

**Thrombin-Activatable Fibrinolysis Inhibitor(TAFI)
Gene Polymorphism In Systemic Sepsis,
Relation To Disseminated Intravascular Coagulation**

Thesis

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Critical Care Medicine**

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

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Acknowledgement

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Thrombin-activatable fibrinolysis inhibitor (TAFI) gene polymorphisms in patients with systemic sepsis ,relation to disseminated intravascular coagulation.

Abstract

Thrombin-activatable fibrinolysis inhibitor (TAFI) is a recently identified as a potent inhibitor of fibrinolysis. TAFI is activated by the thrombin-thrombomodulin complex and activated TAFI suppresses fibrinolysis by removal of carboxy-terminal lysine (and arginine) residues from partly degraded fibrin polymers, preventing the binding of the fibrinolytic components Plasminogen and tissue-type Plasminogen activator to fibrin. Recently TAFI was identified as a link between coagulation and fibrinolysis, as TAFI can be activated by thrombin and once activated potently attenuates fibrinolysis, The plasma TAFI concentration is almost entirely genetically determined, on the bases of this one would predict that DNA polymorphisms that increase TAFI activity would deteriorate the outcome of sepsis and DIC. We investigated whether plasma TAFI levels and polymorphisms located in the TAFI gene could constitute in the pathogenesis and prognosis of sepsis and DIC in 40 patients suffering from sepsis of different etiology admitted the to the Intensive Care Unit of the Cairo University and 16 normal control persons . Their baseline characteristics were similar., There was increased TAFI antigen levels in all patients however no significant difference between Patients with sepsis, severe sepsis and septic shock regarding their TAFI antigen levels [median/interquartile range (IQR) 205/35.3, 234.8/50.3, and 221.6+49.5nmol/l, respectively, $p=0.543$],and also DIC patients .The TAFI 325 Ile genotype (of more antifibrinolytic activity was found in all patients on the contrary all the control person had TAFI 147 Ala of less antifibrinolytic activity .

In conclusion: The TAFI 325 Ile gene polymorphism and plasma activity was significantly high in patients with sepsis and in those with organ failure, suggesting that TAFI may play an important role in the mechanism of organ failure in DIC-associated sepsis.

Keyword : TAFI ,fibrinolysis, sepsis, DIC,thrombin ,TAFI polymorphism,MODS.

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List of Abbreviation

ADP:	Adenosine diphosphate
Ag:	Antigen
APACHE:	Acute physiology and chronic health evaluation
APC:	Activated protein C
ARDS:	Acute respiratory distress syndrome
AT:	Antithrombin
C3:	Complement 3
C5:	Complement 5
CIP:	Critical illness polyneuropathy
CPB:	Carboxypeptidase B
CPN:	Carboxypeptidase N
CPR:	Carboxypeptidase R
CPU:	Carboxypeptidase U
DIC:	Dissiminated intravascular coagulation
EGF:	Endothelial growth factor
ELISA:	Enzyme linked immunosorbent assay
EPCR:	Endothelial protein C receptor
FDPs:	Fibrin degradation products
FM:	Fibrin monomer
Fn:	Fibrin
HELLP:	Hemolysis, Elevated liver enzymes and Low Platelet
HR:	Heart rate
HS:	Heparin sulfate
F:	Fibrinogen
ICU:	Intensive care units

List of Abbreviation

II:	Prothrombin
IL:	Interlukin
IX:	Christmas Factor
Lps:	Lipopolysacarides
MAP:	Main arterial pressure
MODS:	Multiorgan dysfunction syndrome
MOF:	Multiorgan failure
MV:	Mechanical ventilation
NO:	Nitric oxide
PAF:	Platelet activating factor
PAI -1:	Plasminogen activator inhibitor -1
PC:	Protein C
PEEP:	Positive end expiratory Pressure
PGE2:	Prostaglandin E2
Pgn:	Plasminogen
Pn:	Plasmin
PS:	Protein S
PTCI:	Potato tuber carboxypeptidase inhibitor
r-APC:	recombinant activated protein C
ROS:	Reactive oxygen species
RR:	Respiratory rate
SIRS:	Systemic inflammatory response syndrome
SNP:	Single nuclutide polymorphism
TAFI:	Thrombin activable fibrinolysis inhibitor
TAFIa:	Thrombin activable fibrinolysis inhibitor activity
TAT:	Thrombin antithrombin
TF:	Tissue factor

List of Abbreviation

TFPI:	Tissue factor pathway inhibitor
Th:	T helper
Thr:	Threonine
TLR4:	Toll like receptor 4
TM:	Thrombomodulin
TNF α :	Tumour necrosis factor alpha
t-PA:	Tissue plasminogen activator
TXA ₂ :	Thromboxane A ₂
V:	Proaccelerin
VII:	Stable Factor
VIII:	Antihemophilic
X:	Stuart-Prower Factor
XI:	Thromboplastin antecedent
XII:	Hageman Factor
XIII:	Fibrin stabiliser

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Introduction

Sepsis is the leading cause of mortality in non cardiologic intensive care units ⁽¹⁾. Sepsis is generally considered to results from excessive activation of host's inflammatory defense mechanisms. These mechanisms include the release of cytokines and the activation of plasma protein cascade systems such as the complement, contact phase, coagulation and fibrinolytic systems.

The development of multiple organ dysfunction syndromes [MODS] is a frequent complication of sepsis and associated with poor outcome. Though the pathogenesis of MODS is not well understood, coagulation activation is suggested to be critically involved ^(2, 3, 4).

Plasminogen activator inhibitor type -1 (PAI-1) is considered the main cause for the down regulation of fibrinolysis during sepsis other anti-fibrinolytic pathways may contribute to this as well.

Recently thrombin activatable fibrinolysis inhibitor [TAFI] or procarboxypeptidase B or U, a new zymogene was identified as a potent inhibitor of fibrinolysis ^(5,6). Since activation of TAFI by thrombin is an inefficient process, large amounts of thrombin are required ⁽⁷⁾, which are generated upon thrombin mediated activation of F XI ^(8,9).

Thrombomodulin considerably potentiates the activation of TAFI by thrombin ⁽¹⁰⁾ By removing carboxy-terminal lysine and arginine residues from fibrin, activated TAFI [TAFIa] decreases tissue plasminogen activator (tPA) dependent activation of plasminogen and induces inhibition of fibrinolysis ⁽⁶⁾.

Although there are currently no data on TAFI levels in sepsis, but considering to its biochemical activity, TAFI can be postulated to contribute substantially to the inhibition of fibrinolysis in sepsis.

Recently TAFI was identified as a link between coagulation and fibrinolysis ^(11,12), as TAFI can be activated by thrombin and once activated potently attenuates fibrinolysis, ^(5,6) on the bases of this one would predict that DNA polymorphisms that increase TAFI activity would deteriorate the outcome of sepsis .⁽¹³⁾

Therefore ,we will study the prevalence of Thr325Ile dimorphism in the TAFI gene ,which is associated with increased TAFIa stability and activity in 40 patients with Sepsis and relation to disseminated intravascular coagulation [DIC], in comparison with 16 normal healthy volunteer.

TAFI antigen levels are in part dependent on genotype . ^(14,15) Three naturally occurring single nucleotide polymorphisms [SNPs] have been described in the coding region of the TAFI gene . Two of those results in amino acid substitutions, one at position 505A/G resulting in the amino acid substitution Thr 147Ala,⁽¹⁶⁾ the other at position 1040C/T leading to the substitution Thr325Ile .⁽¹⁷⁾ This latter SNP is of particular interest as the presence of the Ile residue increases the stability resulting in enhanced activity of TAFIa and consequently in an increased antifibrinolytic potential . ⁽¹⁷⁾

Because death in severe sepsis is due to multiorgan failure, caused in part by thrombotic occlusion of the microvasculature.