMPs slightly rose up, in which the expression of TIMP1 was mild high. TIMP 2 and 3 were significantly lower expression on their participation in the process of thrombosis. TIMPs may play a major inhibitory role in TDVT.

In summary, this experiment revealed that MMPs may play an important role in TDVT. MMPs were activated during the course of thrombosis, then through the positive feedback role in promoting the activation of plasminogen and occurring the activation cascade. In the course of thrombus insolution, MMPs continued to show a high expression, indicating in which they may have played a positive role in repair. The expression of TIMPs was significantly inhibited both in the thrombus formation and resolution process. Therefore, the imbalance of MMPs/TIMPs can be one of the most important factors to influence the biological states of TDVT, and its mechanism would be further studied.

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基质金属蛋白酶/金属蛋白酶组织抑制因子在大鼠创伤性深静脉血栓形成中的表达及作用**☆

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摘要

背景：创伤性深静脉血栓形成机制复杂，大量研究主要集中在临床观察和流行病学层面，其分子机制研究一直没有新的突破。

目的：应用基因芯片技术研究创伤性深静脉血栓形成过程中基质金属蛋白酶的表达变化规律，探讨其在创伤性深静脉血栓形成中的作用。

方法：SPF 级 8~12 周龄 SD 大鼠 150 只，体质量 250~300 g，随机分为正常对照组 10 只和模型组 140 只。模型组 140 只采用直接钳夹股静脉+双后肢石膏固定方式，建立大鼠创伤性深静脉血栓动物模型。又分为 7 组亚组，创伤即刻组(0.5 h)、血栓形成初始期组(2.5 h)、高峰期血栓形成组(25 h)、高峰期血栓不形成组(25 h)、血栓消退组(72 h)、血栓不消退组(72 h)和创伤后持续无血栓组(168 h)，每组 10 只。在相应时相点无创切取股静脉血管组织，随后抽取总 RNA，采用 Genechip Rat Genome 430 2.0 芯片对股静脉血管组织进行基因表达检测。观察创伤性深静脉血栓形成与不形成和消退与不消退的发生率；运用基因芯片数据分析方法分析基质金属蛋白酶和金属蛋白酶组织抑制因子在各时相点的表达。

结果与结论：模型组死亡 3 只，147 只大鼠进入结果分析。造模后 25 h 血栓形成率约为 50.5%，血栓不形成率约为 49.5%；168 h，有血栓的大鼠中大概有 56.7%发生消退，43.3%的血栓持续存在不消退。基质金属蛋白酶和金属蛋白酶组织抑制因子等均呈不同程度差异表达。血栓不消退状态时，基质金属蛋白酶仍呈高表达，金属蛋白酶组织抑制因子表达在血栓形成过程中处于下调状态，在消退过程呈明显抑制状态。在创伤性深静脉血栓形成与消退演化过程中，创伤后基质金属蛋白酶与创伤性深静脉血栓之间存在密切的关系，基质金属蛋白酶/ 金属蛋白酶组织抑制因子可能是影响血栓生物学状态的重要因素之一。

关键词：深静脉血栓形成；大鼠；创伤；基质金属蛋白酶；金属蛋白酶组织抑制因子

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