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REVIEW

Apolipoprotein A-I: Insights from redox proteomics for its role in neurodegeneration

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b d c eb a d (CSF) a c d ead e e g d ea e g e d g/ea e ef- . cac . A fe a a e e e d- e, ced ffe e ce . b ec e ec , a e ea a , a da a ec e ed c d ead c c g e . I add , f e e e -ba ed b a g . d e e a a bo f a e, c ead e e a e . a eed be e . ed . g d ffe e e d a d c . ed a ge a e e . S , Ta e e a . b d . gge ed a e e c c da e e a / ed a e ba ed eac d d a e e e be de e ed [4].

P e e a e a a d c a e f a de- ec ab e e a a e f e f e e . P e e eg a d ge a a e f PTM f ac a , deac a , a d d e f e b g ca f c . P e d f c ca cc e eac e ge a d eac e ge ec e (ROS, RNS) ca e abe a da e a d e a ec a ge e e a e g e . c ea d f c [5] e ed a da e/ e a e e . C e ed d ce f da- e da age e e c. de ca b a , e e a- , a d b d g f eac e a e a [6]. Red e e c b e e e e e e c e e f e da e e ea e e a de e a f ec . c e da ec a ge e a e e f e e a d e de a g e d ea e ec a [6 10].

U ge e e a d ed e e c , a bo f e- e a bee f d be a ed e de ge e a e d- ded . I e e , ef c e d c a e e a e- e A-I (A A-I), a e e a bee f d be a ed e e e ec . c da e e e de ge e a e d ded , A/ e e d ea e (AD), Pa d ea e (PD), D d e (DS), a d ca co a é e c e a (Tab e 1) ROS d c g c e e a e cage . A A-I a a a e e e de ge e a e d ded a e a Ha e ea e ed a ea e a e e- e A-I f e e a de e a [11].

A A-I a f c a a e e a a

Table 1. Proteomic studies showing changes in ApoA-I expression or oxidation in neurodegenerative disorders

Disease	Sample	Sample size	Methods	Effects on ApoA-I	Reference
AD	CSF	$n = 86$ (pooled samples)	2DE	ApoA-I ↓	Castano et al. 2006
AD	CSF	$n = 27$	2DE (MALDI-TOF-MS + ESI-MS/MS)	Proapolipoprotein ↓	Davidsson et al. 2002[a)]
AD	CSF	$n = 27$	2DE	-	Davidsson et al. 2002[a)]
AD	CSF	$n = 19$	2DE oxyblot (protein carbonyls) + LC-MS/MS	Proapolipoprotein A1 oxidation in AD and controls	Korolainen et al. 2007
AD	CSF	$n = 14$	2DE MALDI TOF	ApoA-I ↓	Puchades et al. 2003[a)]
AD	CSF	$n = 6$	(1DE + LC-MS/MS) 2DE (+ MS/MS)	-	Yin et al. 2009[a)]
AD	Serum	$n = 20$	2DE MALDI TOF MS	ApoA-I ↓	Liu et al. 2005
DOX-treated patients	Plasma	$n = 12$ paired	2DE (MS/MS)	ApoA-I oxidation ↑	Aluise et al. 2011
DS	Maternal plasma from DS pregnancies	$n = 28$	2D DIGE MALDI- TOF MS + ESI QTOF MS/MS	-	Heywood et al. 2011
DS	Maternal serum from DS pregnancies	$n = 36$	iTRAQ + strong cation exchange (SCX) LC-MS/MS	ApoA-I ↓	Kang et al. 2012[a)]
DS	Maternal plasma from DS pregnancies	$n = 24$	2DE + MALDI TOF MS	-	Kolialexi et al. 2008[a)]
DS	Maternal plasma from DS pregnancies	$n = 12$ (pooled samples)	iTRAQ + strong cation exchange (SCX) LC-MS/MS	ApoA-I ↓	Kolla et al. 2010[a)]
DS	Maternal serum from DS pregnancies	$n = 40$ (pooled samples for 2D-CF)	2D DIGE 2D-LC–chromatofocusing (2D-CF) Q-TOF; MS + MS/MS	ApoA-I ↑	Nagalla et al. 2006[a)]
DS	Amniotic fluid from DS pregnancies	$n = 10$	1D SDS-PAGE LC-ESI-MS/MS	ApoA-I preproprotein ↑	Park et al. 2010
DS	Amniotic fluid from DS pregnancies	$n = 20$	2DE oxyblot (PC)	ApoA-I oxidation ↑	Perluigi et al. 2011
DS	Amniotic fluid from DS pregnancies	$n = 18$	2DE + MALDI-TOF MS + nano-ESI MS/MS	-	Tsangaris et al. 2006
DS	Amniotic fluid from DS pregnancies	$n = 26$	2D LC + MALDI TOF MS	ApoA-I ↓	Wang et al. 2009
DS with gout (G)	Serum	$n = 8$	2DE (+MALDI TOF MS)	ApoA-I ↓	Chen et al. 2006
FTD	CSF	$n = 10$	2DE	ProapolipoproteinA1 ↑	Hansson et al. 2004 [11]
PD	CSF	$n = 6$	2D-DIGE (MALDI-TOF + MALDI-TOF/TOF)	ApoA-I (isoform) ↓ ApoA-I (isoform) ↑ proapolipoprotein ↑	Wang et al. 2010
PD	CSF	$n = 6$	(1DE + LC-MS/MS) 2DE (+ MS/MS)	ApoA-I ↓	Yin et al. 2009[a)]
PD	Serum	$n = 22$	iTRAQ (2DE LC-MS/MS)	ApoA-I ↓	Zhang et al. 2012[a)]

a) These studies also showed effects on other apolipoproteins.

Figure 1. Oxidatively modified ApoA-I. The left-hand side of the figure depicts an HDL particle with bound ApoA-I that has not undergone oxidative damage, and as shown, is able to function normally interacting with LCAT, peripheral ABCA1 and scavenger receptor BI (SRB-1). The right-hand side of the figure displays an HDL particle that has undergone extensive oxidative modification on ApoA-I, a process that has been shown to negatively affect the ability of the HDL particle to interact peripherally with ABCA-1, LCAT, and SRB-1. This loss of function of ApoA-I has many consequences such as impaired ABCA1 signaling and cholesterol deposition to HDL, impaired cholesterol to cholesteryl conversion by LCAT, and the inability to dock with SRB-1. See text.

bac , e , a d beca e f e, HDL e a bee f d a ea e ea ca d ac - a d ea e [25 27]. T e a a e c e f HDL A A-I, e be f e ee c e e ad- g f HDL f ce b d g ABCA1 a e a e e e f a E, c a ec -c e e ac - a f a e (LCAT) ac [22, 28] (F g. 1). O ce aded, e c e e e . ed b LCAT, d c g c e e e a d a f g HDL HDL3. HDL3 ca e f c e ac a ge ec e e e a d a e e A, C, a d E f g co de f e , c g c- e de a e ab da , f g HDL2 a ca b e. e de e c e e e e ca e ge ece BI a e e [23, 24]. I e e g , b e a ce d e- a ce a e da e d. ca f HDL, e A A-I, b e e da e a f. c e deg ea e HDL ac SR-B1 a e a d ce a e- a a a e a

e e fac -α (TNF-α) d ced e e f e ac a ce ad e ec e 1 e a e a . ea fac a a-B (NF B) ac a [29].

3 HNE modification of ApoA-I

A A-I a ca a ce be d. ca b d e-

d a e b e f b d g a d e c g e DD f

ce f e a d ec e (APP) [76], a e e c ded b a ge ge e c e 21 [77,78]. O da e e a d a a e a ea g a a e e e a e f AD, a d a . be f d/ed e a e ac a ed g a e bee f d b a eg affec ed b AD [79 81] c ead e g AD a a . fac a d ea e.

Le a 5% f AD ca e a e a c a ed ec. c . a , f e e cc g e ge e e - c d g APP e *presenilin* e . H e , e a f AD ca e a e ad c, a g a e e4 f ea E e , c a a e c e e e ab a d a bee b d A , a bee de . ed a a e g fac [82, 83]. I ea ge de ce . a a e f d e de ge e a . A . be f . d e a e f- c ed e be ee c e e a d AD, f e a e, g a g . c e e e ea c a ed e d ea e [84, 85]. A d ge c APP ce g a bee a e ace d af , c e e c eg f e e b a e [86], a d e b d g f c e e APP affec e ce c ea age. T e a APP deg ada d c e A . affec e ac f c e e LDL a E, e ec e [87] ead g e c c. -

e a HDL e , da e d. ca f A A-I d affec f c f HDL.

8 ApoA-I and PD

Pa y d ea e, e AD, a age ea ed e dege e- a ed ea e a d a g ca a a c. de ge- e f d a g c e e b a a g a, a c ac a, a d f a f Le b d c. e c a f e [125]. Add a , da e e a bee ca ed e d ea e, a d ea ed e e f DNA, d, a d e da a y e f d b a f PD. b ec [126 131].

I a ece e e . d f CSF a e f PD a e a d ea c e , A A-I a be d ffe- e a e e ed. U g 2D-DIGE a A A-I f a be d eg a ed e a d ffe e A A-I f a eg a ed PD [2]. I add , Wa g e a. 2010 f d e-a e e , e a. e ec f A A-I, a eg a ed PDa e . We e b a a e f ed c . e e e. ed g . ca eg a ed A A-I e e CSF [2].

T e ec c g e. e e f e g f 2D a ac e e. We e b g: A e c. d

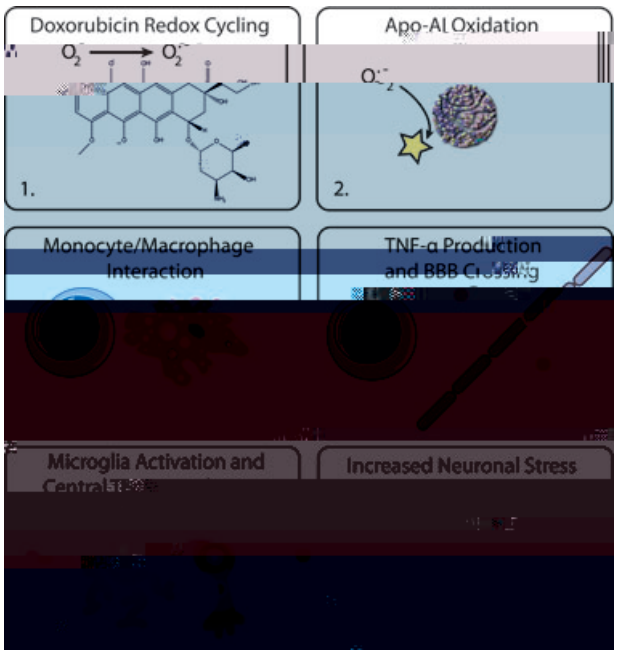

Figure 2. Proposed TNF-α model in this proposed model, peripheral doxorubicin redox cycling between the quinone and semiquinone states within the circulatory system produces the reactive oxygen species superoxide ($O_2^{\cdot-}$) in abundance (Box 1) that oxidatively modifies ApoA-I on HDL particles (Box 2). This modified ApoAI is no longer able to inhibit the monocyte/macrophage interaction (Box 3) and because of this, TNF-α is produced. TNF-α is subsequently able to cross the BBB (Box 4) and activate microglia initiating the production of a host of pro-inflammatory mediators ultimately leading to central TNF-α production as well as increased ROS/RNS (Box 5), which damage neurons and ultimately lead to neuronal death (Box 6). See text.

10 Conclusions and discussion

Red e e c de . ed A -I a a e e ed DS a d e a ec a f c e b a . T , , ed e b c e ca . de e gga e e e f A -I TNF g a g. T a ce e e e ab , ef . , a d a ed b A -I c e e ab , a a , a d e de ge a . O da e PTM f A -I e . d f c a c e e ce - g, d eg a f a a e ce e, a d e de - ge a , a e, ea ga d c g e dec e. A -I a bee f d a a ed e e a d da e da aged c e de ge a ed d de a AD, PD, f e a de e a, a d DS a e a e a a f ca ce a e c e a .

DOX e a ed A -I b e . e e a f a TNF-α e e . U e DOX, a ge a ed TNF-α ca e e BBB a TNFR1 a d TNFR2 e d c - a d ac a ed a ece ca ed e CNS. W e CNS, b TNF-α ece , TNFR1, a d TNFR2, a e ca ed e e b a e f e a a d g a ce - a [147, 148], a d ca c b e e e a dea .

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