BRIEF REPORT

A tumor-binding antibody with cross-reactivity to viral antigens

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Abstract

Background We previously identified in non-small cell lung cancer (NSCLC) patients an autoantibody to complement factor H (CFH) that is associated with non-metastatic disease and longer time to progression in patients with stage I disease. A recombinant human antibody, GT103, was cloned from single B cells isolated from patients with the autoantibody. GT103 inhibits tumor growth and establishes an antitumor microenvironment. The anti-CFH autoantibody and GT103 recognize the epitope PIDNGDIT within the SCR19 domain of CFH. Here, we asked if this autoantibody could have originally arisen as a humoral response to a similar epitope in a viral protein from a prior infection.

Methods Homologous viral peptides with high sequence identity to the core PIDNGDIT epitope sequence were identified and synthesized. NSCLC patient plasma containing anti-CFH autoantibodies were assayed by ELISA against these peptides. GT103 was assayed on a 4345-peptide pathogen microarray.

Results Epitopes similar to the GT103 epitope are present in several viruses, including human metapneumovirus-1 (HMPV-1) that contains a sequence within attachment glycoprotein G that differs by one amino acid. Anti-CFH autoantibodies in NSCLC patient plasma weakly bound to an HMPV-1 peptide containing the epitope. GT103 cross-reacted with multiple viral epitopes on a peptide microarray, with the top hits being peptides in the human endogenous retrovirus-K polymerase (HERV-K pol) protein and measles hemagglutinin glycoprotein. GT103 bound the viral HMPV-1, HERV-K pol, and measles epitope peptides but with lower affinity compared to the GT103 epitope peptide.

Conclusion These findings suggest that memory B cells against a viral target could have affinity matured to produce an antibody that recognizes a similar epitope on tumor cells and exhibits antitumor properties.

Keywords Autoantibodies · Viral epitopes · Antibody cross-reactivity · Molecular mimicry · Humoral immunity

Introduction

Autoantibodies are hallmarks of a variety of human diseases including, but not limited to, those categorized as autoimmune diseases. The human autoantigen atlas (http://biokb.ncpsb.org.cn/aagatlas_portal/index.php#) is comprised of 8045 autoantigens associated with 1073 diseases, including cancer and diseases of immune, musculoskeletal, connective tissue, neural, and cardiovascular systems [1]. Autoantibodies can be used to screen for or diagnose autoimmune diseases such as systemic lupus erythematosus [2], the seropositive form of rheumatoid arthritis [3], and type I diabetes [4], and have been explored as screening and prognostic biomarkers for cancer [5–7]. In addition, the identification of an antigen by the presence of autoantibodies against it holds the promise of development of therapies targeted to it. The Cancer Antigenic Peptide Database (De Duve Institute, Brussels, Belgium; https://caped.icp.ucl.ac.be/Peptide/list), currently contains 474 tumor-associated antigen (TAA) peptide entries, all of which have been shown to be presented on human leukocyte antigen (HLA) proteins and recognized by T cells. Unique antigens are those created by mutation that are particular to individuals and thus would likely not be targets for drug development. Shared neo-antigens include tumor-specific antigens, expressed in many tumors but not

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normal tissues, and tumor-associated antigens that are over-expressed in tumor tissue but also expressed in normal tissue. Viral peptides associated with human malignancy, such as Epstein–Barr virus and human papilloma virus are not included in this database but represent additional potential antigenic targets for therapy.

Interestingly, autoantibodies are also found in healthy individuals. LaBaer and colleagues compiled autoantibody profiles (the "autoantibodyome") of 272 control subjects from case–control biomarker studies [8]. They studied a total of 8282 antigen reactivities and designated 77 autoantibodies, present in 10–47% of individuals, as "common." The 77 autoantibodies were found at similar frequencies in the matched diseased cohorts; thus were not elicited by the disease under study. The number of different autoantibodies increased between the age ranges infancy—6 years and 6–12 years, and plateaued thereafter. Among the common autoantigens, 21 contained sequence matches to viral proteins. These sequence matches could reflect the phenomenon of molecular mimicry, in which antibodies reactive to viral antigens from previously encountered viruses cross-react with normal antigens [9].

Cross-reactivity of autoantibodies as well as T cell receptors (TCRs) against TAAs with viral antigens has also been reported. Using a bioinformatics approach, Ragone et al. [10] performed a global BLAST search with 99 TAA peptides from the Cancer Antigenic Peptide database against all human viral sequences and found 82 viral peptides sharing homology with TAA peptides; cross-reactivity of several of these pairs was confirmed in an ex vivo T cell stimulation assay. Chiou et al. [11] analyzed T cell receptor sequences enriched in non-small cell lung cancer (NSCLC) tumors and discovered that T cells with specificity to the epithelial protein TMEM161A were cross-reactive with epitopes from Epstein–Barr virus. Petrizzo et al. [12] found that neoantigen-specific T cells from hepatocellular carcinoma were cross-reactive with multiple pathogen epitopes.

GT103 is a human monoclonal antibody in clinical trials for NSCLC (ClinicalTrials.Gov IDs NCT04314089 and NCT05617313). GT103 is derived from an autoantibody that was discovered to be preferentially expressed in early stage as opposed to late stage NSCLC [13], and its presence in early stage NSCLC correlates with longer time to recurrence [14]. GT103 recognizes an epitope in the SCR19 domain of the complement regulatory protein complement factor H (CFH) [15]. This epitope is not accessible to antibody in native CFH but is recognized by antibody upon conformational change [15, 16]. GT103, by binding to CFH, causes tumor cell lysis by activating the classical complement pathway, and slows tumor growth in vivo with concomitant promotion of an antitumor microenvironment [16–18]. Since the epitope is masked in the native structure of CFH and is possibly only revealed in the tumor cell microenvironment, we wondered if the exposed epitope stimulates affinity maturation of memory B cells with specificity for a similar epitope originally perceived as foreign. In select patients, the autoantibody produces a beneficial phenotype. Autoimmune diseases have long been associated with cross-reactivity of viral epitopes with self epitopes [19], but this phenomenon in cancer is a more recent area of exploration. Here, we examine the possibility that anti-CFH autoantibodies could have arisen from prior exposure of individuals to a nonself epitope present in a virus.

Materials and methods

Blood sample collection

The Duke University Institutional Review Board (IRB) approved this study with the written consent of each subject. Thousands of blood samples from patients being seen at Duke clinics for treatment or screening for NSCLC were collected and the plasma stored in our IRB-approved −80°C repository. Samples from patients previously shown to be positive or negative for the presence of the anti-CFH autoantibody by the criteria of reference [14] were randomly selected for the current study.

Search criteria

A nonredundant Protein Blast search using PIDNGDIT as the query was run at the NCBI website https://blast.ncbi.nlm.nih.gov/Blast.cgi#. The results were limited to viruses (taxid:10,239).

ELISA

We performed peptide ELISA as previously described in detail [14] using a peptide containing the CFH epitope GPPPP<u>PIDNGDIT</u>SFPGGG-Lys(biotin) [15, 16] or related biotin-conjugated viral peptides as described in the figure legends. (The epitope in the CFH peptide is underlined.) Briefly, wells of a 96-well plate, precoated with NeutrAvidin (ThermoFisher; cat. # 15,129), were washed with PBS/0.1% Tween 20 (PBST) and 2 µg/ml peptide or biotin in PBST added. After a 30 min incubation followed by washing, the wells were loaded with patient plasma or GT103, diluted as described in the figure legends. After a 1.5 h incubation followed by washing, goat antihuman IgG gamma-chain-horse-radish peroxidase secondary antibody (Chemicon; Sigma-Aldrich AP39P) diluted 1:8000 was added to the wells. After a 1 h incubation followed by washing, bound antibody was detected using ABTS/hydrogen peroxide. Absorbance was measured at 405 nm using a 96-well plate spectrophotometer. Mean absorbance from background binding of antibody

to biotin-coated control wells was subtracted from mean absorbance of the corresponding test wells. Reactions were run in duplicate and P values calculated using Student's T-test.

Epitope microarray analysis

We performed binding of GT103 to an infectious disease epitope microarray. The PEPperCHIP® Infectious Disease Epitope Microarray (PEPperPRINT GmbH) covers 3,760 linear B-cell epitopes from 196 different pathogens associated with infectious diseases, as referenced in the Immune Epitope Database (https://www.iedb.org). The 3,760 linear B-cell epitopes were converted into 4,345 different peptides printed in duplicate (8,690 peptide spots) and complemented by polio (KEVPALTAVETGAT, 42 spots), c-myc (EQKLISEEDL, 30 spots) and HA (YPYDVPDYAG, 40 spots) control peptides. The microarray was blocked with blocking buffer (Rockland Immunochemicals MB-070) for 30 min, then incubated with GT103 at a concentration of 1 μg/ml in 10% blocking buffer in phosphate-buffered saline, pH 7.4, 0.05% Tween 20 (PBST-05) for 16 h at 4 °C with orbital shaking. After washing in PBST-05 (3 × 10 s), the microarray was stained with DyLight680- and DyLight800-labeled secondary antibodies recognizing human IgG (H + L) and anti-HA control antibody, respectively, for 45 min at room temperature. After further washing, the microarray was read with an Innopsys InnoScan 710-IR microarray scanner with a scanning resolution of 20 μm and scanning gains of 20 at low laser power (680 nm, red) and 40 at high laser power (800 nm, green). Quantification of spot intensities and peptide annotation were done with PepSlide® Analyzer.

Results

The autoantibody to CFH that is associated with non-metastatic NSCLC, and the completely human monoclonal antibody GT103 from which it was derived, both recognize the epitope PIDNGDIT [15, 16]. To investigate the known prevalence of this epitope in other proteins, the GT103 peptide epitope (PIDNGDIT) was used as the query sequence versus known viral protein sequences using the NCBI BLAST algorithm. Supplementary Table 1 lists the hits resulting from this search, and Supplementary Fig. 1 shows representative alignments. The hits fell within over 80 HMPV-1 isolates that contained amino acid sequences that differed from the query by only one amino acid residue, as well as within human immunodeficiency virus-1. Hits also fell within bacteriophages, most frequently *Caudoviricetes* (*Caudovirales*), a class of phage species that is found in the human gut [20]. Hits appeared in a variety of proteins, including a viral

exonuclease, a tail fiber-like protein, portal protein, attachment glycoprotein G, and envelope glycoprotein.

The similarity in amino acid sequence between the GT103 epitope and the related region in the attachment glycoprotein G of HMPV-1 led us to speculate that anti-CFH antibodies may have arisen from an immune reaction to HMPV-1. As a first step to explore this possibility, we compared binding of anti-CFH autoantibodies in patient plasma to a peptide containing the CFH epitope PIDNGDIT versus a peptide containing the similar HMPV-1 epitope PIDNPDIT. Both peptides were immobilized in an ELISA plate, which was then used to test human plasma samples that had been shown previously to be positive or negative for the presence of the CFH autoantibody. None of the plasma samples from NSCLC patients, whether CFH autoantibody positive or negative, when diluted 1:200, demonstrated detectable antibody binding to the HMPV-1 peptide (Fig. 1). In contrast, the autoantibody-positive samples bound the CFH peptide as expected while the autoantibody-negative samples did not. Binding of antibody from some of the autoantibody-positive samples to the HMPV-1 peptide was detected at 1:2 dilution of plasma (with mean A450 values of 0.8–1.0 for the CFH peptide versus 0.005–0.1 for the HMPV peptide in that assay).

To further investigate the possibility that the anti-CFH autoantibody recognizes viral epitopes, and thus may have originated from an antiviral response, we had GT103 tested on the PEPperCHIP®, an infectious disease epitope peptide microarray. Incubation of GT103 with the array resulted in a moderate to strong antibody response against a number of
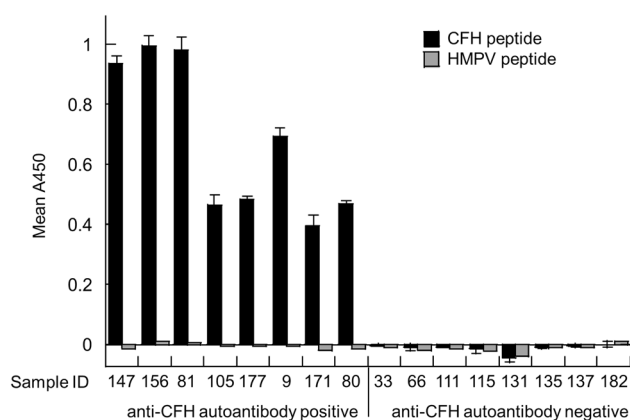
Fig. 1 Binding of plasma antibodies to CFH and HMPV-1 and peptides. Plasma samples from anti-CFH autoantibody-positive and autoantibody-negative patients were diluted 1:200 and tested by ELISA against CFH peptide (GPPPPIDN**G**DITSFPGGG-Lys(biotin)) and HMPV-1 peptide (TSTIPIDN**P**DITPNSGGG-Lys(biotin)) that contains a one amino acid difference (bold) in the consensus region (underlined). After background (biotin-coated well) subtraction, mean of duplicates are reported, with standard deviation given for the CFH peptide ELISA

pathogen peptides at high signal-to-noise ratios (Fig. 2). The top antibody responses were attributed to peptides REPLENALTVFTD (pol protein, human endogenous retrovirus-K), HMTNYLEQPVSNDLS (hemagglutinin glycoprotein, measles virus), TAAVILTPTENHFT (major surface antigen P30 precursor, Toxoplasma gondii), RVEAQLHVWIPPLN (hepatitis C virus subtype 1A), TNYLEQPVSNDLSNC (hemagglutinin glycoprotein, measles virus), and CTPPALNCYWPLNDY (spike glycoprotein, SARS-CoV-1). The array did not include HMPV-1 peptides.

The strongest responses were based on peptides REPLENALTVFTD and HMTNYLEQPVSNDLS that shared the common motifs LE(Q/N)x(L/V)(T/S). Similar motifs were also found with top peptides TAAVILTPTENHFT, RVEAQLHVWIPPLN, or TNYLEQPVSNDLSNC, albeit at slightly lower intensity levels. Therefore, we assume that the cross-reactivity of GT103 was driven by peptides with consensus motifs like [1]LE(Q/N)x(L/V)(T/S)[6], while consensus motifs like TENHFT or VEAQLH with an exchange of [1]L, [3](Q/N) or [6](T/S) were also tolerated to some extent. (Superscripts denote amino acid residue position.) Even though the infectious disease epitopes recognized by GT103 in the microarray do not overtly resemble the CFH epitope (PIDNGDIT), the consensus motif LE(Q/N)x(L/V)(T/S) accurately reflects the amino acid class (i.e., hydrophobic, polar, or charged) within the CFH epitope.

To assess the binding of the anti-CFH antibody to the two top viral peptide hits, we tested epitope peptides from HERV-K and measles virus hemagglutinin protein, along with HMPV-1 and CFH peptides, by ELISA for recognition by GT103. The results are shown in Fig. 3. GT103 bound to all peptides, but with significantly lower affinity to the viral epitope peptides than to the CFH peptide. Binding of GT103 to the HMPV-1 peptide was at least two orders of magnitude weaker than binding to the CFH peptide.
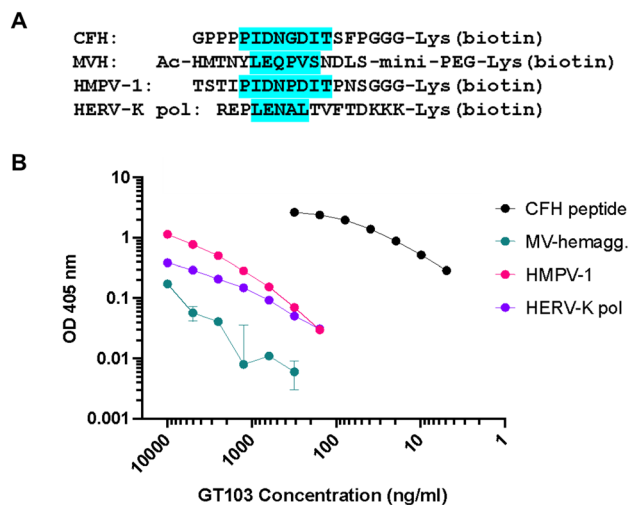
Discussion

It is well established that solid tumors containing tertiary lymphoid structures (TLS), organized aggregates of dendritic cells, and T cells surrounded by B-cell follicles, are associated with a more favorable prognosis [21]. In these structures, B cells are clonally expanded and affinity matured

Peptide	Epitope ID	Human mAb GT103, 1 µg/ml	Source Molecule Name	Source Molecule Accession	Organism Name
REPLENALTVFTD	194870	37.555,8	Pol Protein	5931705	*Human Endogenous Retrovirus K*
HMTNYLEQPVSNDLS	24352	35.989,3	Hemagglutinin Glycoprotein	122986	*Measles Virus*
STAAVILTPTENHFT	167882	18.821,5	Major Surface Antigen P30 Precursor	129348	*Toxoplasma Gondii*
RVEAQLHVWIPPLN	56259	17.359,3	Genome Polyprotein	130455	*Hepatitis C Virus Subtype 1A*
TAAVILTPTENHFTL	167883	13.223,3	Major Surface Antigen P30	211965869	*Toxoplasma Gondii Me49*
TNYLEQPVSNDLSNC	65486	10.333,0	Hemagglutinin Glycoprotein	122985	*Measles Virus Strain Edmonston*
CTPPALNCYWPLNDY	7193	8.155,0	Spike Glycoprotein	29836496	*SARS-CoV-1*
RIEDPPFNSLL	144763	6.434,5	Latent Membrane Protein 2	126379	*Human Herpesvirus 4 (Strain B95-8)*
YEQLNDSSEEEDEIDG	110460	6.416,5	Protein E7	137791	*Human Papillomavirus Type 16*
DLYCYEQLNDSSEE	110808	6.396,8	E7	4927721	*Human Papillomavirus Type 16*
PPALNCYWPLNDYGF	7193	5.720,0	E2 Glycoprotein Precursor	29836496	*Sars Coronavirus Tor2*
GRLHLNDRV	22127	5.116,5	Polyprotein	33413953	*Hepatitis C Virus Subtype 2B*
NFSISI	43916	5.043,8	Spike Glycoprotein Precursor	30173397	*Sars Coronavirus*
TWGENETDVLLLNNT	67257	3.799,5	Polyprotein	190684363	*Hepatitis C Virus Subtype 1B*
RISNLND	54291	3.798,5	Fim2	206598301	*Bordetella Pertussis*
RDHVNLVLNRDVS	53361	3.601,5	Glycoprotein Precursor	30313865	*Andes Virus Chi-7913*
SKLPINPLSNSLLRH	103	2.996,3	Genome Polyprotein	130469	*Hepatitis C Virus*
SDPPLVANQVVTCPD	168002	2.885,3	Major Surface Antigen P30 Precursor	129348	*Toxoplasma Gondii*
CYGVSATKLNDLCFS	7383	2.837,0	E2 Glycoprotein Precursor	29836496	*Sars Coronavirus Tor2*
IKSLPALNSPTVEEC	136010	2.803,3	Vp4-Vp2	38261775	*Human Coxsackievirus B4*
VMIKSLPALNSPTVE	136010	2.644,5	Vp4-Vp2	38261775	*Human Coxsackievirus B4*
EDTLNKVD	11451	2.450,0	Dnak	44588	*Mycobacterium Tuberculosis*
VLSFELLNAPATVCG	69760	2.327,5	E2 Glycoprotein Precursor	29836496	*Sars Coronavirus Tor2*
LNDITKEYEKLLNEI	38186	2.260,5	Merozoite Surface Protein 1 Precursor	1346586	*Plasmodium Falciparum*
RDEVDFCVGLNSFV	53336	2.123,3	Genome Polyprotein	SRC279960	*Hepatitis C Virus Subtype 2A*
LNEEQD	38201	2.041,8	Envelope Glycoprotein	21693239	*Dengue Virus 2 Jamaica/1409/1983*
QPESPARLASAILNA	30831	1.529,0	Non-Structural Protein 1	75545977	*Dengue Virus 4*
TIRGQFSNMSLSLLD	64444	1.487,8	Hemagglutinin Glycoprotein	122985	*Measles Virus Strain Edmonston*
GVSATKLNDLCFSNV	7383	1.486,3	E2 Glycoprotein Precursor	29836496	*Sars Coronavirus Tor2*
DNSNPVVQAEQLNWL	3245	1.455,3	Glucosyltransferase	153640	*Streptococcus Mutans*
SLNEEQ	59350	1.364,5	Envelope Glycoprotein	21693239	*Dengue Virus 2 Jamaica/1409/1983*
VLNRDVSFQDLSD	69673	1.274,0	Glycoprotein Precursor	30313865	*Andes Virus Chi-7913*
GPLTNS	21699	1.244,5	Genome Polyprotein	130458	*Hepatitis C Virus Subtype 1B*
GGPLTN	19965	1.169,0	Genome Polyprotein	130458	*Hepatitis C Virus Subtype 1B*
IGRLHLNDR	26318	1.090,8	Polyprotein	33413953	*Hepatitis C Virus Subtype 2B*
EDLLFNKVTLADAGF	16183	1.044,8	E2 Glycoprotein Precursor	29836496	*Sars Coronavirus Tor2*
LPHSLNDHILEPSIP	85672	1.013,5	Envelope Glycoprotein Gp62	SRC276211	*Human T-Lymphotropic Virus 1*
SGSVQYALNDNA	88585	940,8	Serotype 15 Outer Membrane Protein	75504244	*Neisseria Meningitidis*
SGVLPTSFGNTITC	58291	878,0	Genome Polyprotein	81992783	*Hepatitis C Virus Genotype 3*
KFLNPDREYDFRDLT	30774	857,3	Hemagglutinin Glycoprotein	122985	*Measles Virus Strain Edmonston*

Fig. 2 Binding of GT103 to PEPperCHIP® Infectious Disease Epitope Microarray. The responses are sorted by decreasing spot intensity

A

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CFH:         GPPPPPIDNGDITSFPGGG-Lys(biotin)
MVH:         Ac-HMTNYLEQPVSNDLS-mini-PEG-Lys(biotin)
HMPV-1:      TSTIPIDNPDITPNSGGG-Lys(biotin)
HERV-K pol:  REPLENALTVFTDKKK-Lys(biotin)
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B

Fig. 3 ELISA of GT103 binding to its epitope peptide (CFH peptide) compared to viral epitope peptides. **A** Amino acid sequences of the peptides used in the ELISA (with full epitope or consensus motif highlighted). **B** Binding of GT103 to viral peptides. Biotinylated peptides were immobilized in the wells of an ELISA plate and tested against twofold dilutions of GT103 from 10 to 0.005 µg/ml

in response to tumor antigens [22–26]. Hypothetically, the anti-CFH autoantibody in NSCLC patients could have originated in a number of ways: in one scenario, bone marrow-resident B cells with specificity toward the sterically obscured PIDNGDIT epitope in CFH escape deletion (having never been recognized as self), migrate into the tumor, organize into TLS, and undergo activation and expansion upon encountering the now-exposed epitope in the tumor environment. In another scenario, preexisting memory B cells with specificity toward PIDNGDIT-related epitopes in pathogens encountered during prior infection migrate into the tumor and are activated and expanded upon encountering the CFH epitope there. The anti-CFH autoantibody is also found in the blood of some of our lung cancer screening patients without overt cancer. In non-cancer patients, the anti-CFH autoantibody could have been produced in secondary lymphoid organs such as lymph nodes or spleen in response to antigens derived from nascent, undetectable tumors, or previously eradicated tumors.

Although the origin of the anti-CFH autoantibody may never be definitively known, the evidence presented in this paper supports the possibility that it could have evolved from a weak humoral reaction to a viral antigen, possibly one encountered in childhood, like HMPV-1 or measles, or in reaction to a viral vaccine. Another possibility is that the antibody could have originated in reaction to gut bacteriophage, as these have been shown to interact with innate immune cells [27], and many matches to the epitope sequence appear in *Caudoviricetes* proteins. The weak reactivity of the anti-CFH autoantibody or the recombinant

derivative GT103 toward the viral epitopes tested contrasts with the strong binding (low nanomolar affinity) of GT103 to the CFH epitope [16]. B cells expressing the antibody in adults may have affinity matured and then produced an antibody that binds CFH stronger than the viral epitope that was originally encountered.

Regardless of the origin of the anti-CFH antibody, it is worth recognizing that autoantibodies can have beneficial, neutral, or detrimental effects on the health of the patient. The prevalence of autoantibodies in tumors, and even as part of the normal autoantibodyome, appears to be much higher than commonly thought, as seen in recent publications (8, 11, 25) and databases. Identification of autoantibodies with beneficial effects would allow for the development of antibody therapeutics, or preventative vaccines against infections and tumors based on the antigen. To further study this hypothesis, additional and more comprehensive studies with a broad array of pathogens and in vivo experiments are needed.

Declarations

Competing interests E.F.P., E.B.G., and M.J.C. are founders of Grid Therapeutics. E.F.P. is the CEO of Grid Therapeutics. K.W. has no competing interests to declare that are relevant to the content of this article.

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