Rapid Communication

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From influenza infection to anti-ADAMTS13 autoantibodies via cross-reactivity

DOI: 10.2478/ii-2019-0002
Received February 16, 2019; accepted March 21, 2019; published online May 2, 2019

Abstract: Autoantibodies (AAbs) against von Willebrand factor (vWF)-cleaving protease ADAMTS13 causally relate to thrombotic thrombocytopenic purpura (TTP). How anti-ADAMTS13 AAbs are generated is unknown. Starting from reports according to which influenza infection can trigger TTP by the production of ADAMTS13 AAbs, this study explores influenza viruses and ADAMTS13 protein for common peptide sequences that might underlie anti-influenza immune responses able to cross-react with ADAMTS13. Results document that numerous peptides are shared between influenza A and B viruses and ADAMTS13, thus supporting the hypothesis of cross-reactivity as a mechanism driving the generation of anti-ADAMTS13 AAbs.

Keywords: influenza infection, ADAMTS13, peptide sharing, autoantibodies, cross-reactivity, thrombotic thrombocytopenic purpura

1 Introduction

Thrombotic thrombocytopenic purpura (TTP) is clinically characterized by the occurrence of thrombocytopenia and microangiopathic hemolytic anemia [1-3]. TTP was first described as a pathological entity in 1924 by Moschcowitz [1] and was clearly identified as an autoimmune disorder by Harrington et al. in 1951 [4]. Currently, after 70 years, we know that the majority of TTP patients suffer from acquired TTP caused by the presence of autoantibodies (AAbs) against ADAMTS13 [5-7], a protease that cleaves the von Willebrand factor (vWF) multimers into smaller forms thereby controlling vWF-mediated platelet thrombus formation [8]. However, the molecular basis and the mechanism(s) that lead to the loss of immunotolerance toward ADAMTS13 and permit the production of anti-ADAMTS13 AAbs are still unknown [9].

Therefore, it assumes a scientific relevance the clinical observation by Kosugi et al. [10], that influenza infection triggers TTP by producing anti-ADAMTS13 IgGs. The observation is crucial in light of the fact that the association between influenza infection and TTP is clinically well known [11-29], so making feasible the hypothesis that the anti-influenza immune responses that follow influenza infection may cross-react with ADAMTS13 protein thus generating anti-ADAMTS13 AAbs. To prove or disprove the cross-reactivity hypothesis, the present study analyzed the peptide commonality between influenza virus and ADAMTS13 proteins since, actually, peptide sharing can lead to autoimmunity through cross-reactivity phenomena following pathogen infection. It was found a wide influenza virus vs ADAMTS13 peptide overlap that can represent a cross-reactive molecular platform underlying anti-ADAMTS13 AAb production.

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2 Methods

Sequence analyses were conducted on ADAMTS13 (or A disintegrin and metalloproteinase with thrombospondin motifs 13 or vWF-cleaving protease) and cytoplasmic and perinuclear autoantigens of antineutrophil cytoplasmic antibodies, ie, c-ANCA myeloblastin and p-ANCA myeloperoxidase. The three human proteins are described in detail in the Uniprot database at https://www.uniprot.org [30, 31]. Protein primary sequences were decomposed into overlapping pentapeptides offset by one residue, ie, MGVPF, GVPFF, and VPFFS. Next, each pentapeptide was analyzed for occurrences in viral proteomes using Peptide Match program (https://research.bioinformatics.udel.edu/peptidematch) [32].

Proteomes from nine viruses were analyzed: influenza A virus, H1N1 (NCBI:txid211044), influenza A virus, H3N2 (NCBI:txid385580), influenza A virus, H5N1 (NCBI:txid93838), influenza A virus, H10N7 (NCBI:txid382838), influenza B virus (NCBI:txid518987), and influenza C virus (NCBI:txid11553). Tobacco mosaic virus (NCBI:txid12243), human parvovirus B19 (NCBI:txid648237), and dengue virus (NCBI:txid11059) were used as controls.

The immunologic potential of the shared peptides was explored using the Immune Epitope Database (IEDB, www.iedb.org) resource [33].

3 Results

ADAMTS13 protein sequence was analyzed for peptide sharing with influenza virus proteomes. In addition, c-ANCA myeloblastin and p-ANCA myeloperoxidase, two autoantigens that characterize a group of small vessel vasculitis [34, 35], were analyzed for comparison.

Analyses were extended to human parvovirus B19 because B19 infection, although predominantly affects erythrocytes, shows clinically nonsignificant lymphopenia, neutropenia, and thrombocytopenia [36] and to dengue virus because thrombocytopenia and clotting abnormalities are at the heart of dengue pathology [37]. Tobacco mosaic virus was utilized as a negative TTP-unrelated viral control.

Operationally, the pentapeptide was used as a probe in sequence analyses since, in immunobiology, a functional/structural unit is generally represented by five amino acid (aa) residues [38]. In fact, biological interactions can be described by peptide–protein interactions involving a pentapeptide [39-41, and pertinent references therein]. Alike, the capability of generating immune responses (immunogenicity) as well as the immune recognition process (antigenicity) appears to be circumscribed to the space of five residues [42-52].

4 Peptide sharing between influenza viruses and ADAMTS13

The pentapeptide sharing between the viral proteomes and c-ANCA myeloblastin, p-ANCA myeloperoxidase, and ADAMTS13 is described in Table 1. Main points are as follows:

- On the whole, the viral vs human peptide overlap consists of 24 pentapeptide matches, 17 of which occur in ADAMTS13 and mainly involve influenza A and dengue viruses.
- The viral peptide sharing with the two ANCA autoantigens amounts to seven pentamers and is restricted to influenza B, B19, and dengue viruses.
- Influenza C virus and the negative control tobacco mosaic virus have no pentapeptide sequences in common with any of the three analyzed human proteins.

In commenting data from Table 1, two further observations merit notice. First, the extent of the viral vs human peptide overlap is mathematically unexpected since the probability that two proteins may share a pentapeptide is equal to 20^{-5} (ie, probability 1 out of 3,200,000 or 0.0000003125). Second, the present study examines only reference influenza proteomes, ie, selected proteomes that cover well-studied model organisms [30, 31], and neglects the hundreds of existing influenza subtypes and variants. That is to say that the cross-reactivity scenario between influenza infection and ADAMTS13 might be more intense and varied than

that summarized in Table 1. As an example, the influenza A virus, H5N1 (NCBI:txid176674) shares the additional pentapeptide SLEPC with ADAMTS13 when compared to the, here, analyzed influenza A virus, H5N1 (NCBI:txid93838).

Tab. 1: Description of the pentapeptide sharing between B19, dengue, and influenza proteomes and the ANCA and ADAMTS13 autoantigens

Virus	c-ANCA myeloblastin	p-ANCA myeloperoxidase	ADAMTS13
Tobacco mosaic virus	–	–	–
Human parvovirus B19	–	FEQVM	ALVRP
Dengue virus 1	–	ARASF, SGSAS	AGEKA, AGILA, GAGLA, GANAS, SLRTT, TLRVL
Influenza A virus, H1N1	–	–	GDMLL, GHADL, GILHL, LESSL, PGHAD
Influenza A virus, H5N1	–	–	ALTED, GDMLL, GHADL GILHL, PGHAD
Influenza A virus, H3N8	–	–	ALTED, ELLVA, GDMLL, GHADL, GILHL, PGHAD, QGSLL
Influenza A virus, H10N7	–	–	ALTED, ELLVA, GDMLL, GHADL, GILHL, PGHAD
Influenza B virus	VTVVT, TVVTF	LERKL, RLATE	GGVLL, RQRQR, TGTID
Influenza C virus	–	–	–

5 Immunologic potential of the peptide sharing between influenza viruses and ADAMTS13

The peptide sharing as summarized in Table 1 has a high immunologic potential. In fact, using IEDB [33], a catalog of experimentally validated epitopes, and searching within IEDB epitopes, it was found that almost all of the shared pentapeptides described in Table 1 repeatedly occur in immunoreactive epitopic sequences. Table 2 lists the immunopositive epitopes containing sequences shared between B19, dengue, and influenza proteomes and the ANCA and ADAMTS13 autoantigens and highlights the disproportionately high number of epitopes containing ADAMTS13 pentapeptides.

Tab. 2: Epitopes containing peptides shared between B19, dengue, and influenza proteomes and ANCA and ADAMTS13 autoantigens

c-ANCA myeloblastin		p-ANCA myeloperoxidase		ADAMTS13	
IEDB ID[1]	Epitope sequence[2,3]	IEDB ID[1]	Epitope sequence[2,3]	IEDB ID[1]	Epitope sequence[2,3]
71568	VTVVTtsgs	36432	lhtdFEQVM	358	aapgaatafvGAGLAgaaig
173682	vlqelnVTVVTFfcr	37398	llhtdFEQVM	391	aaqlaapgaatafvGAGLAg
175507	tlvvnklqgllqVTVVTipq	49778	ptstfllhtdFEQVMc	1565	AGILArnlvpmvatv
118332	epgegpvllVTVVTggevkkl	65519	tpcilSGSAS	4870	atafvGAGLAgaaigsvglgk
132262	elnVTVVTFfcrphn	171363	hdldftpepaARASF	18173	fvGAGLAgaaigsv
715422	langTVVTF	171908	kqrlrSGSASpmell	21783	gpSLRTTtv
730502	vhaVTVVTl	173480	tlllrehnRLATElk	31200	kidlwsynaELLVAle
		175982	kaleLERKL	31201	kidlwsynaELLVAlenqhti
		195579	knetwklARASFiev	35002	lavGGVLLflsvnvha
		195784	netwklARASFievk	48949	ppwqAGILArnlvpm
		219932	teLERKLtf	48950	ppwqAGILArnlvpmv

Tab. 2: Continued

c-ANCA myeloblastin	p-ANCA myeloperoxidase		ADAMTS13	
	236113	lFEQVMr	50046	pwqAGILArnlvpmv
	435362	kRLATEfel	53178	raprtgrrlmALTEDtssds
	490162	ARASFpdqay	62654	synaELLVAlenqhti
	534632	sldangvSGSASyyevkfsd	72977	wqAGILArnlvpmva
	539401	ieseknetwklARASFi	74558	ylaGAGLAf
	628468	ylnpLERKL	95135	qAGILArnlvpmvat
	655819	arlaeLERKL	102905	vlgGGVLLlrvipaldsltpaned
	725289	shssSGSASl	113533	idlwsynaELLVAl
	753847	kgttvtvsSGSASaptlf	129078	kidlwsynaELLVAlen
	754288	wgqgtlvtvsSGSASastlfp	130384	ynaELLVAlenqhtidl
	795873	grlelSGSASgaagr	131309	rvALTEDrlp
	803192	kaSGSASgfwps	143423	kidlwsynaELLVAlenqht
	810555	qlSGSASnyavs	180774	TLRVLnlvenwlnnn
			188763	TLRVLqdql
			190640	aGDMLLlwgrltwrk
			190646	asyilirdthSLRTT
			190647	asyilirdthSLRTTa
			190648	asyilirdthSLRTTaf
			190680	rpgGGVLLrygsqlape
			190682	rqhlepTGTIDmrgpg
			190687	syilirdthSLRTT
			195114	aGAGLAfslmkslgg
			195117	AGILArwssfkknga
			195346	GAGLAfsimksvgtg
			222546	geshiGGVLL
			228201	GGVLLlenvrfykee
			422312	ELLVAmenqhtidlads
			422725	sitevwsynaELLVAme
			422849	wsynaELLVAmenqhti
			430467	htdcPGHADy
			448746	sqypELLVAsy
			459203	slvGILHL
			466503	iiyAGEKAqf
			466967	iyAGEKAqf
			474578	aaniiGILHLilwildrl
			478472	geltQGSLL
			491545	griepGDMLL
			534840	eGANASyilirdthSLRTTa
			539613	lrflaipptAGILAr
			541068	alLESSLrqa

Tab. 2: Continued

c-ANCA myeloblastin	p-ANCA myeloperoxidase	ADAMTS13	
		559187	drsiGGVLLdsklvl
		564437	lelepGAGLAl
		576396	redTLRVLaa
		582709	fGGVLLplly.
		585298	krkSLRTTgf
		587265	prgGGVLLfi.
		588256	reqGAGLAl
		593918	aALTEDgrlfmw
		594947	dTLRVLtlw
		595352	fsgQGSLLqpfiyyrf
		598639	lALTEDsevhsw
		602194	sTLRVLynlf
		605046	grlgrGAGLAk
		615393	eiiAGILAy
		621328	lredTLRVL
		638082	ttAGILAtl
		643987	gqnepELLVAhay
		697198	GDMLLlwgrltwrkm
		710401	iatGILHLl
		716337	lpnQGSLLr
		724737	seqGGVLLl
		738679	dlirlcimvGANASd
		738927	flrflaipptAGILA
		740498	TLRVLlvgrdgavyvhhm
		753010	ypELLVAsy
		766470	vtttildreiqevfTLRVLvrdgg
		768115	asyilirdthSLRTTafhg
		768265	rpgGGVLLrygsqlapet
		773323	gvagvGAGLAy
		776377	pvELLVAes
		781091	aeGGVLLpvdrr
		782476	alahGGVLLfpk
		787546	dpmaELLVAsrt
		790759	eyTGTIDgltqa
		792564	GGVLLirclllg
		806468	ltGANASgepht
		822504	ssspGAGLAfgi
		838772	vALTEDqvpalk

[1]Epitope IEDB ID number. Details and references: www.iedb.org. [2]Peptides shared between viruses and human autoantigens (Table 1) in capital letters.

6 Conclusion

Numerous pentapeptides are shared between influenza A and B viruses and ADAMTS13, the autoantigen of TTP (Table 1). The peptide sharing is higher than expected by being very low the chance for two proteins to share a pentapeptide. Moreover, the peptide sharing is immunologically significant by being most of the shared peptides also part of experimentally validated epitopes (Table 2). Hence, the present study substantiates the hypothesis of cross-reactivity involvement in the generation of anti-ADAMTS13 AAbs following influenza infection, in this way flanking previous findings [53-57] that indicate autoimmune cross-reactions as a basic mechanism in the generation of autoimmune diseases following infections.

The data warrant further collaborative research efforts, especially in light of the fact that low levels of ADAMTS13 protease are a risk factor for the development of myocardial infarction [58,59], stroke [59-61], preeclampsia [61], disseminated intravascular coagulation [62], cerebrovascular disease [63], etc.

Acknowledgment: This research received no specific grants from any funding agency in public, commercial, or not-for-profit sectors.

Competing interests: The author declares no conflicts.

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