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Autoepitopes (22 of 27) in rheumatoid arthritis differ from vaccine antigens by a single amino acid residue, ideal for low affinity self reactive T cell mediated autoimmunity and aluminum adjuvant promotes citrullination of vaccine antigens thus the synthesis of ACPA

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Abstract

Rheumatoid arthritis (RA) is an autoimmune disorder. Rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) are known to play a role in RA. RF and ACPA origin is considered unknown.

Vaccines contain numerous residual proteins of food, animal, plant, fungal and bacterial origin, from the manufacturing process. Protein sequence analysis shows that 14 of 14 known RF autoepitopes differ from vaccine antigens by just one amino acid residue. The immune system's cancer surveillance system looks for exactly such antigens. Cancer begins with a single DNA mutation where one base-pair is modified. Proteins encoded by this DNA segment will therefore also exhibit a single amino acid change. So such peptides with a single amino acid change (neoantigens) are strong markers for cancer and result in an anti-cancer immune response, when accompanied by innate immune system co-stimulation. With thousands of such proteins in vaccines, there is an overwhelming anti-cancer immune response following vaccine administration. The adjuvant or live virus in the vaccine provides the requisite innate immune system co-stimulation. Since cancer cells/proteins are very similar to normal cells/proteins, attacking cancer always carries the risk of autoimmunity (collateral damage). Therefore vaccines cause numerous autoimmune diseases by triggering unnecessary anti-cancer immune responses.

In the specific case of RF, the target is the immune system's IgG antibody itself. The immune system produces IgM antibodies (RF) that bind to the IgG antibody. Since this is a case of the immune system attacking its own "soldiers" (friendly fire), it weakens the immune system's ability to fight cancer or infections.

Aluminum adjuvant in vaccines promotes citrullination of the antigens. Therefore the immune system produces antibodies against the regular and citrullinated versions of the antigen. The antibodies synthesized against citrullinated antigens (anti citrullinated protein antibodies (ACPA)) play a major role in RA.

The solution is to immediately remove all non-target antigens from all vaccines and injections.

Introduction

Rheumatoid arthritis (RA) is an autoimmune disease that is mediated by autoantibodies. Rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) are known to play a role in RA (1). RF and ACPA origin is considered unknown. RF are mainly IgM antibodies (1).

Vaccines are manufactured using animal, plant, fungal derived growth media or recombinant organisms. They contain residual quantities of all these proteins. Vaccine makers do not want to spend the money to completely remove these residual proteins. Due to molecular mimicry between these proteins and human self proteins, immune responses directed against vaccine proteins can result in autoimmune diseases.

The general concept of immunization with homologous xenogeneic antigens resulting in autoimmunity has been repeatedly demonstrated for 45 years (2–4). We have described the exact immunological mechanism involved in that process (5,6).

The role of vaccines in RA was previously described (7). Here we perform a detailed analysis of the autoepitopes involved in RA to reveal the specific vaccine antigens that initiate these autoimmune responses.

The RF IgM antibodies are directed against various sites of the the human IgG antibody. The locations on IgG targeted by IgM are hidden (cryptic epitopes). They become accessible when the IgG antibody binds to the antigen (8).

Methods

Protein sequences were obtained from Uniprot (9). Protein sequence alignment was performed using BLASTP (10). The MHC II binding predictions were made on 8/25/2019 using the IEDB analysis resource Consensus tool (11,12).

Rheumatoid Factor

Rheumatoid factor are IgM antibodies directed against human CH3 IgG domain, CH2 and human beta 2-microglobulin (13). IgM involved in RA are synthesized in a T cell dependent manner. (1) The first column in Table 1 shows the targeted IgG associated autoepitopes identified by Williams et al (13). BLASTP was used to check sequence alignment between these peptides and plant, animals, bacterial, fungal proteins present in vaccines. A 100% match would be unlikely to result in autoimmune disorders because the T cells that have high affinity to self antigens would have been negatively selected in the thymus. For every RA autoepitope, one or more vaccine epitopes were identified that had exactly one amino acid residue difference as highlighted in Table 1, column 2. This difference means low affinity self reactive (LASR) T cells that have migrated to the periphery following positive selection in the thymus can recognize these vaccine epitopes (that are slightly different from self) with high affinity (5,6). Such LASR T cells, once activated will bind with low affinity to peptides in column 1, but they

will still be functional thus resulting in autoimmune disease. These T cells interact with B cells and stimulate production of antibodies specific to these peptides (14).
A BLASTP match score of 19.3 was reported when comparing the H1N1 nucleoprotein and human hypocretin receptor 2 (15). This level of protein sequence homology resulted in the H1N1 nucleoprotein containing Pandemrix vaccine to induce narcolepsy (16). As can be observed in Table 1, all match scores are greater than this baseline value of 19.3.

Table 1

Rheumatoid Factor epitopes identified by Williams et al. (13)	Matching peptide from vaccine antigen, single altered amino acid is in bold and underlined	Vaccine antigen organism of origin	Common name	Example vaccines containing the antigen	BLASTP Match score
PREPQVY	PRE**R**QVY	*Gallus gallus*	Chick	MMR (21), MMRV, TBE (22)	22.3
PQVYTLP	PQVY**K**LP	*Saccharomyces cerevisiae*	Baker's yeast	Hep B (23,24), HPV (25)	22.3
TLPPSRE	TLPP**A**RE	*Triticum aestivum*	Wheat	Any Polysorbate 80 containing vaccine (26)	22.7
DGSFFLY	**E**GSFFLY	*Zea mays*	Corn	Any Polysorbate 80 containing vaccine (26)	24.0
WQQGNVF	WQQ**N**NVF	*Zea mays*	Corn	Any Polysorbate 80 containing vaccine (26)	24.4
CSVMHEG	CSV**Q**HEG	*Bos taurus*	Cow	DTaP/TdaP (27)	21.0
EGLHNHY	**D**GLHNHY	*Glycine max*	Soy	Any (19)	24.8
KSLSLSP	KSL**T**LSP	*Zea mays*	Corn	Any Polysorbate 80 containing vaccine (26)	20.6
SVFLFPP	SVFLF**Q**P	*Cavia porcellus*	Guinea pig	Varivax (17)	21.4
KFNWYVD	KF**I**WYVD	*Streptococcus pneumoniae*		Prevnar 13 (19), Pneumovax23 (18)	24.0
NSTYRVVSV	NSTYR**E**VSV	*Streptococcus pneumoniae*		Prevnar 13 (19), Pneumovax23 (18)	25.7
LTVLHQNW	LT**T**LHQNW	*Arachis hypogaea*	Peanut	Any (20)	26.9
SKDWSFY	SKDW**D**FY	*Streptococcus pneumoniae*		Prevnar 13 (19), Pneumovax23 (18)	24.0
LSQPKIVKWD	LS**E**PKIVKWD	*Cavia porcellus*	Guinea pig	Varivax (17)	33.7

Vaccine peptides in column 2 above were checked to verify that they lack 100% protein sequence match to any human self antigen. Therefore, all above vaccine peptides will be recognized by low affinity self reactive (LASR) T cells that have escaped the thymus due to positive selection.

<u>Vaccine induced vaccine failure</u>

Pneumococcal vaccine fails in RA (28). The immune response against *S. pneumoniae* shown in Table 1 above can explain the failure. Antibodies directed against these *S. pneumoniae* peptides can neutralize the vaccine by binding to vaccine antigens and making them invisible and/or inaccessible.

This is not unique to the pneumococcal vaccine. Vaccine induced long term persistent antibodies that have only a minor or no role in disease protection can be potent in neutralizing future vaccines (29), or even make the disease worse (30,31).

<u>Vaccine induced immunosuppression</u>

Anti-antibody antibodies (IgM antibody directed against IgG antibody) caused by vaccines is a cancer enabling mechanism. In general, antibodies are involved in cancer defense and infection defense. Vaccine induced antibodies against other human antibodies affects both cancer defense and infection defense. IgM binding to IgG occurs rarely in nature. It is a vaccine induced chimeric complex. So the way the immune system handles it is unpredictable. The IgM-IgG complex can be treated as a neoantigen, resulting in more immune responses being directed against both IgM and IgG epitopes.

Anti-citrullinated protein antibodies (ACPA)

Numerous vaccines use aluminum salts as adjuvant (19,27,25,23,24). Aluminum adjuvant can promote citrullination of adsorbed vaccine antigens (32).

Many animal proteins were detected in the MMRV vaccine by Corvelva's analysis, including actin and vimentin (33).

Vimentin (Vim1–16; Vim59–74), two peptides derived from fibrinogen (Fibα 27–43; Fibβ 36–52) and one peptide derived from α-enolase (Eno 5–20) were all identified as being involved in RA (34). Fibrinogen α chain, 563-583 and 580-600 the fibrinogen β chain, 62-81 were identified by Fernandes-Cerqueira et al (35).

Below are the results comparing human and animal versions of all the above peptides. A perfect, 100% match between human and animal antigen will rarely result in autoimmune disease due to strong self tolerance. So the results reported below are the strongest imperfect matches.

Of the 13 peptides analyzed below, ~62% had an amino acid difference in only one position, ~8% in two positions and ~30% in three or more positions.

Human fibrinogen Fibα 27–43 vs. porcine peptide

fibrinogen alpha chain isoform X1 [Sus scrofa]
XP_020957142.1 924 1

Alignment statistics for match #1

Score	Expect	Identities	Positives	Gaps
47.7 bits(105)	4e-07	15/17(88%)	15/17(88%)	0/17(0%)

```
Query  1   FLAEGGGVRGPRVVERH  17
           FLAEGGGVRGPR  ERH
Sbjct  55  FLAEGGGVRGPRLTERH  71
```

Human fibrinogen Fibα 27–43 vs. bovine peptide

fibrinogen alpha chain isoform X1 [Bos taurus]
XP_005217494.2 837 1

Alignment statistics for match #1

Score	Expect	Identities	Positives	Gaps
45.6 bits(100)	3e-06	14/17(82%)	15/17(88%)	0/17(0%)

```
Query  1   FLAEGGGVRGPRVVERH  17
           FL EGGGVRGPR VER+
Sbjct  30  FLTEGGGVRGPRLVERQ  46
```

Human fibrinogen Fibβ 36–52 vs. chick peptide

fibrinogen beta chain isoform X1 [Gallus gallus]
XP_025005217.1 412 1

Alignment statistics for match #1

Score	Expect	Identities	Positives	Gaps
29.5 bits(62)	1.3	12/20(60%)	12/20(60%)	6/20(30%)

```
Query  1   NEEGFFS----ARGHRPLDK  16
           NEE   S    AR HRPLDK
Sbjct  32  NEED--SPQIDARAHRPLDK  49
```

Human fibrinogen Fibβ 36–52 vs. bovine peptide

fibrinogen beta chain precursor [Bos taurus]
NP_001136389.1 495 1

Alignment statistics for match #1

Score	Expect	Identities	Positives	Gaps
28.6 bits(60)	2.6	9/10(90%)	9/10(90%)	0/10(0%)

```
Query  8   ARGHRPLDKK  17
           ARGHRP DKK
Sbjct  47  ARGHRPYDKK  56
```

Human α-enolase (Eno 5–20) vs. bovine peptide

TPA: alpha-enolase [Bos taurus]
DAA21263.1 434 1

Alignment statistics for match #1

Score	Expect	Identities	Positives	Gaps
52.0 bits(115)	1e-08	15/16(94%)	16/16(100%)	0/16(0%)

```
Query  1   KIHAREIFDSRGNPTV  16
           K+HAREIFDSRGNPTV
Sbjct  5   KVHAREIFDSRGNPTV  20
```

Human vimentin 1-16 vs. African green monkey peptide

RecName: Full=Vimentin [Chlorocebus aethiops]
P84198.3 466 1

Alignment statistics for match #1

Score	Expect	Identities	Positives	Gaps
52.0 bits(115)	1e-08	15/16(94%)	15/16(93%)	0/16(0%)

```
Query  1   MSTRSVSSSSYRRMFG  16
           M TRSVSSSSYRRMFG
Sbjct  1   MTTRSVSSSSYRRMFG  16
```

Human vimentin 1-16 vs. porcine peptide

vimentin isoform X1 [Sus scrofa]
XP_005668163.1 466 1

Alignment statistics for match #1

Score	Expect	Identities	Positives	Gaps
52.0 bits(115)	1e-08	15/16(94%)	15/16(93%)	0/16(0%)

```
Query  1   MSTRSVSSSSYRRMFG  16
           MSTR VSSSSYRRMFG
Sbjct  1   MSTRTVSSSSYRRMFG  16
```

Human vimentin 59-74 vs. bovine peptide

vimentin [Bos taurus]
AAA53661.1 466 1

Alignment statistics for match #1

Score	Expect	Identities	Positives	Gaps
46.9 bits(103)	8e-07	15/16(94%)	15/16(93%)	0/16(0%)

```
Query  1   GVYATRSSAVRLRSSV  16
           GVYATRSSAVRLRS V
Sbjct  59  GVYATRSSAVRLRSGV  74
```

Human vimentin 26-44 (36) vs. bovine peptide

vimentin [Bos taurus]
AAA53661.1 466 1

Alignment statistics for match #1

Score	Expect	Identities	Positives	Gaps
57.1 bits(127)	7e-11	18/19(95%)	18/19(94%)	0/19(0%)

```
Query  1    SSRSYVTTSTRTYSLGSAL  19
            S RSYVTTSTRTYSLGSAL
Sbjct  26   STRSYVTTSTRTYSLGSAL  44
```

Human vimentin 415-433 ((36)) vs. porcine peptide

vimentin isoform X1 [Sus scrofa]
XP_005668163.1 466 2

Alignment statistics for match #1

Score	Expect	Identities	Positives	Gaps
60.0 bits(134)	6e-12	18/19(95%)	19/19(100%)	0/19(0%)

```
Query  1     LPNFSSLNLRETNLDSLPL  19
             LPNFSSLNLRETNL+SLPL
Sbjct  415   LPNFSSLNLRETNLESLPL  433
```

Fibrinogen α chain, 563-583 vs. Chick peptide

RNA-binding motif protein, X chromosome [Gallus gallus]
NP_001073196.1 385 3

Alignment statistics for match #1

Score	Expect	Identities	Positives	Gaps
25.7 bits(53)	8.9	10/13(77%)	11/13(84%)	1/13(7%)

```
Query  7     EFPSRGKS-SSYS  18
             E+PSRG S SSYS
Sbjct  242   EYPSRGYSLSSYS  254
```

Fibrinogen α chain, 580-600 vs. bovine peptide

Chain A, Fibrinogen alpha chain [Bos taurus]
2BAF_A 166 1

Alignment statistics for match #1

Score	Expect	Identities	Positives	Gaps
35.0 bits(75)	0.005	14/21(67%)	14/21(66%)	1/21(4%)

```
Query  1     SKQF-TSSTSYNRGDSTFESK  20
             SKQF  SST  NRG S  ESK
Sbjct  144   SKQFVSSSTTVNRGGSAIESK  164
```

Fibrinogen β chain, 62-81 vs. bovine peptide

fibrinogen beta chain precursor [Bos taurus]
NP_001136389.1 495 1

Alignment statistics for match #1

Score	Expect	Identities	Positives	Gaps
47.7 bits(105)	2e-07	15/16(94%)	15/16(93%)	0/16(0%)

```
Query  2   PPPISGGGYRARPAKA  17
           PPPISGGGYRARPA A
Sbjct  67  PPPISGGGYRARPATA  82
```

The results above once again make it clear that numerous animal proteins in vaccine are ideally suited to cause LASR T cell mediated autoimmunity.

ACPA is more common in younger patients (34) consistent with exposure to more aluminum adjuvanted vaccines.

Skin homing markers

CD4+ T cells involved in RA express the CCR4 skin-homing marker consistent with the site of priming (37,38). Intramuscular and subcutaneous vaccine administration results in the vaccine antigens being transported to skin draining lymph nodes where the activated CD4+ T cells are imprinted with CCR4 skin homing markers.

HLA-DRB1 binding affinity comparison

HLA-DRB1 is associated with RA.

Human and animal peptides were compared using IEDB for binding affinity to HLA-DRB1(39) and found to be similar.

Example comparing human and porcine vimentin epitopes:

Allele	#	Start	End	Peptide	Method used	Percentile rank
HLA-DRB1*04:04	1	1	15	LPNFSSLNLRETNLD	Consensus (smm/nn/sturniolo)	4.14
HLA-DRB1*04:04	2	1	15	LPNFSSLNLRETNLE	Consensus (smm/nn/sturniolo)	4.14
HLA-DRB1*04:05	1	1	15	LPNFSSLNLRETNLD	Consensus (smm/nn/sturniolo)	4.87
HLA-DRB1*04:05	2	1	15	LPNFSSLNLRETNLE	Consensus (smm/nn/sturniolo)	5.63
HLA-DRB1*04:01	1	1	15	LPNFSSLNLRETNLD	Consensus (smm/nn/sturniolo)	10.94
HLA-DRB1*04:01	2	1	15	LPNFSSLNLRETNLE	Consensus (smm/nn/sturniolo)	10.94

Conclusion

Residual animal, plant, fungal, aeroallergen proteins (non-target proteins in general) in vaccines cause numerous disorders (40) including rheumatoid arthritis. The solution is to immediately remove all non-target antigens from vaccines using technologies such as affinity chromatography (41).

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