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T-Cell Epitopes in Type 1 Diabetes Autoantigen Tyrosine Phosphatase IA-2: Potential for Mimicry with Rotavirus and Other Environmental Agents

Margo C. Honeyman, Natalie L. Stone, and Leonard C. Harrison

Autoimmunity and Transplantation Division, The Walter and Eliza Hall Institute of Medical Research, Parkville, Australia

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Abstract

The tyrosine phosphatase IA-2 is a molecular target of pancreatic islet autoimmunity in type 1 diabetes. T-cell epitope peptides in autoantigens have potential diagnostic and therapeutic applications, and they may hold clues to environmental agents with similar sequences that could trigger or exacerbate autoimmune disease. We identified 13 epitope peptides in IA-2 by measuring peripheral blood T-cell proliferation to 68 overlapping, synthetic peptides encompassing the intracytoplasmic domain of IA-2 in six at-risk type 1 diabetes relatives selected for HLA susceptibility haplotypes.

The dominant epitope, VIVMLTPLVEDGVKQC (aa 805–820), which elicited the highest T-cell responses in all at-risk relatives, has 56% identity and 100% similarity over 9 amino acids (aa) with a sequence in VP7, a major immunogenic protein of human rotavirus. Both peptides bind to HLA-DR4(*0401) and are deduced to present identical aa to the T-cell receptor. The contiguous sequence of VP7 has 75% identity and 92% similarity over 12 aa with a known T-cell epitope in glutamic acid decarboxylase (GAD), another autoantigen in type 1 diabetes. This dominant IA-2 epitope peptide also has 75–45% identity and 88–64% similarity over 8–14 aa to sequences in Dengue, cytomegalovirus, measles, hepatitis C, and canine distemper viruses, and the bacterium *Haemophilus influenzae*. Three other IA-2 epitope peptides are 71–100% similar over 7–12 aa to herpes, rhino-, hanta- and flaviviruses. Two others are 80–82% similar over 10–11 aa to sequences in milk, wheat, and bean proteins. Further studies should now be carried out to directly test the hypothesis that T-cell activation by rotavirus and possibly other viruses, and dietary proteins, could trigger or exacerbate β-cell autoimmunity through molecular mimicry with IA-2 and (for rotavirus) GAD.

Introduction

The recently identified pancreatic islet autoantigen in type 1 diabetes, IA-2, is a 106 kD member of the protein tyrosine phosphatase family (1,2) and an integral membrane protein of neuroendocrine secretory granules (3). Circulating autoantibodies that recognize predominantly the cytoplasmic domain of IA-2 can be detected in up to 88% of people with recently diagnosed type 1 diabetes and in about half of islet cell antibody (ICA)-positive, first-degree type 1 diabetes relatives in whom they indicate high risk for clinical disease (4). The cytoplasmic domain of IA-2 has 80% sequence identity with another tyrosine phosphatase, IAR (5), also known as IA-2 β (6) or phogrin (7), which also reacts with antibodies in type 1 diabetes (8). T-cell proliferative responses to IA-2 were reported to be increased in at-risk relatives and in people with recently di-

Address correspondence and reprint requests to: Dr. Margo C. Honeyman or Leonard C. Harrison, The Walter and Eliza Hall Institute of Medical Research, Royal Melbourne Hospital, Victoria 3050, Australia. Phone: 61-3-9345 2555; Fax: 61-3-9347 0852; E-mail: honeyman@wehi.edu.au

agnosed type 1 diabetes (9). T-cell epitope peptides in autoantigens have potential diagnostic and therapeutic applications and may hold clues to environmental agents that could trigger or exacerbate autoimmune disease. We identified T-cell epitope peptides within the intracytoplasmic domain of IA-2 and examined them for sequence similarities with microorganisms and dietary proteins as a basis for molecular mimicry.

Materials and Methods

Subjects

Peripheral blood was obtained from six at-risk, ICA-positive first-degree relatives of people with type 1 diabetes (4 male, 2 female, mean age 28.5 ± 15.0, range 10–50) and two healthy control subjects (2 males, ages 30 and 48). Subjects were selected for type 1 diabetes–associated HLA haplotypes, i.e., DR4-DQ8 homozygous (two at-risk relatives, one control), DR3-DQ2 homozygous (two at-risk relatives, one control), and DR4-DQ8/DR3-DQ2 heterozygous (two at-risk relatives). All relatives had antibodies to IA-2. Within 14 months of the study, both DR4-DQ8 homozygous relatives developed clinical type 1 diabetes and the first-phase insulin release in response to intravenous glucose in both DR3-DQ2 homozygous relatives fell to below the first percentile, indicating imminent clinical disease. The study was approved by the Ethics Committee at the Institute and was conducted with informed consent.

IA-2 Antibody Assay

Antibodies to IA-2 (IA-2 Ab) were measured by immunoprecipitation of ^{35}S-methionine-labeled full-length recombinant IA-2 (4). IA-2 was synthesized from cDNA cloned into the *Eco*R1 site of the Bluescript KS vector in the presence of ^{35}S-methionine, in the TNT-reticulocyte lysate system (Promega, Madison, WI). The assay has a sensitivity of 60% and specificity of 97% for newly diagnosed type 1 diabetes and was standardized in the Third Combined Autoantibody Workshop (Florida, 1996). The upper limit of the normal range (mean + 3 SD of healthy controls) is 3 units. Results were expressed as a percentage of counts precipitated by a reference serum. The intra- and interassay coefficients of variation (CV) were 1% and 4%, respectively.

Tissue Typing

HLA alleles were typed by the standard microlymphocytotoxic method for all recognized HLA class I alleles. HLA-DR and DQ types were determined by sequence-specific oligotyping, following the International Histocompatibility Workshop protocol.

Peptides

A set of 68 16-mer peptides was synthesized (Chiron Technologies, Melbourne, Australia). Sixty-two peptides overlapping by 10 aa spanned the cytoplasmic domain of human IA-2 (aa 601–979). Six additional 16-mers (aa 713–728, 779–794, 795–810, 831–846, 845–860, 959–974) covered sequences predicted to bind to DR4(*0401) (10,11). Peptides were synthesized by Fmoc chemistry and solid-phase synthesis, with free amino and free acid carboxy-termini, using base-labile or acid-labile resins as appropriate. Each peptide was dissolved in 100 μl 40% acetonitrile in degassed phosphate buffered saline (PBS) and shaken at 4°C overnight, checked for solubility, sonicated in an immersion sonicator for up to 60 min at room temperature (RT) if necessary, then diluted to 1 mg/ml in PBS. Each peptide was dispensed into 12 wells of a sterile 96-well round-bottomed tissue culture tray (Linbro) and stored at −80°C.

HLA-DR4 Binding

Peptide binding to purified DR4(*0401) was measured directly by a competition enzyme linked immunosorbant assay (ELISA), as previously described (12,13).

T-Cell Proliferation Assays

Peripheral blood mononuclear cells (PBMC) were separated from heparinized venous blood by Ficoll-Hypaque density centrifugation, washed twice in RPMI 1640 medium, and diluted to 10^6 cells/ml in RPMI1640 medium containing 10% autologous serum, 20 mM Hepes, and 10^{-5} M 2-mercaptoethanol (complete medium). Two × 10^5 cells were added in 200 μl of complete medium to each well of freshly thawed, peptide-containing 96-well trays. Each peptide was tested at 10 μg/ml in replicates of 12. The first row of each tray contained six wells without antigen (basal) and six wells with 1.8 Lyons flocculating units (Lfu)/ml of preservative-free tetanus toxoid (Commonwealth Serum Lab-

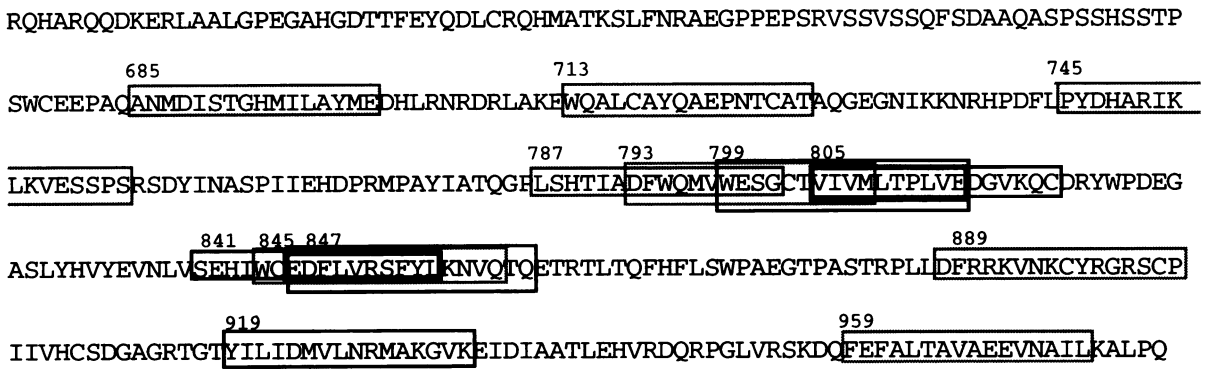


Fig. 1. Summary of identified T-cell epitope peptides in tyrosine phosphatase IA-2. Bolded boxes contain sequences common to overlapping epitope peptides; unbolded boxes contain epitope peptides presented by both DR3-DQ2 and DR4-DQ8 haplotypes; stippled boxes contain epitope peptides presented only by the DR4-DQ8 haplotype.

oratories, Melbourne); the last row of each tray contained six wells with 0.18 Lfu of tetanus toxoid and six wells without antigen. After incubation for 6 days in 5% CO_2 at 37°C, 37 kBq ^{3}H-thymidine (ICN, 2.5 TBq/mmol) was added per well; the cells were harvested semi-automatically 7 hr later and ^{3}H-thymidine incorporation measured by liquid scintillation counting. As T-cell responses to peptides approximate a Poisson rather than a normal distribution, proliferation was expressed as the percent positive of the 12 replicate wells. Positive wells were defined as having cpm > mean + 2 SD of the 12 basal wells for that plate. A T-cell response to a peptide was defined as positive wells ≥40%; this threshold was the mean + 2 SD of the 136 responses of the controls to all peptides (mean 6%, SD 17%). T-cell epitopes were defined as being within peptides that elicited a response in two at-risk relatives with the same HLA haplotype, e.g., both DR4-DQ8 homozygotes, or one DR4-DQ8 homozygote and at least one DR3-DQ2/DR4-DQ8 heterozygote. The reproducibility of T-cell proliferation to tetanus (1.8 Lfu/ml) was tested by repeat assays weekly for 4 weeks in three subjects; intra-assay CVs ranged from 13.1% to 18.9% and the interassay CV from 14.2% to 26.2%.

Database Searches

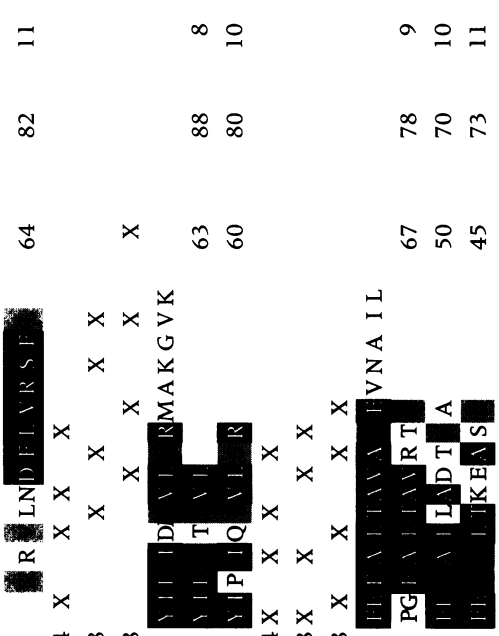
Similarities to the sequences of epitope peptides or their common overlapping sequences were sought using FASTA 2 software. Databases searched were Genbank (GBTrans) (1997), Swissprot (1997), Protein Research Foundation of Japan (PRFJ) (1997), and Ooi Japan (OOIJ) (1983). No statistical significance was assigned to search results because the databases included many sequences homologous to IA-2, e.g., B220, CD45, IA-2 β, phogrin, IAR, and other tyrosine phosphatases. Infectious or dietary agents were selected on the basis of potential biological relevance, as in other studies (14), from the first 60 best matches in the PRFJ and OOIJ databases and from the first 100 in the larger GBTrans and Swissprot databases.

Results

From 68 16-mer peptides encompassing cytoplasmic IA-2, 11 peptides (from aa 685, 713, 745, 787, 793, 805, 841, 845, 847, 919, and 959) elicited T-cell responses in relatives homozygous for DR4-DQ8 and two peptides (from aa 799 and 889) elicited responses in one DR4-DQ8 homozygous and one DR4-DQ8/DR3-DQ2 heterozygous relative (Fig. 1). All these epitope peptides bound to HLA-DR4 (Table 1). Five peptides (from aa 799, 805, 841, 847, 919) elicited responses in the DR3-DQ2 homozygous relatives, and the first four of these also elicited responses in the matched control. Notably, peptide EDF LVRSFYLKNVQTQ (aa 847–862) elicited responses in both DR3-DQ2 and DR4-DQ8 homozygous controls, as well as in one DR3-DQ2 homozygous, one heterozygous, and both DR4-DQ8 homozygous at-risk relatives. Peptide VIVMLTPLVEDGVKQC (aa 805–820) elicited a response in all at-risk relatives and in the DR3-DQ2 homozygous control; in each case it was the

Table 1. Comparison of T-cell epitope peptides in IA-2 with sequences of environmental agents

Environmental Agent	Peptide/Protein	aa	Experimental DR4 Binding Affinity (μM)	Sequence†	% Identity	% Similarity	#aas
				DR4 X X X X			
				DQ8 X X X X			
				DQ8 X X X X			
	IA-2	805–820	2.5	VIVMITPLVEDGVKQC			
Rotavirus A (serotype 3)	Glycoprotein VP7	41–51		IV I PL NA	56	100	9
Dengue virus	Capsid protein C	104–112		VL MI IPTV	67	78	9
Cytomegalovirus (CMV, HHV5*)	Major capsid	854–864		VGEMI IELVED	64	73	11
Canine distemper	Haemagglutinin	89–99		VIDV ITPIKII	75	88	8
Measles	Haemagglutinin	88–96		VKDV ITPLKII	63	75	8
Hepatitis C (strains J, T)	E2 genome polyprotein	374–384		IVMLLF GVD	45	64	11
Haemophilus influenzae	HI1338	96–110		VIDI IEVLKD GVE	50	71	14
				DR4 X X X X			
				DQ8 X X X X			
	IA-2	685–700	9.0	ANM D ISTGH ILAYME			
Epstein-Barr (HHV4, strain B95-8)	BRRF2	179–188		ALRGH QLAY	71	86	7
Epstein-Barr (HHV4, strain B95-8)	BTRF1	93–102		ISLA ILAP	56	78	9
Rhinovirus 14 (common cold)	Genome polyprotein	455–464		IS ILAY	50	100	10
				DR4 X X X X			
				DQ8 X X X X			
	IA-2	787–802	10.0	LSHT ADFWQMVWE S			
Hantavirus	M polyprotein precursor	48–63		LPPV ADTAQMV PE S	58	75	12
Japanese encephalitis	Genome polyprotein	2956–2971		EAVDDPRFWEMVDE ER	71	71	7
Kunjin, West Nile encephalitis,	Genome polyprotein	2956–2971		EAVDDPKFWEMVDE ER	71	71	7
Murray Valley encephalitis	Genome polyprotein	2956–2972		EAVDDPKFWEMVDE ER	71	71	7
				DR4 X X X X			
				DQ8 X X X X			
	IA-2	841–856	6.0	SEH IWCEDFLVRSF L			
Wheat	NADH ubiquinone reductase	568–580		KRV LNDFLVRSF	64	82	11



Vicia faba (broad bean)	NADH ubiquinone reductase	85–97																64		82	11
			DR4	X			X	X		X											
			DQ8					X		X		X	X								
			DQ8							X		X		X				X			
	IA-2	919–934	1.5																		
Herpes simplex (HHV1)	Surface glycoprotein	2 to 9																63		88	8
Cow's milk	Kappa casein	26–35																60		80	10
			DR4	X			X	X		X											
			DQ8	X			X			X		X									
			DQ8	X			X			X		X									
	IA-2	859–874	1.0																		
CMV (HHV5), H. saimiri	Major capsid	1033–1043																67		78	9
Papilloma 28, 18	Replication protein E1	392–402																50		70	10
Vaccinia, Variola (HHV6)	E2L polyprotein	431–441																45		73	11

*HHV = human herpes virus; †potential anchor residues for binding to DR4 and DQ8 are denoted by x.

highest response (relatives, 86 ± 20% positive wells; control 100% positive wells). Alignment of the IA-2 epitope peptides with related sequences in human tyrosine kinase IAR (5) revealed identities of 86 ± 12% and similarities of 92 ± 10% (mean ± SD).

Epitope peptides of IA-2 shared identity or similarity with several environmental agents (Table 1). The dominant epitope peptide VIVML TPLVEDGVKQC had sequence identities of 75–45% and similarities of 100–64% over 8–11 aa to sequences within the VP7 protein of rotavirus (serotype 3, strain P), the capsid protein C of Dengue flavivirus, the major capsid protein of human cytomegalovirus, the hemagglutinin proteins of canine distemper virus (known to infect humans) and the closely related measles virus, and the E2 protein of hepatitis C virus. It also had 50% identity and 71% similarity over 14 aa with the HI 1338 protein of the bacterium *Haemophilus influenzae*. Most of the sequence similarities were in the region of overlap VIVMLTPLVE (aa 805–814) with the preceding epitope peptide (aa 799–814). The rotavirus VP7 protein also had 75% identity and 92% similarity over 12 aa (aa 18–29) (or 75% and 100% over 9 aa) to GAD65 (aa 117–128), and GAD67 (aa 123–134) (Table 2).

Peptide aa 685–700 had 56–71% identity and 78–86% similarity to the BTRF1 and BRRF2 proteins of Epstein-Barr virus, and 50% identity and 100% similarity over 10 aa to the genome polyprotein of rhinovirus 14, the common cold virus.

Peptide aa 787–802 had 58% identity and 75% similarity over 12 aa to the M polyprotein precursor of hantavirus, and 71% identity and similarity over 7 aa to sequences within the genome polyprotein of other members of the Flavivirus family, i.e., Japanese encephalitis, Kunjin, West Nile, and Murray Valley encephalitis viruses. Most of the sequence similarities were in the region of overlap DFWQMVWESG (aa 793–802) with the succeeding epitope peptide (aa 793–808).

Peptide aa 841–856 had 64% identity and 82% similarity over 11 aa to proteins in wheat and broad beans, and epitope peptide aa 919–934 had 60% identity and 80% similarity over 10 aa to kappa casein in cow's milk. Most of the sequence similarities were in the region of overlap EDFLVRSFYL (aa 847–856) with the two succeeding epitope peptides (aa 845–860, 847–856).

Peptide aa 919–934 had 63% identity and

Table 2. Sequence similarities between IA-2, rotavirus, and GAD 65 and 67

Protein	Sequence†
	DR4 X X X X X X X X X
	DQ8 X X X X X X X X X
IA-2 aa801–816	- - - - - - - - - - - - - - - - W C E D E D G
Rotavirus VP7 aa16–49	S V I I \ \ \ \ K S T R I M D F I I Y R F L L \ \ I P I
GAD65 aa115–129	N I I \ \ \ K S D R S
GAD67 aa121–135	D I I \ \ \ R K D R S

†Potential anchor residues for binding to DR4 and DQ8 are denoted by x.

88% similarity over 8 aa to the surface glycoprotein of herpes simplex virus. Peptide aa 959–974 had 67% identity and 78% similarity over 9 aa to the major capsid protein of cytomegalovirus (HHV5) and herpes saimiri virus (which can infect human lymphocytes), and 50% identity and 70% similarity over 10 aa to replication protein E1 of papilloma virus strains 28 and 18. It also had 45% similarity and 73% similarity over 11 aa to the E2L polyprotein of vaccinia and variola (HHV6) viruses. No sequence similarities were detected with the remaining three epitope peptides, aa 713–728, 745–760, and 889–904.

Discussion

Thirteen peptides within the intracytoplasmic domain of IA-2, all of which could be presented by HLA-DR4 encoded by the DR4-DQ8 haplotype, elicited T-cell responses in at-risk relatives. The overlap of these peptides suggests that the number of epitopes was possibly nine. Five peptides, between aa 799–934, elicited responses in relatives bearing either the DR4-DQ8- or DR3-DQ2-susceptible HLA haplotypes. The remaining peptides elicited responses only in relatives bearing the DR4-DQ8 haplotype. At least two sources of these epitopes are indicated by the very high degree of homology between the two tyrosine phosphatases, IA-2 and IAR.

Interestingly, four peptides elicited responses in the DR3-DQ2 homozygous control, and one of these four also elicited responses in the DR4-DQ8 homozygous control. Other evidence demonstrates that T cells in normal individuals are capable of reacting to autoantigens (9,15–17). The important inference, however, is that these four epitope peptides (shared sequences VIVM LTPLVE, EDFLVRSFYL) should contain the strongest clues to cross-reactive epitopes, e.g., in environmental agents that could trigger or exacerbate islet autoimmunity.

The contribution of environment to type 1 diabetes can be gauged from the lack of concordance for disease in the majority of identical twins (18). However, the environmental factors responsible remain enigmatic. Some viruses such as Coxsackievirus (19) and rubella (20), as well as the rodenticide "Vacor" (21), directly damage pancreatic islet β-cells and are associated with β-cell autoimmunity, but such examples are rare, and evidence for persisting infection of β-cells is lacking (22). Infectious agents could also trigger β-cell autoimmunity indirectly (re-

viewed in ref. 23), particularly by activating T cells cross-reactive with islet proteins, a mechanism termed molecular mimicry.

Molecular mimicry has been proposed between the islet autoantigen glutamic acid decarboxylase 65 (GAD65) (aa 257–273) and the P2C protein of Coxsackievirus B4, which share 59% identity and 76% similarity over 17 aa (24). This peptide from GAD65 elicits T-cell responses in humans with type 1 diabetes (17) and in the nonobese diabetic (NOD) mouse model (25). T-cell responses to Coxsackie virus B (strain unstated) have been reported in recently diagnosed type 1 diabetes (14). However, the only reasonably direct evidence for molecular mimicry in type 1 diabetes is the experimental demonstration that infection with lymphocytic choriomeningitis virus (LCMV) triggers immune-mediated β-cell destruction in mice that transgenically express an LCMV glycoprotein or nucleoprotein in their β-cells (26,27).

Evidence for a role of viral infection close to diagnosis of type 1 diabetes is the finding that IgM responses to Coxsackievirus (28) and T-cell responses to both Coxsackievirus and adenovirus, but not to the herpesviruses, or to mumps, polio, tick-borne encephalitis virus, or rotavirus (14), were higher in people at diagnosis than in controls. The dominant IA-2 epitope peptide aa 805–820 has high identity and similarity over 8–11 aa to sequences within several viruses. The nonamer in this peptide predicted to bind to DR4 (11) is in fact V**IV**M**LTPL**V. The most likely anchor residues for binding [Table 1 (10,11)] are unbolded; the bolded residues are therefore most likely to be T-cell receptor contact residues (TCR-CR) potentially critical for molecular mimicry. The strongest similarity is with the VP7 protein of human rotavirus (serotype 3, strain P, reovirus family). VP7 contains the sequence I**IVILSPL**L (aa 41–49) with identical TCR-CR; although the anchor residues differ, they are equally effective for DR4 binding (11). By using HLA-DQ8(*0302) binding peptides curated in the MHCPEP Database (29) to derive a matrix for DQ8 (Honeyman, Brusic, Harrison, manuscript in preparation), two overlapping decamers in the same IA-2 region were also predicted to bind to DQ8 (Table 1), which is consistent with the high T-cell responses seen to this epitope. The first DQ8 frame, I**IVILSPL**L**L**N, has 100% similarity to VP7 in its potential TCR-CR. VP7 is one of the two immunogenic proteins that confer serotype specificity and is currently being used by others to develop a rotavirus vaccine.

Jones and Crosby (14) noted a sequence similarity between GAD 65 (aa 108–137) and rotaviral VP7 protein, although they could not elicit increased T-cell responses to whole rotavirus (strain unstated) in people with recently diagnosed type 1 diabetes. The cited GAD65 sequence contains a T-cell epitope peptide, MNILLQYVVKSFDRST (aa 115–130, with 88% homology to GAD67, aa 121–136), in mice transgenic for human HLA-DR4 (30). We have identified this epitope (aa 115–129) in at-risk relatk; 4tives and healthy controls homozygous for DR4-DQ8 (Honeyman, Stone and Harrison, unpublished data). The predicted DR4-binding nonamer within the GAD65 peptide is I**LLQYV VK**S, and for VP7 it is V**LLNYVLK**S; in GAD 67 the equivalent region is I**LLNYVRK**T. GAD65 therefore has 100% similarity and 80% identity with VP7 in the potential TCR-CR. The region of VP7 containing both sequence similarities is immunologically interesting. It contains many hydrophobic potential anchor residues for HLA class II molecules and an epitope for cytotoxic T cells in C57/B16 mice immunized with rotavirus (31), adjacent to the sequences with similarity to GAD65 and IA-2. The GAD and IA-2 similarities raise the interesting possibility that rotavirus infection could simultaneously activate T cells to two type 1 diabetes autoantigens (see also below).

Rotavirus is a major enteric pathogen of early childhood that causes regular winter outbreaks of gastroenteritis in daycare centers. Children can have multiple infections by different serotypes. Early-age daycare was found to confer increased risk for type 1 diabetes (32), consistent with a link between rotavirus and type 1 diabetes. Serologically, herd immunity is almost complete by age 5 (33). Nevertheless, proliferative CD4 T-cell responses have been detected in humans within 4 to 6 weeks following rotavirus reinfection (34). These CD4 T cells were of the CD45RA-negative (memory), α4β7 integrin-high subset, indicating that gastrointestinal immune responses generate α4β7-positive T-cell memory. An interesting convergence is that GAD-responsive T cells from people with recently diagnosed type 1 diabetes are α4β7 positive (35) and T cells in the early phase of insulitis in NOD mice are β7-integrin high (36). These data suggest that rotavirus-responsive CD4, β7-positive T cells could migrate selectively to the islets. The similarities of the other viruses with peptide VIVMLTPLVEDGVKQC and with the other IA-2 epitope peptides include anchor resi-

dues for DR4(*0401), but the potential TCR-CR are not quite as remarkable as for rotavirus.

IA-2 epitope peptide aa 919–934, as well as being similar to the surface glycoprotein of herpes simplex virus, has 60% identity and 80% similarity over 10 aa that include the predicted DR4-binding nonamer **ILIDMVLNR**, with bovine kappa casein **YIPIQYVLSR** (aa 26–35), although the similarity of the potential TCR-CR is only 40%. While the role of bovine milk proteins as potential aetiologic agents in type 1 diabetes is controversial (37), T-cell responses to whole casein have been reported in type 1 diabetes (38). There is also a high similarity of the common sequence EDFLVRSFYL (aa 847–856) of the IA-2 epitope peptides encompassing aa 841–898 with sequences in wheat and broad bean proteins. Peptide aa 841–856 contains a DR4-binding motif **WCEDFLVRS** (cf. **VLNDFLVRS** in wheat and beans) and a predicted DQ8 binding motif **IWCEDFLVRS** (cf. **RVLNDFLVRS** in wheat and beans). The class II MHC molecule of NOD mice, I-A^{g7}, is the structural counterpart of human DQ8(*0302), and NOD mice fed casein supplement (L. C. Harrison, unpublished results), wheat flour, and to a lesser extent, soya bean meal (39), have an accelerated onset of diabetes.

In conclusion, we have identified T-cell epitope peptides in the intracytoplasmic domain of the type 1 diabetes autoantigen, tyrosine phosphatase IA-2, whose sequence analysis suggests that immunity to rotavirus (whose VP7 sequence mimics epitopes in both IA-2 and GAD) and possibly other viruses and dietary proteins could predispose to type 1 diabetes by activating cross-reactive T cells. Further studies are now required to directly test this hypothesis.

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