SUPPLEMENTAL MATERIAL

The effects of post-translational modifications of fibrinogen on clot formation, clot structure and fibrinolysis – a systematic review

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Supplemental Methods: Literature search
Supplemental Tables I-VII
Supplemental References

Supplemental Methods: Literature search

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('protein processing'/de OR 'post-translationally modified protein'/de OR 'adenosine diphosphate ribosylation'/exp OR 'citrullination'/de OR 'deubiquitination'/de OR 'neddylation'/de OR 'protein acetylation'/de OR 'protein carbonylation'/de OR 'protein dephosphorylation'/de OR 'protein glycosylation'/de OR 'protein methylation'/de OR 'protein phosphorylation'/de OR 'protein prenylation'/de OR 'sumoylation'/de OR 'ubiquitination'/de OR 'acylation'/exp OR 'adenylation'/de OR 'ammonification'/de OR 'glucuronidation'/de OR 'glycosylation and deglycosylation'/de OR 'hydroxylation'/de OR 'methylation'/de OR 'nitration'/de OR 'phosphorylation and dephosphorylation'/exp OR 'sulfation'/de OR 'carboxylation and decarboxylation'/exp OR (((post-translational* OR posttranslational*) NEAR/3 (modification* OR modified OR modify)) OR ((protein*) NEAR/6 (processing)) OR ((fibrinogen*) NEAR/6 (acetylation* OR carbonylation* OR dephosphorylation* OR phosphorylation* OR prenylation* OR ribosylation* OR citrullination* OR deubiquitination* OR neddylation* OR sumoylation* OR ubiquitination* OR oxidation* OR oxydation* OR acylation* OR Acetylation* OR biotinylation* OR carbamoylation* OR carbamylation* OR formylation* OR Friedel-Crafts-reaction* OR lipoylation* OR glycation* OR myristylation* OR palmitoylation* OR adenylation* OR ammonification* OR glucuronidation* OR glycosylation* OR hydroxylation* OR methylation* OR nitration* OR sulfation* OR homocysteinylation* OR acetylated* OR carbonylated* OR dephosphorylated* OR phosphorylated* OR prenylated* OR ribosylated* OR citrullinated* OR deubiquitinated* OR neddylated* OR sumoylated* OR ubiquitinated* OR oxidated* OR oxydated* OR acylated* OR Acetylated* OR biotinylated* OR carbamoylated* OR carbamylated* OR formylated* OR Friedel-Crafts-reaction* OR lipoylated* OR myristylated* OR palmitoylated* OR adenylated* OR ammonificated* OR glucuronidated* OR glycosylated* OR hydroxylated* OR methylated* OR nitrated* OR sulfated* OR homocysteinylated* OR glycated* OR carboxylation* OR decarboxylation* OR carboxylated* OR decarboxylated* OR lipidation* OR lipidated*))):ab,ti)
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AND
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AND
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(exp Blood Coagulation/ OR Polymerization/ OR exp Fibrin/ OR (coagulat* OR ((blood OR fibrin* OR hemostatic OR haemostatic) ADJ6 (clot*)) OR fibrin-deposition* OR ((fibrin) ADJ3 (format* OR polymerization* OR polymerisation*)) OR fibrinolys* OR blood-clot-lys* OR fibrinogenolys* OR ((plasminogen*) ADJ3 (activ*)) OR ((fibrin) ADJ6 (network* OR stabilit* OR stable OR structure*)) OR ((fibrinogen*) ADJ6 (behavior* OR behaviour* OR function*)) OR ((clot*) ADJ3 (permeab* OR densit* OR stiffness*)) OR ((fiber* OR fibre* OR fibrin*) ADJ6 (thickness))).ab,ti.)

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AND
((fibrinogen* OR ((clot*) NEAR/2 (factor-i OR factor-1)) OR clottagen*))
AND
((coagulat* OR ((blood OR fibrin* OR hemostatic OR haemostatic) NEAR/5 (clot*)) OR fibrin-deposition* OR ((fibrin) NEAR/2 (format* OR polymerization* OR polymerisation*)) OR fibrinolys* OR blood-clot-lys* OR fibrinogenolys* OR ((plasminogen*) NEAR/2 (activ*)) OR ((fibrin) NEAR/5 (network* OR stabilit* OR stable OR structure*)) OR ((fibrinogen*) NEAR/5 (behavior* OR behaviour* OR function*)) OR ((clot*) NEAR/2 (permeab* OR densit* OR stiffness*)) OR ((fiber* OR fibre* OR fibrin*) NEAR/5 (thickness)))))

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Supplemental Table I. Effects of oxidation of fibrinogen

Author	Method	Clottability	Cleavage by thrombin	Rate of polymerization	Initiation of polymerization	Maximum turbidity	Diameter of fibers	Stiffness of clot	Permeability	Density	Cross-linking	Plasmin digestion of fibrinogen	Clot lysis
Palos et al. (1949) [1]	Fibrinogen + molecular oxygen			=									
Sizer et al. (1951) [2]	Bovine fibrinogen + tyrosinase	↓		↓			↓						
Krugelis et al. (1954) [3]	Fibrinogen or plasma + tyrosinase			↓									
Zieve et al. (1966) [4]	Irradiation of fibrinogen			↓									
Inada et al. (1978) [5]	Photooxidation of fibrinogen	↓	=	↓		↓							
Ishida et al. (1978) [6]	Fibrinogen + 0-150 mM H_2O_2			↓		↓							
Shacter et al. (1995) [7]	Fibrinogen + 25 mM ascorbate + 100 μM $FeCl_3$		↓	↓		↓							
	γ-irradiation of fibrinogen		=	↓									
Upchurch et al. (1998) [8]	Fibrinogen + 25 mM ascorbate + 100 μM $FeCl_3$			↑									
Lupidi et al. (1999) [9]	Fibrinogen + 0-80 μM peroxynitrite		=	↓									
Roitman et al. (2004) [10]	UV-irradiation of fibrinogen			↓				↓		↓			=
Vadseth et al. (2004) [11]	Fibrinogen + 60 nM MPO + 100 μM H_2O_2							↓	↓				
Nowak et al. (2007) [12]	Fibrinogen + 10 μM peroxynitrite			=	=	=						=	
	Fibrinogen + 100 or 1000 μM peroxynitrite			↓	↓	↓						↓	
Andrades et al. (2009) [13]	Bovine fibrinogen or human plasma + 1 mM glylcolaldehyde			↓	↓	↓	↓						↓
Azizova et al. (2009) [14]	Fibrinogen + 50-500 μM $FeSO_4$ + 10-250 μM H_2O_2			↓									
Piryazev et al. (2009) [15]	Fibrinogen + 50-500 μM $FeSO_4$ - H_2O_2			↓		↓							=

Rosenfeld et al. (2009) [16]	Fibrinogen + 200-600 nmol ozone			↓	↑		↑						
Tetik et al. (2011) [17]	Fibrinogen + 100 µM Fe^{3+}/ascorbate			↓	↓			↓					↓
Weigand et al. (2012) [18]	Fibrinogen + 50 or 150 µmol HOCl/g fibrinogen			=		↓	↓	↓	↓	↑	=		↓
Xu et al. (2012) [19]	Bovine fibrinogen + 9 mM reactive carbonyl compounds		↓	↓		↓ (ns)							
Rosenfeld et al. (2013) [20]	Fibrinogen + 300 nmol ozone			↓			↑						
Stikarova et al. (2013) [21]	Fibrinogen + 10 mM MDA					↓ (ns)	↓			↑			
	Fibrinogen + 1.25 mM NaOCl			↓		↓	↓		↑				
	Fibrinogen + 100 µM SIN-1					↓ (ns)	↓			↑			
Becatti et al. (2014) [22]	Fibrinogen + 0.01-1 mM AAPH			↓	↓	↓							↓
Rosenfeld et al. (2014) [23]	Fibrinogen + 50-200 nmol ozone										↑		
Torbitz et al. (2015) [24]	Fibrinogen + 1, 2 or 4 mM HOCl			↑									
Harutyunyan et al. (2017) [25]	Rat plasma + 0.05-0.2 (L) or 0.2-0.8 (H) mM Fe^{2+}/H_2O_2			L= H↑									
Wang et al. (2018) [26]	Fibrinogen + 0.5 mM H_2O_2 + 3 mg/ml Fe_3O_4			↓			↓	↓↑		↑	↑		
Yurina et al. (2019) [27]	Fibrinogen + 50, 500 or 1500 µmol HOCl/mg fibrinogen			↓		↓							
Paton et al. (2010) [28]	Fibrinogen from MI patients			↑	=	↑	↑			↓			
Becatti et al. (2014) [22]	Fibrinogen from MI patients			↓	↓	↓	↓						↓
Becatti et al. (2016) [29]	Fibrinogen from patients with Behçet disease			↓	↓	↓							↓
Hugenholtz et al. (2016) [30]	Fibrinogen from cirrhosis patients			=		=			↓	=			
	Plasma from cirrhosis patients			↓		=	=		↓	=			
White et al. (2016) [31]	Plasma from trauma patients			↓				↓					↑

Abbreviations: AAPH, 2′-azobis(2-amidinopropane) dihydrochloride; Fe^{2+}, ferrous ion; Fe^{3+}, ferric ion; $FeCl_3$, iron(III)chloride; Fe_3O_4, iron(II),(III)oxide; $FeSO_4$, iron(II)sulfate; H_2O_2, hydrogen peroxide; HOCl, hypochlorous acid; MDA, malondialdehyde; MI, myocardial infarction; MPO, myeloperoxidase; NaOCl, sodium hypochlorite; SIN-1, 3-morpholinosydnonimine (forms peroxynitrite).

Supplemental Table II. Effects of nitration of fibrinogen

Author	Method	Clottability	Cleavage by thrombin	Rate of polymerization	Initiation of polymerization	Maximum turbidity	Diameter of fibers	Stiffness of clot	Permeability	Density	Cross-linking	Plasmin digestion of fibrinogen	Clot lysis
Bijak et al (2012) [32]	Fibrinogen + 1 μM peroxynitrite			↑		↑							
Nowak et al (2007) [12]	Fibrinogen + 10 μM peroxynitrite			=	=	=						=	
Ding et al (2014) [33]	Bovine fibrinogen + 8.7 μM peroxynitrite + manganese			↓									
Bijak et al (2012) [32]	Fibrinogen + 10 or higher μM peroxynitrite			↓		↓	↓			↑			
Lupidi et al. (1999) [9]	Fibrinogen + 0-80 μM peroxynitrite		=	↓									
Vadseth et al. (2004) [11]	Fibrinogen + 100 μM nitrite				↑	↑							
Nowak et al (2007) [12]	Fibrinogen + 100 or 1000 μM peroxynitrite			↓	↓	↓						↓	
Bijak et al (2013) [34]	Fibrinogen + 100 μM peroxynitrite			↓		↓							
Gole et al. (2000) [35]	Fibrinogen + 1 mM peroxynitrite			↑									
Helms et al (2017) [36]	Fibrinogen + 5 μM ProliNONOate			↓ (ns)			↑	=		↓			
Ponzcek et al (2008) [37]	Fibrinogen + 10 μM NO_2BF_4			↑	↑	↑							
Ponzcek et al (2008) [37]	Fibrinogen + 0.1 or 1 mM NO_2BF_4			↓	↓	↓							
Vadseth et al (2004) [11]	Fibrinogen from CAD patients		=	↑	↑	↑	↓	↓	↑		↑	=	=
Parastatidis et al (2007) [38]	Depletion of nitrated fibrinogen from			↑		↑							

	CAD patients (only 3)												
Parastatidis et al (2008) [39]	Fibrinogen from smokers			↑		↑	=	↑					↓
	Depletion of nitrated fibrinogen			↑									
Heffron et al (2009) [40]	Plasma from volunteers receiving 1 ng/kg LPS			↑		=							

Abbreviations: CAD, coronary artery disease; LPS, lipopolysaccharide.

Supplemental Table III. Effects of glycosylation of fibrinogen

Author	Method	Clottability	Cleavage by thrombin	Rate of polymerization	Initiation of polymerization	Maximum turbidity	Diameter of fibers	Stiffness of clot	Permeability	Density	Cross-linking	Plasmin digestion of fibrinogen	Clot lysis
Glycosylation													
Gligorijevic et al (2018) [41]	Fibrinogen from aging people			=		=	=		=				
Deglycosylation													
Gilman et al (1984) [42]	Rabbit hepatocytes + tunicamycin			=									
Langer et al (1988) [43]	Fibrinogen + PNG-Asn amidase		=	↑		↑	↑		↑		=	=	
Sialylation (increased sialic acid level compared to normal)													
Gralnick et al (1978) [44]	Fibrinogen from patients with hepatoma		=	↓	↓	=					=	=	=
Martinez et al (1978) [45]	Fibrinogen from patients with liver disease			↓									
Martinez et al (1983) [46]	Fibrinogen from patients with liver disease			↓	↓	↓							
Maghzal et al (2005) [47]	Fibrinogen from patients taking fibrates			↓	↓								
Desialylation													
Chandrasekhar et al (1962) [48]	Bovine fibrinogen + neuraminidase			↑									
Laki et al (1962) [49]	Bovine fibrinogen + periodate	↓											

Gentry et al (1976) [50]	Fibrinogen + neuraminidase			=				=			=		
Martinez et al (1977) [51]	Fibrinogen + neuraminidase		=	↑	↑	↑					=		
Martinez et al (1978) [45]	Fibrinogen with increased sialic acid + neuraminidase			↑									
Diaz-Maurino et al (1981) [52]	Fibrinogen + neuraminidase			↑									
Diaz-Maurino et al (1982) [53]	Fibrinogen + neuraminidase			↑									
Martinez et al (1983) [46]	Fibrinogen with increased sialic acid + neuraminidase			↑									
Dang et al (1989) [54]	Fibrinogen + neuraminidase			↑		↑	↑						
Okude et al (1993) [55]	Fibrinogen + neuraminidase		=		=	↑		↓			↓		
El-Fasakhany et al (2003) [56]	Bovine fibrinogen + neuraminidase			↑									
Maghzal et al (2005) [47]	Fibrinogen from pregnant women			↑ (ns)	↑ (ns)								

Abbreviations: PNG-Asn amidase, peptide-N-(N-acetyl-β-glucosaminyl)asparagine amidase.

Supplemental Table IV. Effects of glycation of fibrinogen

Author	Method	Clottability	Cleavage by thrombin	Rate of polymerization	Initiation of polymerization	Maximum turbidity	Diameter of fibers	Stiffness of clot	Permeability	Density	Cross-linking	Plasmin digestion of fibrinogen	Clot lysis
Norton et al (2017) [57]	Fibrinogen + 5 or 10 mM glucose (90 or 180 mg/dL)												
Hood et al (2018) [58]	Fibrinogen + 6 or 10 mM glucose (108 or 180 mg/dL)									↑			
Dunn et al (2005) [59]	Fibrinogen + 0-20 mM glucose (0-360 mg/dL)		=		↓	↓	=		↓	↑	=		
Ney et al (1985) [60]	Fibrinogen + 5 or 20 mM glucose (90 or 360 mg/dL)		=	=							=	↓	=

Kanska et al (2005) [61]	Bovine fibrinogen + 25 mM glucose (450 mg/dL)	↑									↓	
McVerry et al (1981) [62]	Fibrinogen + 30 mM glucose (540 mg/dL)			=								
Krantz et al (1987) [63]	Fibrinogen + 20 or 50 mM glucose (360 or 900 mg/dL)		=	↑		↑				=	↓	
Norton et al (2017) [57]	Fibrinogen + 25 or 50 mM glucose (450 or 900 mg/dL)											
Mirmiranpour et al (2012) [64]	Fibrinogen + 50 mM glucose (900 mg/dL)			↑								
Mirshahi et al (1987) [65]	Fibrinogen + 100 mM glucose (1800 mg/dL)		=	=						=		↓
Brownlee et al (1983) [66]	Fibrinogen + 50 or 500 mM glucose (900 mg/dL or 9 g/dL)											↓
Murakami et al (1990) [67]	Rat fibrinogen + 500 mM glucose (9 g/dL)	=										↓
Robinson et al (1991) [68]	Fibrinogen + 500 mM glucose (9 g/dL)	↑										
Lutjens et al (1988) [69]	Fibrinogen from type 1 diabetics			↓	=	=					α↓ γ=	↑	
Robinson et al (1991) [68]	Fibrinogen from diabetics	↑											
Dunn et al (2005) [59]	Fibrinogen from type 2 diabetics		↑		↑	↑			↓	↑	α↑ γ=		
Pieters et al (2008) [70]	Fibrinogen from type 2 diabetics			↑			=	=	↓		=		↓
Pieters et al (2006) [71]	Plasma from type 2 diabetics			=	=	=			=	=			
Li et al (2016) [72]	Plasma from type 2 diabetics							=					

Supplemental Table V. Effects of acetylation of fibrinogen

Author	Method	Clottability	Cleavage by thrombin	Rate of polymerization	Initiation of polymerization	Maximum turbidity	Diameter of fibers	Stiffness of clot	Permeability	Density	Cross-linking	Plasmin digestion of fibrinogen	Clot lysis

Caspary et al (1956) [73]	Fibrinogen + NS-diacetylthioethanolamine		=	↓									
Philips et al (1973) [74]	Bovine fibrinogen + N-acetylimidazole	=		=				↓					
Wegrzynowicz et al (1975) [75]	Bovine fibrinogen + acetic anhydride		=	↓									
Bjornsson et al (1989) [76]	Fibrinogen + acetic anhydride			↓									↑
Upchurch et al (1998) [8]	Fibrinogen + 0.18 mg/ml aspirin			=									
He et al (2001) [77]	Fibrinogen + 0.16-12.96 mM aspirin (30-2330 mg/L)			↓		↓					↓		
Ajjan et al (2009) [78]	Hamster fibrinogen + 1, 10 or 100 mg/L aspirin				↓	↑	↑	↓	↑	↓			↑
He et al (2009) [79]	Fibrinogen + 0.07 mM aspirin (13 mg/L)			=			↑		↑	↓			↑
Bjornsson et al (1989) [76]	Plasma from volunteers taking 650 mg aspirin 2x/day			↑		↑							↑
Williams et al (1995) [80]	Plasma from patients with SAP taking 75 mg aspirin			↓		↓	↑						↑
Fatah et al (1996) [81]	Plasma from patients with SAP taking 75 or 160 mg aspirin								↑	↓			
Jörneskog et al (1998) [82]	Plasma from type 1 diabetics taking 75 mg aspirin						↑		↑				
Williams et al (1998) [83]	Plasma from volunteers taking 75 mg aspirin						↑		↑				=
	Plasma from volunteers taking 320 mg aspirin						=		↑				
Antovic et al (2005) [84]	Plasma from volunteers taking 37.5 mg aspirin						↑		↑				
	Plasma from volunteers taking 320 or 640 mg aspirin						=		↑				
Ajjan et al (2009) [78]	Fibrinogen from volunteers taking 150 mg aspirin				=	↑	↑						↑

Abbreviations: SAP, stable angina pectoris.

Supplemental Table VI. Effects of phosphorylation of fibrinogen

Author	Method	Clottability	Cleavage by thrombin	Rate of polymerization	Initiation of polymerization	Maximum turbidity	Diameter of fibers	Stiffness of clot	Permeability	Density	Cross-linking	Plasmin digestion of fibrinogen	Clot lysis
Phosphorylation													
Hanna et al (1984) [85]	Fibrinogen separated in different fractions		↑										
Heldin et al (1987) [86]	Fibrinogen + protein kinase C		=	=			↓				=		
Forsberg et al (1989) [87]	Fibrinogen + protein kinase C					↓	↓						
Forsberg et al (1990) [88]	Fibrinogen + protein kinase C											↓	
Martin et al (1991) [89]	Fibrinogen + protein kinase A					↓	↓					↓	
	Fibrinogen + protein kinase C					↓	↓						
	Fibrinogen + casein kinase I					=	=					↓	
	Fibrinogen + casein kinase II					↑	↑					↓	
Heldin (1987) [90]	Fibrinogen + casein kinase II					↑							
Suk et al (1997) [91]	Fibrinogen + casein kinase II			↑		↑							
Martin et al (1992) [92]	Fibrinogen from patients after hip surgery					↑	↑					↓	
Dephosphorylation													
Blombäck et al (1963) [93]	Fibrinogen + alkaline phosphatase	=		↓									
Forsberg et al (1989) [87]	Fibrinogen + alkaline phosphatase					↑	↑						
Forsberg et al (1990) [88]	Fibrinogen + alkaline phosphatase											=	
Martin et al (1991) [89]	Fibrinogen + alkaline phosphatase					↑	↑						
Martin et al (1992) [92]	Fibrinogen + alkaline phosphatase					↑	↑						

Supplemental Table VII. Effects of other modifications of fibrinogen

Author	Method	Clottability	Cleavage by thrombin	Rate of polymerization	Initiation of polymerization	Maximum turbidity	Diameter of fibers	Stiffness of clot	Permeability	Density	Cross-linking	Plasmin digestion of fibrinogen	Clot lysis
Homocysteinylation													
Sauls et al (2003) [94]	Rabbit model of homocysteinuria			↑			↓			↑			↓
Lauricella et al (2006) [95]	Plasma + 500 μM hcys			=		↑	↑			↑			↓
Sauls et al (2006) [96]	Fibrinogen + 300 μM hcys	=					↓			↑			↓
	Fibrinogen + 30 mM hcys	↓											
Marchi et al (2008) [97]	Plasma + 13, 19, 52 μM hcys			↓	↓	↓	=						↓
	Plasma + 251 μM hcys			=	=	=					=		
	Fibrinogen + 408 μM hcys			↓	↓	↓					=		
Rojas et al (2009) [98]	Plasma + 50-500 μM hcys							↑					
Sauls et al (2011) [99]	Fibrinogen + 300 μM hcys											↓	↓
Citrullination													
Nakayama-Hamada et al (2008) [100]	Fibrinogen + PAD4	↓	↓	↓		↓							
Okumura et al (2009) [101]	Fibrinogen + PAD2	↓	↓	↓		↓							
Damiana et al (2019) [102]	Fibrinogen + 0.7-20 μg/ml PAD2			↓		↓	↓			↓			↑ (ns)
Carbamylation													
Binder et al (2017) [103]	Fibrinogen + 5 or 100 mM KOCN		=	↓	↓	↓	↓			↑	↓		↓
Guanidinylation													
Schuett et al (2017) [104]	Fibrinogen + 1 M o-methylisourea bisulfate						↓						
	Plasma from patients on hemodialysis						↓		↓				

Abbreviations: hcys, homocysteine; PAD, peptidyl arginine deiminase; KOCN, potassium cyanate.

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