Proteome-Wide Epstein-Barr Virus Analysis of Peptide Sharing with Human Systemic Lupus Erythematosus Autoantigens

Darja Kanduc PhD

Department of Biosciences, Biotechnologies, and Biopharmaceutics, University of Bari, Bari, Italy

ABSTRACT: **Background:** Although cross-reactions between Epstein-Barr virus (EBV) and human systemic lupus erythematosus (SLE) autoantigens occur, a complete analysis of the potential EBV peptide cross-reactome has not been performed.

Objectives: To analyze the whole EBV proteome searching for peptides common to SLE-related proteins and endowed with an immunological potential.

Methods: Fifty-one SLE-related proteins were analyzed for hexapeptide sharing with EBV proteome using publicly available databases.

Results: An extremely high number of hexapeptides are shared between 34 human SLE autoantigens and EBV proteins. The peptide sharing mostly occurs with complement components C4 and Interleukin-10 (IL-10).

Conclusion: This study thoroughly describes the EBV vs. SLE autoantigens peptide overlap and powerfully supports cross-reactivity as a major mechanism in EBV-associated SLE etiopathogenesis.

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KEY WORDS: cross-reactivity, complement components C4, Epstein-Barr virus (EBV), Interleukin-10 (IL-10), systemic lupus erythematosus (SLE)-related proteins

Systemic lupus erythematosus (SLE) is a multifactorial disease clinically characterized by different symptoms and biochemically defined by autoantibody development [1]. Genetic factors [2], complement deficiencies [3], drugs such as procainamide and hydralazine, heavy metals, ultra-violet light, and infection [4] seem to contribute to SLE etiopathogenesis. Among the infectious agents, Epstein-Barr virus (EBV) has repeatedly been associated with SLE [5-13]. Clinical and laboratory data on elevated anti-EBV Ab titres in SLE were firmly established by Evans and colleagues in 1971 [14]. The data led to identifying SLE autoantigens that are recognized by anti-EBV antibodies [15]. More specifically, amino acid epitopic sequences shared between SLE autoantigens and EBV proteins were identified. An example is the epitope TKYKQRNGWSHK that is present in the SLE autoantigen SS-A/Ro ribonucleoprotein and cross-reacts with a peptide from the latent viral protein EBV nuclear antigen-1 (EBNA-1) [15].

These studies helped our understanding of the immune relationship between EBV and SLE. However, only immune responses to a number of EBV antigens have been investigated [16,17] and, as of now, there is no analysis of the overlap between the peptide in the entire EBV proteome and SLE autoantigens. A proteome-wide EBV analysis seems to be important since it might help discover epitopic sequences capable of contributing to the EBV vs. SLE autoantigens cross-reactivity. Hence, in the present study we explored the whole EBV proteome for hexapeptide sharing with SLE-related antigens. Data are reported on a vast viral vs. human hexapeptide overlap that, in particular, involves complement components C4 and IL-10.

PATIENTS AND METHODS

Sequence analyses were conducted on a set of 51 SLE-related proteins that were retrieved from the Uniprot database (https://www.uniprot.org) [18] using the keywords 'SLE' and 'lupus' [Supplementary Table 1]. The 51 SLE-related proteins are reported as UniProtKB/Swiss-Prot entry names in text, unless when discussed in detail. Protein primary sequences were decomposed into overlapping hexapeptides offset by one residue, for example MLPAAP, LPAAPG, and PAAPGK. Next, each hexapeptide was analyzed for occurrences in EBV, strain ag876 (NCBI: txid82830), proteome using the Peptide Match program (https://research.bioinformatics.udel.edu) [19]. Tobacco mosaic virus (TMV, NCBI: txid12243) was used as a negative SLE-unrelated viral control.

The immunologic potential of the shared peptides was explored using the Immune Epitope Database (IEDB, www.iedb.org) [20].

RESULTS

Analysis of the hexapeptide sharing between SLE-related proteins and the EBV proteome showed that 34 SLE-related proteins share a total of 171 hexapeptides with the EBV proteome [Table 1]. The extent of the viral vs. human peptide overlap

Table 1. Hexapeptide sharing between human SLE-related proteins and the EBV proteome*

SLE-related proteins**	No. of shared hexapeptides	Shared hexapeptides
BANK1	1	PAAPGK
BLK	3	KKPDKE, RLRRCH, RQSLRL
CD19	3	LQCLKG, TAPSYG, YAAPQL
CD22	1	QAAVTS
CO4A	7	ALERGL, ASAGLL, FSDGLE, PQAPAL, PTAAAA, SDGLES, SYVRVT
CO4B	7	ADLRGV, ALERGL, ASAGLL, FSDGLE, PQAPAL, SDGLES, SYVRVT
CR1	2	SSPAPR, VVVLLA
CR2	1	PPPPVI
EEA1	3	AEDNEV, ATISQL, LEKERE
IL10	104	AENQDP, AFNKLQ, AFSRVK, ALSEMI, AMSEFD, CENKSK, CHRFLP, CQALSE, DAFSRV, DFKGYL, DIFINY, DLRDAF, DNLLLK, EDFKGY, EEVMPQ, EFDIFI, EKGIYK, EMIQFY, ENKSKA, ENLKTL, ESLLED, EVMPQA, FDIFIN, FINYIE, FKGYLG, FLPCEN, FNKLQE, FSRVKT, FYLEEV, GCQALS, GENLKT, GIYKAM, GYLGCQ, HRFLPC, HVNSLG, IEAYMT, IFINYI, INYIEA, IQFYLE, IYKAMS, KAMSEF, KESLLE, KGIYKA, KGYLGC, KLQEKG, KNAFNK, KSKAVE, KTLRLR, LEDFKG, LEEVMP, LGCQAL, LGENLK, LKESLL, LKTLRL, LLEDFK, LLKESL, LLLKES, LPCENK, LQEKGI, LRDAFS, LRDLRD, LRLRLR, LRLRRC, LRRCHR, LSEMIQ, MIQFYL, MLRDLR, MPQAEN, MSEFDI, NAFNKL, NKLQEK, NKSKAV, NLKTLR, NLLLKE, NSLGEN, NYIEAY, PCENKS, PQAENQ, QAENQD, QALSEM, QEKGIY, QFYLEE, RCHRFL, RDAFSR, RDLRDA, RFLPCE, RLRLRR, RLRRCH, RRCHRF, RVKTFF, SEFDIF, SEMIQF, SKAVEQ, SLGENL, SLLEDF, SRVKTF, TLRLRL, VKTFFQ, VMPQAE, VNSLGE, YIEAYM, YKAMSE, YLEEVM, YLGCQA
ITAM	3	GTSGSG, LLLLAL, NATLKG
KPCD	2	INQKLL, LLEKRR
LARP6	3	DVDELE, SPGTSP, VDELED
LY9	1	VVGENT
LYAM2	1	PSASGS
MAGB2	1	AAAAAA
PDCD1	1	PSPSPR
RFIP5	2	RSELGR, SRSELG
RO60	1	VVAFSD
RSMB	2	AAAAAA, RGENLV
RSMN	4	AAAAVA, IPQAPA, PIPQAP, RGENLV
RU17	2	ERPGPS, SRERAR
RU2B	1	AGAARD
S10A9	1	HEGDEG
SELPL	1	KAKSPG
SMD1	3	GRGRGG, GRGRGR, RGRGRG
TNAP3	4	LVTLKD, RLVRSP, SLESGS, STLKET
TNFL6	3	PPPPPP, RRPPPP, VLVALV
TREX1	2	LAAHGR, NLLLAF
TRI68	1	ERSQRP
TRNK1	6	EEEEDE, EQIQEF, LLLDAS, RGRGRG, SDLRSL, VGSKEH
UB2L3	1	VCLPVI
XRCC5	1	LSGGDQ
XRCC6	2	IISSDR, LTKHFQ

*Using TMV as a negative viral control, no hexapeptide sharing with the SLE-related proteins was found, with the exception of complement components C4, which have a hexapeptide (FSLGSK) in common with TMV

**SLE-related proteins are reported by SwissProt/UniProtKB accession. Disease association and references are available at www.uniprot.org, OMIM, and PubMed databases

EBV = Epstein-Barr virus, SLE = systemic lupus erythematosus, TMV = tobacco mosaic virus

is unexpected since the probability that two proteins share a hexapeptide is equal to 20^{-6} (i.e., 0.0000015625%).

The shared hexapeptides are not evenly distributed throughout the 34 SLE-related proteins with peptide sharing ranging from 1 to 104 matches. The highest number of matches is present in IL-10. Indeed, the EBV proteome contains an IL-10 protein homolog [21], thus explaining the very high extent of hexapeptide sharing with the SLE-related protein IL-10 [Table 1] and substantiating the strict evolutionary relationship between viruses and the origin of eukaryotic cells [22].

In addition, peptide sharing has a high immunologic potential. In fact, using IEDB [20], a collection of experimentally validated epitopes, we found that many of the shared pentapeptides between EBV and SLE-related proteins also recur in a high number of immunoreactive epitopic sequences [Table 2].

DISCUSSION

A whole-proteome analysis of EBV vs. SLE-related autoantigens was conducted at the hexapeptide level to search for peptide commonalities that might trigger cross-reactions potentially leading to SLE disease. The data [Table 1, Table 2] show a large viral vs. SLE antigens peptide overlap and are of interest due to whether EBV is a trigger for systemic lupus and other autoimmune diseases [13]. Our results support the possibility of cross-reactivity in the EBV-induced SLE pathogenesis. Moreover, this study might help researchers to investigate still unexplained phenomena, such as the presence of high concentrations of extremely avid anti-IL-10 antibodies in healthy blood donors [23,24] as well as why low C4 levels persist in many lupus nephritis patients after disease remission [3].

Table 2. Immunopositive epitopes containing peptides shared between EBV and SLE-related proteins

IEDB ID*	Epitope sequence**	IEDB ID	Epitope sequence
5713	aYAAPQLfpvsditq	529216	vpmrQAAVTStslt
19704	ggdnhgRGRGRGRGRGGgrpgapg	529217	vpmrQAAVTStslti
45501	npVCLPVIvapylf	529218	vpmrQAAVTStsltik
53195	raRGRGRGrgekrp	541886	evlPTAAAAa
69476	vlfaatAAAAAAvdrgdpp	551423	epgtwkisarFSDGLE
120103	mvvtrtekdsyVVAFSDemvpcpvt	592869	rpvafsvvPTAAAAv
121250	ekdsyVVAFSDemvpcpvttdm	641585	dnpLSGGDQy
138887	qaYAAPQLf	642360	ESLLEDFKGYLGCQAL
170653	dsyVVAFSDemvpcp	645027	INYIEAYMTmkir
173111	rtekdsyVVAFSDem	651556	vlfgtdgtdnpLSGGDQy
237637	apenayqaYAAPQLfpvsdi	684188	tkASAGLLkmmr
237923	sapqpapenayqaYAAPQLf	693926	ASAGLLlggggqgsg
238040	yqaYAAPQLfpvsditqnqq	694326	epvgtasqASAGLLl
239351	aetAAAAAAVAa	694327	epvstasqASAGLLl
430363	gtdgtdnpLSGGDQy	696559	tasqASAGLLlgggg
430371	gtdnpLSGGDQy	699685	atAAAAAAy
431719	pLSGGDQy	763513	nSYVRVTasdpl
466103	gtdnpLSGGDQ	763514	nSYVRVTasdpldt
477608	egtAAAAAA	772530	gdfnSYVRVTasd
478876	gtAAAAAAr	776210	pnmipdgdfnSYVRVTasd
495328	SRVKTFFQm	776376	pvafsvvPTAAAAvslk
523585	pgtkgtAAAAAAAAAA	778765	SYVRVTasd
527160	tAAAAAAAAAAA	780300	HVNSLGENLKTLRLR
527587	tkgtAAAAAAAAAA	780356	thfpgnlpnMLRDLR

*Epitope IEDB ID number. Details and references are available from www.iedb.org
**Peptides shared between EBV and human SLE-related proteins [Table 1] in capital letters

CONCLUSIONS

Finally, it must be stressed that the peptide overlap of EBV vs. SLE-related proteins and the immunologic potential are much higher than stated since pentapeptides are also immune determinants endowed with immunogenicity and antigenicity [25].

Correspondence
Dr. D. Kanduc
Department of Biosciences, Biotechnologies, and Biopharmaceutics, University of Bari, Bari 70125, Italy
Phone: (39-08) 914-8602
email: dkanduc@gmail.com

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Supplemental Table 1. List of the 51 SLE-related autoantigens retrieved at random from UniProtKB database (http://www.uniprot.org/) [18] using the keywords "SLE" and "lupus". Proteins are reported by UniProt entry. Further details and references are available from the OMIM and PubMed databases

2B11	HLA class II histocompatibility antigen, DRB1-1 beta chain (MHC class II antigen DRB1*1) (DR-1) (DR1)
BANK1	B-cell scaffold protein with ankyrin repeats
BLK	Tyrosine-protein kinase Blk (EC 2.7.10. 2) (B lymphocyte kinase) (p55-Blk)
CD19	B-lymphocyte antigen CD19 (B-lymphocyte surface antigen B4) (Differentiation antigen CD19) (T-cell surface antigen Leu-12) (CD antigen CD19)
CD22	B-cell receptor CD22 (B-lymphocyte cell adhesion molecule) (BL-CAM) (Sialic acid-binding Ig-like lectin 2) (Siglec-2) (T-cell surface antigen Leu-14) (CD antigen CD22)
CO4A	Complement C4-A (Acidic complement C4) (C3 and PZP-like alpha-2-macroglobulin domain-containing protein 2) [Cleaved into: Complement C4 beta chain; Complement C4-A alpha chain; C4a anaphylatoxin; C4b-A; C4d-A; Complement C4 gamma chain]
CO4B	Complement C4-B (Basic complement C4) (C3 and PZP-like alpha-2-macroglobulin domain-containing protein 3) [Cleaved into: Complement C4 beta chain; Complement C4-B alpha chain; C4a anaphylatoxin; C4b-B; C4d-B; Complement C4 gamma chain]
CR1	Complement receptor type 1 (C3b/C4b receptor) (CD antigen CD35)
CR2	Complement receptor type 2 (Cr2) (Complement C3d receptor) (Epstein-Barr virus receptor) (EBV receptor) (CD antigen CD21)
CTLA4	Cytotoxic T-lymphocyte protein 4 (Cytotoxic T-lymphocyte-associated antigen 4) (CTLA-4) (CD antigen CD152)
DNAS1	Deoxyribonuclease-1 (Deoxyribonuclease I) (DNase I) (Dornase alfa)
DPB1	HLA class II histocompatibility antigen, DP beta 1 chain (HLA class II histocompatibility antigen, DP(W4) beta chain) (MHC class II antigen DPB1)
EEA1	Early endosome antigen 1 (Endosome-associated protein p162) (Zinc finger FYVE domain-containing protein 2)
FCG2B	Low affinity immunoglobulin gamma Fc region receptor II-b (IgG Fc receptor II-b) (CDw32) (Fc-gamma RII-b) (Fc-gamma-RIIb) (FcRII-b) (CD antigen CD32)
FCG3B	Low affinity immunoglobulin gamma Fc region receptor III-B (Fc-gamma RIII-beta) (Fc-gamma RIII) (Fc-gamma RIIIb) (FcRIII) (FcRIIIb) (FcR-10) (IgG Fc receptor III-1) (CD antigen CD16b)
GRP1	RAS guanyl-releasing protein 1 (Calcium and DAG-regulated guanine nucleotide exchange factor II) (CalDAG-GEFII) (Ras guanyl-releasing protein)
IL10	Interleukin-10 (IL-10) (Cytokine synthesis inhibitory factor) (CSIF)
ITAM	Integrin alpha-M (CD11 antigen-like family member B) (CR-3 alpha chain) (Cell surface glycoprotein MAC-1 subunit alpha) (Leukocyte adhesion receptor MO1) (Neutrophil adherence receptor) (CD antigen CD11b)
KPCD	Protein kinase C delta type (EC 2.7.11.13) (Tyrosine-protein kinase PRKCD) (EC 2.7.10.2) (nPKC-delta) [Cleaved into: Protein kinase C delta type regulatory subunit; Protein kinase C delta type catalytic subunit (Sphingosine-dependent protein kinase-1) (SDK1)]
LA	Lupus La protein (La autoantigen) (La ribonucleoprotein) (Sjoegren syndrome type B antigen) (SS-B)
LARP6	La-related protein 6 (Acheron) (Achn) (La ribonucleoprotein domain family member 6)
LY9	T-lymphocyte surface antigen Ly-9 (Cell surface molecule Ly-9) (Lymphocyte antigen 9) (SLAM family member 3) (SLAMF3) (Signaling lymphocytic activation molecule 3) (CD antigen CD229)
LYAM2	E-selectin (CD62 antigen-like family member E) (Endothelial leukocyte adhesion molecule 1) (ELAM-1) (Leukocyte-endothelial cell adhesion molecule 2) (LECAM2) (CD antigen CD62E)
LYAM3	P-selectin (CD62 antigen-like family member P) (Granule membrane protein 140) (GMP-140) (Leukocyte-endothelial cell adhesion molecule 3) (LECAM3) (Platelet activation dependent granule-external membrane protein) (PADGEM) (CD antigen CD62P)
MAGB2	Melanoma-associated antigen B2 (Cancer/testis antigen 3.2) (CT3.2) (DSS-AHC critical interval MAGE superfamily 6) (DAM6) (MAGE XP-2 antigen) (MAGE-B2 antigen)
PCNA	Proliferating cell nuclear antigen (PCNA) (Cyclin)
PDCD1	Programmed cell death protein 1 (Protein PD-1) (hPD-1) (CD antigen CD279)
PSME3	Proteasome activator complex subunit 3 (11S regulator complex subunit gamma) (REG-gamma) (Activator of multicatalytic protease subunit 3) (Ki nuclear autoantigen) (Proteasome activator 28 subunit gamma) (PA28g)
PTN22	Tyrosine-protein phosphatase non-receptor type 22 (EC 3.1.3. 48) (Hematopoietic cell protein-tyrosine phosphatase 70Z-PEP) (Lymphoid phosphatase) (LyP) (PEST-domain phosphatase) (PEP)
RFIP5	Rab11 family-interacting protein 5 (Rab11-FIP5) (Gamma-SNAP-associated factor 1) (Gaf-1) (Phosphoprotein pp75) (Rab11-interacting protein Rip11)
RO60	60 kDa SS-A/Ro ribonucleoprotein (60 kDa Ro protein) (60 kDa ribonucleoprotein Ro) (RoRNP) (Ro 60 kDa autoantigen) (Sjoegren syndrome antigen A2) (Sjoegren syndrome type A antigen) (SS-A)
RSMB	Small nuclear ribonucleoprotein-associated proteins B and B' (snRNP-B) (Sm protein B/B') (Sm-B/B') (SmB/B')
RSMN	Small nuclear ribonucleoprotein-associated protein N (snRNP-N) (Sm protein D) (Sm-D) (Sm protein N) (Sm-N) (SmN) (Tissue-specific-splicing protein)
RU17	U1 small nuclear ribonucleoprotein 70 kDa (U1 snRNP 70 kDa) (U1-70K) (snRNP70)
RU2B	U2 small nuclear ribonucleoprotein B" (U2 snRNP B")
RUXE	Small nuclear ribonucleoprotein E (snRNP-E) (Sm protein E) (Sm-E) (SmE)
S10A8	Protein S100-A8 (Calgranulin-A) (Calprotectin L1L subunit) (Cystic fibrosis antigen) (CFAG) (Leukocyte L1 complex light chain) (Migration inhibitory factor-related protein 8) (MRP-8) (p8) (S100 calcium-binding protein A8) (Urinary stone protein band A)

S10A9	Protein S100-A9 (Calgranulin-B) (Calprotectin L1H subunit) (Leukocyte L1 complex heavy chain) (Migration inhibitory factor-related protein 14) (MRP-14) (p14) (S100 calcium-binding protein A9)
SELPL	P-selectin glycoprotein ligand 1 (PSGL-1) (Selectin P ligand) (CD antigen CD162)
SLAF6	SLAM family member 6 (Activating NK receptor) (NK-T-B-antigen) (NTB-A) (CD antigen CD352)
SMD1	Small nuclear ribonucleoprotein Sm D1 (Sm-D1) (Sm-D autoantigen) (snRNP core protein D1)
TNAP3	Tumor necrosis factor alpha-induced protein 3 (TNF alpha-induced protein 3) (EC 2.3.2. -) (EC 3.4.19. 12) (OTU domain-containing protein 7C) (Putative DNA-binding protein A20) (Zinc finger protein A20)
TNFL4	Tumor necrosis factor ligand superfamily member 4 (Glycoprotein Gp34) (OX40 ligand) (OX40L) (TAX transcriptionally-activated glycoprotein 1) (CD antigen CD252)
TNFL6	Tumor necrosis factor ligand superfamily member 6 (Apoptosis antigen ligand) (APTL) (CD95 ligand) (CD95-L) (Fas antigen ligand) (Fas ligand) (FasL) (CD antigen CD178) [Cleaved into: Tumor necrosis factor ligand superfamily member 6, membrane form; Tumor necrosis factor ligand superfamily member 6, soluble form (Receptor-binding FasL ectodomain) (Soluble Fas ligand) (sFasL); ADAM10-processed FasL form (APL); FasL intracellular domain (FasL ICD) (SPPL2A-processed FasL form) (SPA)]
TNIP1	TNFAIP3-interacting protein 1 (A20-binding inhibitor of NF-kappa-B activation 1) (ABIN-1) (HIV-1 Nef-interacting protein) (Nef-associated factor 1) (Naf1) (Nip40-1) (Virion-associated nuclear shuttling protein) (VAN)
TREX1	Three-prime repair exonuclease 1 (3'-5' exonuclease TREX1) (Deoxyribonuclease III) (DNase III)
TRI68	E3 ubiquitin-protein ligase TRIM68 (RING finger protein 137) (RING-type E3 ubiquitin transferase TRIM68) (SSA protein SS-56) (SS-56) (Tripartite motif-containing protein 68)
TRNK1	TPR and ankyrin repeat-containing protein 1 (Lupus brain antigen 1 homolog)
UB2L3	Ubiquitin-conjugating enzyme E2 L3 (E2 ubiquitin-conjugating enzyme L3) (L-UBC) (UbcH7) (Ubiquitin carrier protein L3) (Ubiquitin-conjugating enzyme E2-F1) (Ubiquitin-protein ligase L3)
XRCC5	X-ray repair cross-complementing protein 5 (86 kDa subunit of Ku antigen) (ATP-dependent DNA helicase 2 subunit 2) (ATP-dependent DNA helicase II 80 kDa subunit) (CTC box-binding factor 85 kDa subunit) (CTC85) (CTCBF) (DNA repair protein XRCC5) (Ku80) (Ku86) (Lupus Ku autoantigen protein p86) (Nuclear factor IV) (Thyroid-lupus autoantigen) (TLAA) (X-ray repair complementing defective repair in Chinese hamster cells 5 (double-strand-break rejoining))
XRCC6	X-ray repair cross-complementing protein 6 (5'-deoxyribose-5-phosphate lyase Ku70) (5'-dRP lyase Ku70) (70 kDa subunit of Ku antigen) (ATP-dependent DNA helicase 2 subunit 1) (ATP-dependent DNA helicase II 70 kDa subunit) (CTC box-binding factor 75 kDa subunit) (CTC75) (CTCBF) (DNA repair protein XRCC6) (Lupus Ku autoantigen protein p70) (Ku70) (Thyroid-lupus autoantigen) (TLAA) (X-ray repair complementing defective repair in Chinese hamster cells 6)

Capsule

Getting the most out of muscles

Materials that convert electrical, chemical, or thermal energy into a shape change can be used to form artificial muscles. Such materials include bimetallic strips, host-guest materials, or coiled fibers or yarns. **Kanik** et al. developed a polymer bimorph structure from an elastomer and a semicrystalline polymer where the difference in thermal expansion enabled thermally actuated artificial muscles. Iterative cold stretching of clad fibers could be used to tailor the dimensions and mechanical response, making it simple to produce hundreds of meters of coiled fibers. **Mu** et al. described carbon nanotube yarns in which the volume-changing material is placed as a sheath outside the twisted or coiled fiber. This configuration can double the work capacity of tensile muscles. **Yuan** et al. produced polymer fiber torsional actuators with the ability to store energy that could be recovered on heating. Twisting mechanical deformation was applied to the fibers above the glass transition temperature and then stored via rapid quenching.

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Eitan Israeli

Capsule

Human resident memory T cells hit the road

Skin and other barrier tissues are home to long-lived tissue-resident memory T cells (T_{RM}) that function as sentries capable of rapidly responding to previously encountered antigens. **Klicznik** and co-authors investigated the relationship between human skin CD4+ TRM and human blood CD4+ memory T cells expressing skin-homing markers by comparing immunophenotypes, gene expression, and T cell receptor sequences. Shared phenotype, function, and clonotypes between blood and skin CLA+CD103+CD4+ T cells indicated that blood CD4+CLA+CD103+ T cells were previously skin resident. Analysis of immunodeficient mice bearing human skin xenografts revealed that human skin CD4+ TRM can exit the skin, reenter the circulation, and be a home to secondary human skin sites.

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Eitan Israeli