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REVIEW

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A listing of human tumor antigens recognized by T cells: March 2004 update

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Abstract The technological advances occurred in the last few years have led to a great increase in the number of tumor associated antigens (TAA) that are currently available for clinical applications. In this review we provide a comprehensive list of human tumor antigens as reported in the literature updated at Feburary 2004. The list includes all T cell-defined epitopes, while excluding analogs or artificially modified epitopes, as well as virus-encoded and antibodies-recognized antigens. TAAs are listed in alphabetical order along with the epitope sequence and the HLA allele which restricts recognition by T cells. Data on the tissue distribution of each antigen are also provided together with an extensive bibliography that allows a rapid search for any additional information may be needed on each single antigen or epitope. Overall, the updated list is a database tool for clinicians, scientists and students who have an interest in the field of tumor immunology and immunotherapy.

Keywords Antigens · Epitopes · T cells · Tumor

Abbreviations

AFP	Alpha (α)-fetoprotein
AIM-2	Interferon-inducible protein absent in melanoma 2
ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
707-AP	707 alanine proline
APL	Acute promyelocytic leukemia
ART-4	Adenocarcinoma antigen recognized by T cells 4
BAGE	B antigen
bcr-abl	Breakpoint cluster region-Abelson
CAMEL	CTL-recognized antigen on melanoma
CAP-1	Carcinoembryonic antigen peptide-1
CASP-8	Caspase 8
CDC27	Cell division cycle 27
CDK4	Cyclin-dependent kinase 4
CEA	Carcinoembryonic antigen
CLCA2	Calcium-activated chloride channel 2
CML	Chronic myelogenous leukemia
CT	Cancer-testis (antigen)
CTL	Cytotoxic T lymphocytes
Cyp-B	Cyclophilin B
DAM	Differentiation antigen melanoma (the epitopes of DAM-6 and DAM-10 are equivalent, but the gene sequences are different. DAM-6 is also called MAGE-B2 and DAM-10 is also called MAGE-B1)
ELF2	Elongation factor 2
Ep-CAM	Epithelial cell adhesion molecule
EphA2, 3	Ephrin type-A receptor 2, 3
Ets	E-26 transforming specific (family of transcription factors)
ETV6-AML1	Ets variant gene 6 / acute myeloid leukemia 1 gene ETS
FGF-5	Fibroblast growth factor 5
FN	Fibronectin
G250	Glycoprotein 250
GAGE	G antigen
GnT-V	*N*-Acetylglucosaminyltransferase V
Gp100	Glycoprotein 100 kDa
HAGE	Helicase antigen
HER-2/neu	Human epidermal receptor 2/ neurological

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HLA-A*0201-R170I	Arginine (R) to isoleucine (I) exchange at residue 170 of the α-helix of the α2-domain in the HLA-A2 gene
H/N	Head and neck
HSP70-2 M	Heat shock protein 70-2 mutated
HST-2	Human signet-ring tumor 2
hTERT	Human telomerase reverse transcriptase
iCE	Intestinal carboxyl esterase
IL-13Rα2	Interleukin 13 receptor α2 chain
KIAA0205	Name of the gene as it appears in databases
LAGE	L antigen
LDLR/FUT	Low density lipid receptor / GDP-L-fucose:β-D-galactosidase 2-α-L-fucosyltransferase
MAGE	Melanoma antigen
MART-1/Melan-A	Melanoma antigen recognized by T cells-1 / melanoma antigen A
MART-2	Melanoma Ag recognized by T cells-2
MC1R	Melanocortin 1 receptor
M-CSF	Macrophage colony-stimulating factor gene
MHC	Major histocompatibility complex
MSI	Microsatellite instability
MUC1, 2	Mucin 1, 2
MUM-1, -2, -3	Melanoma ubiquitous mutated 1, 2, 3
NA88-A	NA cDNA clone of patient M88
Neo-PAP	Neo-poly(A) polymerase
NPM/ALK	Nucleophosmin/anaplastic lymphoma kinase fusion protein
NSCLC	Non–small cell lung carcinoma
NY-ESO-1	New York esophageous 1
OA1	Ocular albinism type 1 protein
OGT	*O*-Linked *N*-acetylglucosamine transferase gene
ORF	Open reading frame
OS-9	Name of the gene as it appears in databases
P15	Protein 15
p190 minor bcr-abl	Protein of 190-kDa bcr-abl
Pml/RARα	Promyelocytic leukemia / retinoic acid receptor α
PRAME	Preferentially expressed antigen of melanoma
PSA	Prostate-specific antigen
PSMA	Prostate-specific membrane antigen
PTPRK	Receptor-type protein-tyrosine phosphatase kappa
RAGE	Renal antigen
RCC	Renal cell carcinoma
RU1, 2	Renal ubiquitous 1, 2
SAGE	Sarcoma antigen
SART-1, -2, -3	Squamous antigen rejecting tumor 1, 2, 3
SCC	Squamous cell carcinoma
SSX-2	Synovial sarcoma, X breakpoint 2
Survivin-2B	Intron 2-retaining survivin
SYT/SSX	Synaptotagmin I / synovial sarcoma, X fusion protein
TAA	Tumor-associated antigen
TEL/AML1	Translocation Ets-family leukemia/acute myeloid leukemia 1
TGFβRII	Transforming growth factor β receptor 2
TPI	Triosephosphate isomerase
TRAG-3	Taxol resistant associated protein 3
TRG	Testin-related gene
TRP-1	Tyrosinase-related protein 1, or gp75
TRP-2	Tyrosinase-related protein 2
TRP-2/INT2	TRP-2/intron 2
TRP-2/6b	TRP-2/novel exon 6b
TSTA	Tumor-specific transplantation antigens
WT1	Wilms' tumor gene

Introduction

Since the cloning of *MAGE-1* [188], the first gene reported to encode a human tumor antigen recognized by T cells, molecular identification and characterization of novel tumor-associated antigens (TAAs) has rapidly evolved, in part due to the availability of new technology. Molecular cloning of single TAAs by screening tumor-derived cDNA libraries with autologous tumor-specific T lymphocytes has been integrated with novel strategies such as (1) reverse immunology (epitope prediction on the basis of known HLA-binding motifs performed by dedicated software and sometimes supported by proteasome-cleavage programs); (2) biochemical methods which elute and fractionate TAA peptides naturally expressed on tumor cells in the context of HLA molecules by chromatography and mass spectrometry, and (3) DNA microarray technology which allows comparison of gene expression profiles in tumor tissues and normal counterparts (representational difference analysis [RDA], differential display [DD], suppression subtractive hybridization [SSH], and serial analysis of gene expression [SAGE]).

Interestingly, these new technologies are shedding light on the involvement of a number of TAAs (both shared and unique) in the mechanisms of neoplastic transformation. This may allow novel tumor immunotherapeutic strategies based on administration of TAAs

indispensable for maintaining the neoplastic state (e.g., N- and K-RAS), and/or the formulation of single patient-tailored vaccines which would comprise a large part of the individual patient's TAA repertoire, including strongly immunogenic unique tumor antigens.

Thus, it is important to categorize all these new antigens, particularly for the HLA allele restricting their recognition by T cells and for their tissue distribution. To this end, we survey here TAAs so identified and briefly comment on each. The list presented in the tables below includes all T cell–defined epitopes encoded by TAAs and published by February 2004. Analogs or artificially modified epitopes are excluded from the list, as well as all viral encoded antigens. Only TAAs recognized by T cells (either $CD8^+$ or $CD4^+$) are listed, given their potential importance in the control of tumor growth. Antigens identified by antibodies are excluded, but a large collection of them, as detected by the SEREX technology, can be found in the database of the Institute for Cancer Research (http://www.licr.org/SEREX.html). It is of note that many tumor antigens (e.g., MAGE, NY-ESO-1) are now known to be recognized by both T cells and antibodies in the same cancer patient [30, 77].

In the tables herein, TAAs are listed in alphabetic order along with the epitope sequence and the HLA allele which restricts recognition by T cells. Furthermore, data on the tissue distribution of each antigen are provided, making this list an important source for easily retrieving data concerning human TAAs. Tables 1, 2, 3, and 4 collect different groups of class I HLA-restricted TAAs, whereas class II HLA-restricted counterparts are grouped under different subsets in Table 5. Table 6 assembles all characterized class I and class II HLA-restricted immunogenic fusion proteins. The separation of class I and class II HLA-restricted TAAs of corresponding groups into different tables is only justified by the fact that the number of the latter is still lower.

Moreover, some information is given to the reader in order to facilitate a comprehensive understanding of the data presented. All those TAAs in Tables 1, 2, and 3 which also include class II HLA-restricted immunogenic epitopes are shown in bold. Finally, splicing aberrations, point mutations, and fusion junctions in epitopes listed in Tables 3, 4, 5 and 6 are underlined. The bibliography (alphabetically ordered) allows a rapid search for more detailed information at the single antigen or epitope level. Overall, the updated list is intended to be a database tool for clinicians, scientists, and students who have an interest in the field of tumor immunology and immunotherapy.

Classification of tumor antigens

Cancer-testis antigens—class I HLA-restricted antigens (Table 1) and class II HLA-restricted antigens (subset of Table 5)

A milestone in tumor immunology was certainly the cloning of *MAGE-1* [188] and the subsequent characterization of the first T cell–defined antigenic epitope a year later [181]. Those findings were rapidly followed by the identification of new members within this group of TAAs [16, 186]: the *MAGE*, *BAGE*, and *GAGE* families of genes were established. The antigens belonging to this group, now including also NY-ESO-1 and its alternative ORF products (LAGE, CAMEL), were originally called cancer-testis (CT) antigens because of their expression in histologically different human tumors and, among normal tissues, only in spermatocytes/spermatogonia of testis and, occasionally, in placenta. An alternative but less popular designation of these TAAs is "germline antigens."

These TAAs have represented one of the main components of the antitumor vaccines tested in the clinic during the last decade. CT antigens result from re-activation of genes which are normally silent in adult tissues [42], but are transcriptionally activated in different tumor histotypes [43]. Their expression in testis does not provide targets for an autoimmune reaction because cells of testis do not express class I and II HLA molecules [80]. Despite the fact that the CT antigens are probably the best characterized tumor targets, their physiological function remains largely unknown [135].

Considering that new genes of this group have been cloned (CT9 [157], CT10 [64], LAGE [107], MAGE-B5, MAGE-B6, MAGE-C2, MAGE-C3, and MAGE-D [112, 113], HAGE, SAGE [118], SSX-2 [8], and TRAG-3 [218]), the question arises as to how many more genes encoding CT antigens remain to be discovered and how many epitopes may exist that could be of use in cancer immunotherapy.

Differentiation antigens—class I HLA-restricted antigens (Table 2) and class II HLA-restricted antigens (subset of Table 5)

These TAAs are shared between tumors and the normal tissue from which the tumor arose; most are found in melanomas and normal melanocytes [6]. Many of these melanocyte lineage-related proteins are involved in the biosynthesis of melanin. Interestingly, novel differentiation TAAs are being found in epithelial tissues and tumors such as prostate and breast carcinomas, providing new tools for immunotherapy specifically directed against these solid tumors.

This group of TAAs, despite representing self-antigens, has been, and still is being, commonly used in current cancer vaccination trials, often together with CT antigens.

Widely occurring, overexpressed TAAs—class I HLA-restricted antigens (Table 3) and class II HLA-restricted antigens (subset of Table 5)

Genes encoding widely expressed TAAs have been detected in histologically different types of tumors (often

Table 1 Class I HLA-restricted cancer-testis antigens. These antigens were found to be expressed by normal spermatocytes and/or spermatogonia of testis. Occasionally, *MAGE-3*, *MAGE-4* and the *GAGE* genes were found to be expressed also in placenta [38, 40]. The NY-ESO-1 antigen was found to be expressed also in normal ovary cells [30]

Gene	HLA allele	Peptide epitope	References	Tissue distribution among tumors[a]
BAGE	Cw16	AARAVFLAL	Boël et al. [16]	Melanoma, myeloma (stage III); lung, bladder, and breast carcinomas; H/N SCC,[b] NSCLC[b]
CAMEL	A2	MLMAQEALAFL	Aarnoudse et al. [1]	Melanoma, myeloma (stage III); NSCLC, H/N SCC, esophageal SCC, infiltrating bladder carcinoma, prostate and breast carcinoma; sarcoma
DAM-6, -10 (MAGE-B1, B2)	A2	FLWGPRAYA	Fleischhauer et al. [52]	Melanoma, skin tumors, mammary and ovarian carcinomas [115]; lung carcinoma [39, 115]; seminomas [39]
GAGE-1, -2, -8	Cw6	YRPRPRRY	Van den Eynde et al. [186] and De Backer et al. [40]	Melanoma; myeloma (stage III), lung carcinoma, H/N SCC, esophageal SCC; infiltrating bladder carcinoma, prostate[b] and breast[b] carcinomas; sarcoma[b]
GAGE-3, -4, -5, -6, -7B	A29	YYWPRPRRY	De Backer et al. [40]	Similar to *GAGE-1, -2, -8*
IL-13Rα2	A*0201	WLPFGFILI	Okano et al. [133]	Glioblastoma multiforme
MAGE-A1	A1	EADPTGHSY	Traversari et al. [181]	Melanoma, myeloma (stage III), lung carcinoma, H/N SCC, esophageal SCC, superficial and infiltrating bladder carcinoma; prostate,[b] colorectal,[b] and breast[b] carcinomas, sarcoma.[b] (For minor pattern of expressions, also see [41, 42, 188])
	A3	SLFRAVITK	Chaux et al. [28]	
	A24	NYKHCFPEI	Fujie et al. [53]	
	A28	EVYDGREHSA	Chaux et al. [28]	
	B37	REPVTKAEML	Tanzarella et al. [171]	
	B53	DPARYEFLW	Chaux et al. [28]	
	Cw2	SAFPTTINF	Chaux et al. [28]	
	Cw3	SAYGEPRKL[c]	Chaux et al. [28]	
	Cw16	SAYGEPRKL[c]	van der Bruggen et al. [190]	
MAGE-A2	A2	KMVELVHFL	Visseren et al. [193]	The same as *MAGE-A1*
	A2	YLQLVFGIEV	Visseren et al. [193]	
	A24	EYLQLVFGI	Tahara et al. [168]	
	B37	REPVTKAEML	Tanzarella et al. [171]	
MAGE-A3	A1	EADPIGHLY	Gaugler et al. [56]	The same as *MAGE-A1*
	A2	FLWGPRALV	van der Bruggen et al. [189]	
	A24	TFPDLESEF	Oiso et al. [131]	
	A24	IMPKAGLLI	Tanaka et al. [169]	
	B44	MEVDPIGHLY	Herman et al. [68] and Fleischhauer et al. [51]	
	B52	WQYFFPVIF	Russo et al. [154]	
	B37	REPVTKAEML	Tanzarella et al. [171]	
	B*3501	EVDPIGHLY	Benlalam et al. [14]	
MAGE-A4	A2	GVYDGREHTV	Duffour et al. [48]	The same as *MAGE-A1*
MAGE-A6	A34	MVKISGGPR	Zorn and Hercend [220]	The same as *MAGE-A1*
	B37	REPVTKAEML	Tanzarella et al. [171]	
	B*3501	EVDPIGHVY	Benlalam et al. [14]	
MAGE-A10	A2	GLYDGMEHL	Huang et al. [73]	The same as *MAGE-A1*, with the exception of colorectal and breast carcinomas
MAGE-A12	Cw7	VRIGHLYIL	Panelli et al. [136] and Heidecker et al. [67]	The same as *MAGE-A1*
NA88-A	B13	MTQGQHFLQKV	Moreau-Aubry et al. [120]	Melanoma
NY-ESO-1	A2	SLLMWITQCFL	Jäger et al. [77]	The same as *CAMEL*
	A2	SLLMWITQC	Jäger et al. [77]	
	A2	QLSLLMWIT	Jäger et al. [77]	
	B*3501	MPFATPMEA	Benlalam et al. [14]	
NY-ESO-1a (CAG-3)	A31	ASGPGGGAPR	Wang et al. [204]	
SSX-2	A2	KASEKIFYV	Ayyoub et al. [8]	Melanomas; lymphomas; H/N, colon carcinomas
TRAG-3	A*0201	ILLRDAGLV	Zhu et al. [218]	Melanomas; leukemias; NSCLC, prostate and breast carcinomas

[a]See also van der Bruggen et al. [191] for a more detailed tissue distribution

[b]These epitopes share different HLAs—that is they are recognized by specific T cells when presented by different HLA alleles. This phenomenon is important, as it allows an epitope to be employed for cancer immunotherapy in a larger number of patients

[c]Frequency of expression less than 10%

Table 2 Class I HLA-restricted differentiation antigens. These TAAs can only be expressed in normal and neoplastic cells of the same lineage. Those antigens which also present class II HLA-restricted epitopes are in bold type

Gene	HLA allele	Peptide epitope	References	Normal tissue/tumor
CEA	A2	YLSGANLNL (CAP-1)[a]	Tsang et al. [183]	Embryonic tissue; normal epithelia differentiation overexpressed in colon and other adenocarcinomas
	A3	HLFGYSWYK	Kawashima et al. [92]	
Ep-CAM	A2	GLKAGVIAV	Nagorsen et al. [123]	Epithelia overexpressed in colon and other adenocarcinomas
Gp100	A2	KTWGQYWQV	Bakker et al. [11]	Melanocyte/melanoma
	A2	AMLGTHTMEV	Tsai et al. [182]	
	A2	MLGTHTMEV	Tsai et al. [182]	
	A2	SLADTNSLAV	Tsai et al. [182]	
	A2	ITDQVPFSV	Kawakami et al. [86]	
	A2	LLDGTATLRL	Kawakami et al. [85]	
	A2	YLEPGPVTA	Cox et al. [38]	
	A2	VLYRYGSFSV	Kawakami et al. [86]	
	A2	RLMKQDFSV	Kawakami et al. [88]	
	A2	RLPRIFCSC	Kawakami et al. [88]	
	A3	LIYRRRLMK	Kawakami et al. [88]	
	A3	ALNFPGSQK	Kawashima et al. [91]	
	A3	SLIYRRRLMK	Kawashima et al. [91]	
	A3	ALLAVGATK	Skipper et al. [165]	
	A24	VYFFLPDHL	Robbins et al. [149]	
	A*6801	HTMEVTVYHR	Sensi et al. [163]	
	B*3501	VPLDCVLYRY	Benlalam et al. [14]	
	Cw8	SNDGPTLI	Castelli et al. [27]	
Mammaglobin-A	A3	PLLENVISK	Jaramillo et al. [79]	Mammary gland / breast cancer
		KLLMVLMLA	Jaramillo et al. [79]	
		TTNAIDELK	Jaramillo et al. [79]	
		AIDELKECF	Jaramillo et al. [79]	
Melan-A/MART-1[b]	A2	AAGIGILTV	Coulie et al. [36] and Kawakami et al. [83]	Melanocyte/melanoma
	A2	EAAGIGILTV	Schneider et al. [162]	
	A2	ILTVILGVL	Castelli et al. [26]	
	B*3501		Benlalam et al. [14]	
	B45	AEEAAGIGIL	Schneider et al. [162]	
	B45	AEEAAGIGILT	Schneider et al. [162]	
MC1R	A2	TILLGIFFL	Salazar-Onfray et al. [156]	Melanocyte/melanoma
	A2	FLALIICNA	Salazar-Onfray et al. [156]	
OA1	A*2402	LYSACFWWL	Touloukian et al. [180]	Melanocyte/melanoma
P polypeptide	A2	IMLCLIAAV	Touloukian et al. [179]	Melanocyte/melanoma
PSA	A1	VSHSFPHPLY	Corman et al. [34]	Prostate gland / prostate carcinoma
	A2	FLTPKKLQCV	Correale et al. [35]	
	A2	VISNDVCAQV	Correale et al. [35]	
TRP-1 (or gp75)	A31	MSLQRQFLR	Wang et al. [202]	Melanocyte/melanoma
TRP-2	A2	SVYDFFVWL[c]	Parkhurst et al. [137]	Melanocyte/melanoma
	A2	TLDSQVMSL	Noppen et al. [125]	
	A31	LLGPGRPYR[d]	Wang et al. [201]	
	A33	LLGPGRPYR[d]	Wang et al. [203]	
	Cw8	ANDPIFVVL	Castelli et al. [27]	
Tyrosinase	A1	KCDICTDEY	Kittlesen et al. [99]	Melanocyte/melanoma
	A1	SSDYVIPIGTY	Kawakami et al. [88]	
	A2	YMDGTMSQV	Wolfel et al. [208]	
	A2	MLLAVLYCL	Wolfel et al. [208]	
	A24	AFLPWHRLF	Kang et al. [81]	
	B44	SEIWRDIDF	Brichard et al. [20]	
	B*3501	TPRLPSSADVEF	Benlalam et al. [14]	

[a]CAP-1 is an alternative name of this peptide

[b]Two different groups simultaneously discovered this gene and gave it two different names: MART-1 [84] and Melan-A [36], respectively

[c]This peptide was shown to be a CTL target also in glioblastoma multiforme restricted by HLA-A2 [111]

[d]These epitopes share different HLA-A3 subtypes. This allows an epitope to be employed for cancer immunotherapy in a larger number of patients

with no preferential expression on a certain type of cancer) as well as in many normal tissues, generally with lower expression levels.

It is possible that many of the epitopes processed and potentially presented by normal tissues are below the threshold level for T-cell recognition, while their over-

Table 3 Class I HLA-restricted, widely occurring, overexpressed TAAs. Underlined amino acids in the epitopes indicate splicing aberration. Those antigens which also present class II HLA-restricted epitopes are in bold type

Gene	HLA allele	Peptide epitope	References	Tissue distribution	
				Tumors	Normal tissues
Adipophilin	A2	SVASTITGV	Schmidt et al. [159]	RCC, melanoma; breast, colon, and ovarian carcinomas; CML, multiple myeloma	Adipocytes, macrophages
AIM-2[a]	A1	RSDSGQQARY	Harada et al. [66]	Melanoma; neuroblastoma; Ewing's sarcoma; breast, ovarian, and colon carcinomas	Weakly expressed in lung, brain, liver, and testis
AFP	A2	GVALQTMKQ	Butterfield et al. [22]	Hepatocellular carcinoma, and yolk-sac tumors. Also detected in hilar bile duct carcinoma; pleomorphic adenoma of parotid gland; prostate, pancreatic, bladder, and thyroid papillary carcinomas [75]	Synthesized by the fetal liver and yolk sac. Low levels in adult brain, heart, skeletal muscle, prostate, stomach, pancreas, adrenal gland, salivary gland, liver, small intestine, and peripheral blood [75]
ART-4	A24	AFLRHAAL DYPSLSATDI	Kawano et al. [90] Kawano et al. [90]	Lung, esophageal, H/N, gastric, cervical, endometrial, ovarian, and breast cancers; leukemias	High expression in fetal liver, adult pancreas, and ovary. Significant expression in heart, brain, placenta, liver, lung, kidney, spleen, thymus, prostate, testis, small intestine, colon, and PBMCs
CLCA2	A2	LLGNCLPTV SLQALKVTV	Konopitzky et al. [105] Konopitzky et al. [105]	SCLC; pancreatic, and esophageal carcinomas	Lung (very low levels by Northern blot), trachea, mammary gland
Cyp-B	A24	KFHRVIKDF DFMIQGGDF	Gomi et al. [60] Gomi et al. [60]	NSCLC; T-cell leukemia; lymphosarcoma; bladder, ovarian, uterine, and esophageal carcinomas	Ubiquitously expressed in normal tissues
EphA2	A*0201	IMNDMPIYM VLAGVGFFI	Alves et al. [2]	Overexpressed in breast, colon, lung, prostate, and gastric carcinomas; metastatic melanomas; tumor neovasculature	Lung, kidney, skin, ovary, thymus
FGF-5	A3	NTYASPRFK[b]	Hanada et al. [65]	RCC; prostate, and breast carcinomas	Brain and kidney (low expression)
G250	A2	HLSTAFARV	Vissers et al. [194]	RCC; colon, ovarian, and cervical carcinomas	Epithelial cells of gastric mucosa
GnT-V	A2	VLPDVFIRC(V)[c]	Guilloux et al. [63]	Melanoma; brain tumors; sarcoma	Breast and brain (low expression)
HER-2/neu	A2	KIFGSLAFL	Fisk et al. [50]	Melanoma, ovarian, gastric, pancreatic [141],[d] and breast carcinomas	Epithelial cells
	A2	IISAVVGIL	Peoples et al. [142]		
	A2	RLLQETELV	Kono et al. [104]		
	A2	VVLGVVFGI	Rongcun et al. [151]		
		ILHNGAYSL	Rongcun et al. [151]		
		YMIMVKCWMI	Rongcun et al. [151]		
	A24	TYLPTNASL	Okugawa et al. [134]		
	A3	VLRENTSPK	Kawashima et al. [92]		
HST-2 (FGF-6)	A31	YSWMDISCWI	Suzuki et al. [167]	Gastric signet-ring cell carcinoma	Not determined
hTERT	A2	ILAKFLHWL	Vonderheide et al. [195]	Lung, prostate, and ovarian carcinomas; multiple myeloma; melanoma; sarcoma; acute leukemias; non-Hodgkin's lymphomas	Hematopoietic stem cells and progenitors; germinal center cells; basal keratinocytes; gonadal cells; certain proliferating epithelial cells
	A2	ILAKFLHWL	Minev et al. [119]		
		RLVDDFLLV	Minev et al. [119]		
	A3	KLFGVLRLK	Vonderheide et al. [196]		
iCE	B7	SPRWWPTCL	Ronsin et al. [152]	RCC	Kidney, colon, small intestine, liver, heart, pituitary gland, adrenal gland, prostate, stomach

Livin (ML-IAP)	A2	SLGSPVLGL RLASFYDWPL	Schmollinger et al. [161]	High levels in melanoma [7, 197], colon, and prostate carcinomas, B-cell lymphomas, erythroleukemia and promyelocytic leukemia. Lower expression in breast and cervical carcinomas, and AML [7]. Good expression in superficial bladder cancer (and not in normal tissue) [58]	Two isoforms. Expressed during normal fetal development. Detected in adult heart, testis, ovary, thymus, spleen, lymph node, PBLs, and bone marrows. Low levels in prostate, small intestine, colon, brain, placenta, liver, skeletal muscle, kidney, and pancreas. Not detectable in other adult tissues, including melanocytes [197]. A different pattern of expression is given by other authors by means of RT-PCR analyses: fetal kidney, heart, and spleen. In adult tissues: high levels in heart, placenta, lung, spleen, and ovary. Low levels in brain, skeletal muscle, kidney, and PBLs [7]
M-CSF	B*3501	LPAVVGLSPGEQEY[e]	Probst-Kepper et al. [145]	RCC	Liver, kidney
MUC1	A11	STAPPAHGV	Domenech et al. 1995 [45]	Aberrantly glycosylated forms in breast or ovarian cancer	Ductal epithelial cells and activated T cells
	A2	STAPPVHNV	Brossart et al. [21]		
MUC2	A2	LLNQLQVNL	Bohm et al. [17]	Ovary, pancreas, and breast mucinous tumors; colon carcinoma of nonmucinous type	Colon, small intestine, bronchus, cervix, and gall bladder
		MLWGWREHV	Bohm et al. [17]		
PRAME	A24	LYVDSLFFL	Ikeda et al. [74]	Melanoma; H/N and lung SCC; NSCLC [185]; RCC; sarcoma; leukemias [184]	Testis, endometrium, ovary, adrenals, kidney, brain, and skin
	A2	VLDGLDVLL	Kessler et al. [93]		
		SLYSFPEPEA	Kessler et al. [93]		
		ALYVDSLFFL	Kessler et al. [93]		
		SLLQHLIGL	Kessler et al. [93]		
PSMA	A1	HSTNGVTRIY	Corman et al. [34]	Prostate cancer; tumor-associated neovasculature of several solid tumors	Prostate epithelium (cytosolic and PSMA-2 isoform), ventral striatum and brain stem (PSMA-2 isoform), liver (PSMA-2 isoform), small intestine, kidney, spleen, and colon
	A24	LYSDPADYF	Horiguchi et al. [72]		
		NYARTEDFF	Horiguchi et al. [72]		
P15	A24	AYGLDFYIL	Robbins et al. [147]	Melanoma	Testis, spleen, thymus, liver, kidney, lung, and retina
P53	A24	AIYKQSQHM	Umano et al. [184]	Esophageal, gastric, colon, pancreatic, and gall bladder carcinomas	Ubiquitous (low level)
	B46	SQKTYQGSY[f]	Azuma K et al. [10]		
RAGE	B7	SPSSNRIRNT	Gaugler et al. [57]	Melanoma; sarcomas; mesotheliomas; H/N tumors; bladder, renal, colon, and mammary carcinomas	Retina only
RU1	B51	VPYGSFKHV	Morel et al. [121]	Melanoma; renal and bladder carcinomas	Testis, kidney, heart, skin, brain, ovary, liver, lung, lymphocytes, thymus, fibroblasts
RU2	B7	LPRWPPPQL	Van den Eynde et al. [187]	Melanoma; sarcomas; leukemia; brain, esophageal and H/N tumors; renal, colon, thyroid, mammary, bladder, prostatic, and lung carcinomas	Testis, kidney, liver, and urinary bladder
SART-1	A24	EYRGFTQDF	Kikuchi et al. [97]	H/N SCC; esophageal SCC; NSCLC; uterine cancer	Proliferating cells during the M phase. Fetal liver; adult testis, heart, placenta, skeletal muscle, pancreas, spleen, thymus, prostate, uterus, and small intestine [164]
	A*2601	KGSGKMKTE	Shichijo et al. [164]		

Table 3 (Contd.)

Gene	HLA allele	Peptide epitope	References	Tissue distribution Tumors	Normal tissues
SART-2	A24	DYSARWNEI	Nakao et al. [124]	H/N SCC; esophageal SCC; lung adenocarcinoma; melanoma; RCC; uterine adenocarcinoma; brain tumors	Although no significant expression was observed at protein level by Western blot in different tissues, high mRNA expression was observed by Northern blot in heart, placenta, spleen, and ovary. Whereas a lower mRNA expression was seen in lung, skeletal muscle, kidney, testis, small intestine, and PBLs
		AYDFLYNYL	Nakao et al. [124]		
		SYTRLFLIL	Nakao et al. [124]		
SART-3	A24	VYDYNCHVDL	Yang et al. [211]	The same as SART-2	The same as SART-2
		AYIDFEMKI	Yang et al. [211]		
	A2	LLQAEAPRL	Ito et al. [76]		
		RLAEYQAYI	Ito et al. [76]		
SOX10	A2	SAWISKPPGV	Khong and Rosenberg, 2002 [95]	Overexpressed in melanomas	Abundantly expressed in migratory neural crest during early stages of development. In adult, expression found in melanocytes, brain, heart, lungs, adrenal and salivary glands, colon, intestine, bladder, pancreas, prostate, and testis
Survivin	A2	ELTLGEFLKL	Andersen et al. [3], Schmitz et al. [160], Andersen et al. [4], Casati et al. [25], and Schmidt et al. [158]	Abundantly expressed in carcinomas (NSCLC and SSC of the lung; esophagus, liver, pancreas, colon, breast, ovary, bladder, and prostate); CLL and diffuse large B-cell lymphomas; melanoma and nonmelanoma skin cancers; neuroblastoma	Expressed during normal fetal development. High expression in testis, thymus, and placenta. Low expression in stomach, intestine, spleen, lung, kidney, prostate, pancreas, and heart. Transiently expressed in normal proliferating cells during the G2/M phase
	A2	TLPPAWQPFL	Schmitz et al. [160]		
Survivin-2B[g]	A24	AYACNTSTL	Hirohashi et al. [70]	The same as survivin	Thymus
TRG	B52 B62	YQLCLTNIF[h]	Ohkouchi et al. [128]	Breast, lung, colon, and prostate carcinomas	Low expression in heart, liver, and pancreas
WT1	A2	RMFPNAPYL	Oka et al. [132]	Gastric, colon, lung, breast, ovary, uterine, thyroid, and hepatocellular carcinomas; leukemia (including AML, ALL, and CML)	Kidney, ovary, testis, spleen
	A24	CMTWNQMNL	Ohminami et al. [130]		
		RWPSCQKKF	Azuma et al. [9]		
707-AP[i]	A2	RVAALARDA	Morioka et al. [122]	Melanoma	None

[a]Unspliced transcript containing intron 2. The immunogenic peptide is entirely contained within the intronic sequence
[b]The peptide is generated by a post-translational protein splicing
[c]VLPDVFIRC(V) is the nonamer, and decamer peptides are both recognized by CTLs. The immunogenic peptide is entirely contained within the intronic sequence
[d]Tissue distribution among tumors as described in the given references when different from the paper first reporting the sequence of the epitope
[e]The immunogenic peptide is encoded by an alternative ORF
[f]The epitope derives from mutated p53 protein, but does not contain the mutation
[g]This is a splicing variant of survivin, retaining a part of intron 2 as a cryptic exon
[h]The TRG gene is located in an intron of the putative tumor suppressor gene testin
[i]The immunogenic peptide sequence seems to be associated to an as-yet-unidentified antigen that is expressed in the majority of melanomas and in some tumors of other histological origin, but not in normal cells, as defined serologically [98]. However, as the tissue of the testis was not tested, it will not be clear to which category the antigen may belong until more information is available

Table 4 Class I HLA-restricted tumor-specific antigens, including both unique and shared antigens. Underlined amino acids in the epitopes indicate mutations or splicing aberration. Normal tissues never express these epitopes. The table does not include other tumor-specific antigens such as fusion proteins, which are listed in Table 6

Gene	HLA allele	Peptide epitope	Tissue expression in tumors	References
Unique				
α-Actinin-4	A2	FIASNGVKLV	Lung carcinoma	Echchakir et al. [49]
β-Catenin	A24	SYLDSGIHF	Melanoma	Robbins et al. [148]
Caspase-8	B35	FPSDSWCYF	H/N tumor	Mandruzzato et al. [116]
CDK-4	A2	ACDPHSGHFV	Melanoma	Wölfel et al. [209]
ELF2	A68	ETVSEQSNV	Lung SCC	Hogan et al. [71]
*HLA-A*0201-R170I*	A2	CVEWLR IYLENGK	RCC	Brändle et al. [19]
HSP70–2 M	A2	SLFEGIDIY	RCC	Gaudin et al. [55]
KIAA0205	B44*03	AEPINIQTV	Bladder cancer	Gueguen et al. [62]
Malic enzyme	A2	FLDEFMEGV	SCC of the lung	Karanikas et al. [82]
MART-2	A1	FLEGNEVGKTY	Melanoma	Kawakami et al. [89]
MUM-1	B44	EEKLIVVLF	Melanoma	Coulie et al. [37]
MUM-2	B44	SELFRSGLDY	Melanoma	Chiari et al. [31]
	Cw6	FRSGLDSYV		
MUM-3	A28	EAFIQPITR	Melanoma	Baurain et al. [12]
Myosin	A3	KINKNPKYK	Melanoma	Zorn and Hercend, 1999 [219]
OS-9	B44	KELEGILLL	Melanoma	Vigneron et al. [192]
Shared				
BING-4	A2	MCQWGRLWQL[a]	Melanoma	Rosenberg et al. [153]
K-RAS	B35	VVVGA VGVG	Pancreatic and colorectal adenocarcinomas	Gjertsen et al. [59]
N-RAS	A1	ILDTAG REEY	Melanoma	Linard et al. [109]
OGT	A2	SLYKFSPFPL[b]	Colon carcinomas (MSI^+)	Ripberger et al. [146]
TGFαRII	A2	RLSSCVPVA[b]	Colon carcinomas (MSI^+)	Linnebacher et al. [110]
TRP-2/INT2	A68	EVISCKLIKR[c]	Melanoma, glioblastoma multiforme [111]	Lupetti et al. [114]
TRP-2–6b	A2	ATTNILEHY[d]	Melanoma, glioblastoma multiforme	Khong et al. [94]

[a]The peptide derives from an alternative ORF
[b]The peptide derives from a translational frameshift
[c]The immunogenic peptide is entirely contained within the intronic sequence
[d]The immunogenic peptide is encoded by exon 6b, one of the two novel exons alternatively spliced from intron 6

expression in tumor cells can trigger an anticancer response by breaking previously established tolerance.

Interestingly, these widely expressed gene products have revealed a broad spectrum of mechanisms involved in generating T cell–defined epitopes, such as splicing aberrations leading to cryptic epitopes encoded by nonspliced introns, alternative ORFs, and even a case of post-translational splicing (FGF-5, Table 3). Surprisingly, many of these aberrations are also found in normal tissues, although at low levels, thus revealing a possible as-yet-unknown role for alternative forms of these antigens [144].

It is worth noting that some of the widely expressed/overexpressed TAAs were discovered by DNA microarray technologies, combined with new immunological tools such as reverse immunology and tetramer staining [207]. Among the most interesting TAAs of this group are the antiapoptotic proteins (livin, survivin), hTERT, and tumor suppressor proteins (e.g., p53).

Unique and shared tumor-specific antigens—class I HLA-restricted antigens (Table 4) and class II HLA-restricted antigens (subset of Table 5)

Unique TAAs arise from point mutations of normal genes (such as β-catenin, CDK4, etc.) [148, 209]. Some of these molecular changes are associated with neoplastic transformation and/or progression. In mouse models unique antigens have been shown to be more immunogenic than other groups of shared antigens [47]; because unique antigens are responsible of the rejection of tumor transplants in mice, they have been defined as tumor-specific transplantation antigens (TSTA). In humans, response to the unique TAAs appears to be associated with a good prognosis for the patient [12, 82, 127].

Unfortunately, the major drawback of these antigens is that they are generally expressed only in the tumor where they were first identified. Thus, unique TAAs are the most specific targets for immunotherapy, but this potential advantage must be balanced against the logistical difficulty of their widespread clinical use. However, novel immunotherapeutic strategies are pointing to single patient–tailored antitumor vaccinations, with the aim of designing in a short time personalized vaccines comprising all possible tumor antigens expressed by the patient's own tumor (including unique TAAs) [13, 207].

Few altered tumor-specific but shared antigenic epitopes have been identified, which are generated by different mechanisms occurring in tumor but not in normal cells, such as splicing aberrations (e.g., TRP-2/INT2 and TRP-2/6b), and point mutations (N-RAS and K-RAS) [59, 94, 109, 114]. Generally, these alterations are an obligatory step in neoplastic transformation, thus generating TAAs which are both widespread in different cancers and capable of inducing a true tumor-specific

Table 5 Class II HLA-restricted antigens

Gene	HLA allele	Peptide epitope	Tissue expression		References
			Tumors	Normal tissues	
(A) Epitopes from nonmutated protein antigens					
Cancer-testis antigens					
CAMEL	DR11 DR12	PWKRSWSA	The same as NY-ESO-1 (see below)	The same as NY-ESO-1 (see below)	Slager et al. [166]
LAGE-1	DRB1*1301	ILSRDAAPLPRPG[a]	The same as NY-ESO-1 (see below)	The same as NY-ESO-1 (see below)	Wang et al. [200]
MAGE-A1	DRB1*1301 DRB1*1302	LLKYRAREPVTKAE[b]	Melanoma, myeloma (stage III), lung carcinoma, H/N SCC, esophageal SCC, superficial and infiltrating bladder carcinoma	Testis, placenta	Chaux et al. [28]
MAGE-A2	DRB1*1301 DRB1*1302	LLKYRAREPVTKAE[b]	The same as *MAGE-A1*	The same as *MAGE-A1*	Chaux et al. [28]
MAGE-A3	DRB1*1101	TSYVKVLHHMVKISG	The same as *MAGE-A1*	The same as *MAGE-A1*	Manici et al. [117]
	DRB1*1301, DRB1*1302	LLKYRAREPVTKAE[b]			Chaux et al. [28]
	DRB1*1301, DRB1*1302	AELVHFLLLKYRAR[b]	Melanoma, lung and breast carcinomas, H/N SCC	Testis, placenta	Chaux et al. [29]
	DR1, DR4, DR11[c]	RKVAELVHFLLLKYR[b] GDNQIMPKAGLLIIV TSYVKVLHHMVKISG	Melanoma, lung and breast carcinomas, H/N SCC	Testis, placenta	Consogno et al. [33]
	DR1, DR4, DR7, DR11[c]	FFPVIFSKASSSLQL[b]			Consogno et al. [33]
MAGE-A6	DRB1*1301, DRB1*1302	LLKYRAREPVTKAE[b]	The same as *MAGE-A1*	The same as *MAGE-A1*	Chaux et al. [28]
	DRB1*0401	ESEFQAALSRKVAKL, LLKYRAREPVTKA-EMLGSVVGNWQ, VGNWQYFFPVIFSKA-SDSLQLVFGIELMEVD, IFSKASDSLQLVFGIE, LTQYFVQENYLEYRQVPG			Tatsumi et al. [172]
NY-ESO-1	DRB4*0101	VLLKEFTVSG	Melanoma; myeloma (stage III); lung carcinoma; H/N SCC; esophageal SCC; infiltrating bladder, prostate, and breast carcinomas	Testis, placenta (very low levels)	Zeng et al. [217]
	DRB4*0101–0103	PLPVPGVLLKEFTVSGNI VLLKEFTVSGNILTIRLT AADHRQLQLSISSCLQQL			Jager et al. [78]
Differentiation antigens					
CEA	DR9	YACFVSNLATGRNNS	Overexpressed in colon carcinoma and other adenocarcinomas	Epithelial differentiation antigen	Kobayashi et al. [103]
	DR*03, DR*0405, DR*07, DR*1101, DR*1104, DR*14[c]	LWWVNNQSLPVSP			Campi et al. [24]
Gp100	DRB1*0401	WNRQLYPEWTEAQRLD	Melanoma	Melanocytes	Li et al. [108]
	DRB1*0701	TGRAMLGTHTMEVTVYH			Lapointe et al. [106]
	DRB1*0401	IYRRRLMKQDFSVPQLPHS			Kierstead et al. [96]
MART-1/Melan-A	DRB1*0401	RNGYRALMDKSLHVGTQ-CALTRR	Melanoma	Melanocytes	Zarour et al. [216]
PSA	DRB1*0401	ILLGRMSLFMPEDTG SLFHPEDTGQVFQ QVFQVSHSFPHPLYD NDLMLLRLSEPAELT KKLQCVQLHVISM GVLQGITSMGSEPCA	Melanoma	Melanocytes, prostate gland	Corman et al. [34]

Tyrosinase	DRB1*0401	QNILLSNAPLGPQFP DYSYLQDSDPDSFQD SYLQDSDPDSFQD	Melanoma	Melanocytes	Topalian et al. [176] Topalian et al. [177]
	DRB1*1501	RHRPLQEVYPEANAPIGHNRE			Kobayashi et al. [101]
	DRB1*0405	EIWRDIDFAHE			Kobayashi et al. [102]
	DRB1*0401	YGQMKNGSTPMFNDINIYDL ALHIYMDGTMSQVQGSA			Kierstead et al. [96]
Widely expressed antigens					
Annexin II	DRB1*0401	DVPKWISIMTERSVPH	Melanoma	Endothelial, mesothelial, and some epithelial cells; peripheral nerves; part of meninges [45]	Li et al. [108]
EphA3	DRB1*1101	DVTFNIICKKCG	Overexpressed in melanoma, SC and NSCLC, sarcomas, and RCC	High expression in retina, and in fetal brain. Significant expression in bladder, prostate, and colon. Low expression in several other normal tissues but hematopoietic cells. Melanocytes do not express the protein	Chiari et al. [32]
HER-2/neu	DR11	GSYVSRLLGICL VPIKWMALESILRRRF	Melanoma; ovarian, gastric, pancreatic [141], and breast carcinomas	Epithelial cells	Anderson et al. [5]
MUC1	DR3	PGSTAPPAHGVT	Breast and ovarian cancers; multiple myeloma; B-cell lymphoma	None[d]	Hiltbold et al. [69]
WT1	DRB1*0401	PQQMGSDVRDLNALL	Gastric, colon, lung, breast, ovary, uterine, thyroid, and hepatocellular carcinomas; leukemia (including AML, ALL, and CML)	Kidney, ovary, testis, spleen	Knights et al. [100]
(B) Epitopes from mutated protein antigens. Underlined are the mutated amino acids and the peptide sequences deriving from mutations or splicing aberration					
Unique					
CDC27	DRB1*0401	FSWAMDLDPKGA[e]	Melanoma	None	Wang et al. [205]
FN	DR2	MIFE KHGFRRTTPP	Melanoma	None	Wang et al. [199]
Neo-PAP	DR7	RVIKNSIRLTL[e]	Melanoma	None	Topalian et al. [178]
PTPRK	DRB1*1001	PYYFAAELPP RNLPEP	Melanoma	None	Novellino et al. [127]
TPI	DRB1*0101	GELIG ILNAAKVPAD	Melanoma	None	Pieper et al. [143]
Shared					
*TGFβ*RII	DR (not identified)	SLVRLSSCVPVALMSA- MTTSSSQ[f]	Colon carcinomas (MSI^+)	None	Saeterdal et al. [155]

[a]This epitope is specifically recognized by $CD4^+$ T-regulatory cells that were cloned by limiting dilution from TILs deriving from a fresh melanoma sample. These cells significantly suppressed autologous effector $CD4^+$ T cells following a LAGE epitope ligand-specific activation

[b]These epitopes share different HLA-DR due to the known promiscuity of peptide binding to HLA-DR molecules. This allows an epitope to be potentially used for cancer immunotherapy in a larger number of patients

[c]In the paper, not all the HLA-DR alleles were completely subtyped

[d]All epithelial tissues express highly glycosylated mucins, whereas tumor cells often show hypoglycosylated mucins with a normal protein sequence

[e]The mutation is not located in the region encoding the peptide

[f]The peptide derives from a translational frameshift

Table 6 Epitopes derived from chimeric proteins originated by gene translocation and fusion processes that do not normally occur in normal tissues. Therefore, these antigens are tumor-specific. Underlined are the sequences after the junction point

Gene	HLA allele	Peptide epitope	Tissue distribution among tumors	References
HLA class I–restricted epitopes				
abl-bcr alb-b3(b2a2)	A*0201	FVEHDDESPGL	CML	Wagner et al. [198]
abl- bcr alb-b4(b3a2)	A*0201	FVEHDLYCTL	CML	Wagner et al. [198]
bcr-abl[a]	A2	FMVELVEGA KLSEQESLL MLTNSCVKL	CML	Buzyn et al. [23]
bcr-abl p210(b3a2)	A2	SSKALQRPV	CML	Yotnda et al. [213]
	A3	ATGFKQSSK KQSSKALQR		Greco et al. [61]
	A3, A11	HSATGFKQSSK		Bocchia et al. [15]
	A3	KQSSKALQR		Norbury et al. [126]
	B8	GFKQSSKAL		Norbury et al. [126]
ETV6/AML	A2	RIAECILGM	ALL	Yotnda et al. [214]
NPM/ALK[b]	A2*0201	SLAMLDLLHV GVLLWEIFSL	NPM/ALK: in anaplastic large cell lymphomas ALK: in neuroblastomas	Passoni et al. [139]
SYT/SSX	B7, B42	QRPYGYDQIM	Synovial sarcoma	Worley et al. [210]
HLA class II–restricted epitopes				
abl-bcr alb-b3(b2a2)	DRB1*0701	GPHCNVFVEHDDESPGLYG	CML	Wagner et al. [198]
bcr-abl p190 (e1a2)	DRB1*1501	EGAFHGDAEALQRPVAS	ALL	Tanaka et al. [170]
bcr-abl p210 (b2a2)	DRB5*0101	IPLTINKEEALQRPVAS	CML	ten Bosch et al. [175]
bcr-abl p210 (b3a2)	DRB1*0401	ATGFKQSSKALQRPVAS[c]	CML	ten Bosch et al. [174]
	DRB1*1501	ATGFKQSS KALQRPVAS[c]		ten Bosch et al. [173]
	DRB1*0901	ATGFKQSS KALQRPVAS[c]		Yasukawa et al. [212]
	DRB1*1101	LIVVIVHSATGFKQSS KALQRPVA		Pawelec et al. [140]
	DR11	IVHSATGFKQSS KALQRPVASDFEP		Bocchia et al. [15]
DEK-CAN	DRB4*0103	TMKQICKK EIRRLHQY	AML	Ohminami et al. [129]
LDLR/FUT[d]	DRB1*0101	GGAPPVTWRRAPAPG WRRAPAPGAKAMAPG	Melanoma	Wang et al. [206]
pml/RARα	DR11	NSNHVASGAGEAAIETQSSSSEEIV [43]	APL	Gambacorti-Passerini et al. [54]
TEL/AML1	DP5, DP17	IGRIAECILGMNPSR	AML	Yun et al. [215]

[a]These bcr-abl epitopes derive from the BCR part of the chimeric protein and do not span the fusion junction. BCR is ubiquitously expressed in normal cells. From an immunotherapeutic point of view these peptides could be considered as widely/overexpressed epitopes rather than as tumor-specific fusion protein-derived epitopes

[b]The two epitopes occur entirely within the ALK region of the antigen, and do not span the fusion junction. CTLs directed against these two epitopes recognize both NPM/ALK$^+$ lymphomas and ALK$^+$ neuroblastomas. The ALK protein is normally expressed only in pericytes and scattered glial cells of selected regions of the CNS, such as the hypothalamus

[c]These epitopes share different HLA-DR alleles. This allows an epitope to be employed for cancer immunotherapy in a larger number of patients

[d]The antigen is unique to the melanoma patient examined, and the epitopes do not span the junction region. However, the fusion between the two proteins does generate the epitopes, as they derive from the antisense translation of the FUT sequence of the fusion protein

reaction mediated by the newly generated epitope. Also important is the spectrum of different tumors which could be targeted by these shared tumor-specific antigens, extending from melanoma (N-RAS-61m) [109] to pancreatic and colorectal adenocarcinomas (K-RAS) [59], and from MSI$^+$ colon carcinomas to glioblastoma multiforme [94, 110].

Class II HLA-restricted antigens (Table 5)

As already mentioned above, the separation of class I and class II HLA-restricted TAAs of corresponding groups into separate tables is only justified by the fact that the number of class II HLA-restricted antigens is smaller than that of the class I HLA-restricted counterpart.

Stimulation of the CD4$^+$ T-helper cells is considered to be a pivotal step in raising an efficient and durable immune response to tumors. Therefore, the identification of TAA epitopes recognized by such lymphocytes is a crucial step in the long-sought improvement of the antitumor immune response that could result in increased clinical efficacy.

The first epitope presented by a class II HLA molecule and capable of provoking a CD4$^+$ T-cell response was identified in 1994 as the melanoma differentiation antigen tyrosinase [176]. Then a gap of 4 years followed during which only one additional epitope was characterized [177], before other genes encoding class II HLA-restricted peptides were discovered. However, as technical and methodological approaches for identifying CD4$^+$ T-cell epitopes of tumor antigens have become available (among others, invariant chain-cDNA

Table 7 Frequency of epitopes recognized by a given HLA allele. In the case of cancer-testis and melanoma differentiation groups, the TAAs most frequently used in clinical trials are outlined

TAA	No. of epitopes	HLA-A	%	HLA-B	%	HLA-C	%	HLA-DR	%
Cancer-testis									
MAGE-1, -2, -3, -4, -6, -10, -12	42	14	33.3	9	21.4	4	9.5	15	35.7
GAGE-1, -2, -3, -4, -5, -6, -7B, -8	2	1	50	0		1	50	0	
NY-ESO-1	9	4	44.4	1	11.1	0		4	44.4
Other cancer-testis antigens	11	6	54.5	1	9.1	2	18.2	2	18.2
Melanoma differentiation									
Gp100	21	16	76.2	1	4.8	1	4.8	3	14.3
MART-1/Melan-A	7	3	42.8	3	42.8	0		1	14.3
Tyrosinase	14	5	35.7	2	14.3	0		7	50
Other melanoma and nonmelanoma differentiation antigens	28	19	67.8	0		1	3.6	8	28.6
Widely expressed	71	59	83.1	7	9.8	0		5	7
Unique and shared tumor-specific	28	15	53.6	6	21.4	1	3.6	6	21.4
Fusion protein	28	13	46.4	2	7.2	0		13	46.4

fusion libraries [204], humanized transgenic mice [217], and biochemical approaches [143]), an exponential increase in reporting such epitopes has been seen. Indeed, at the present time, class II HLA-restricted TAA epitopes have been identified which cover all the known types of TAAs, from differentiation to CT antigens, and from widely expressed/overexpressed to tumor-specific unique antigens, as shown in Table 5.

It is of note that the mutated proteins subgroup also includes a shared tumor-specific antigen (TGFβRII) which is characteristic of MSI^+ colon carcinomas [155].

Class I and class II HLA-restricted fusion proteins (Table 6)

In several malignancies, particularly in some forms of leukemias, the molecular mechanism of carcinogenesis involves translocation of chromosomes which results in fusion of distant genes. This often causes the synthesis of fusion proteins which characterize each type of disease (e.g., BCR-ABL in CML, DEK-CAN and TEL/AML1 in AML, ETV6/AML and NPM/ALK in ALL, pml-RARα in APL, and SYT/SSX in synovial sarcomas) and generate new $CD8^+$ and/or $CD4^+$ T-cell epitopes generally spanning the fusion junction. This provides new T-cell epitopes falling within the group of non-self, shared, class I and class II HLA-restricted tumor-specific antigens, which can be employed in a large number of patients and tumor histologies [138].

Among these TAAs, only LDLR/FUT can be considered a unique antigen.

Frequency of epitope recognition by HLA-A, HLA-B, HLA-C, and HLA-DR alleles (Table 7)

Table 7 summarizes the distribution of epitopes recognized in the context of different HLA loci. Data show that the majority of epitopes of a given group of TAAs is restricted by HLA-A, though in several cases (e.g., NY-ESO-1, tyrosinase) the percentage of HLA-DR restriction is equal to or higher than class I HLA-restriction. This table suggests that a wide spectrum of tumor epitopes is available for the construction of antitumor vaccines potentially capable of stimulating both tumor-specific $CD4^+$ and $CD8^+$ T cells.

Conclusions

Several excellent and timely reviews on tumor antigens have been periodically published during the last few years [18, 87, 150]. The present contribution is a comprehensive list of all available TAAs, their T-cell epitopes and HLA restriction, despite the fact that the features of each antigen can be easily found in the corresponding bibliography. A similar database can be found in http://www.cancerimmunity.org/peptidedatabase/Tcellepitopes.htm. We hope that our work will be of interest to many tumor immunologists and students. Needless to say, we may have inadvertently missed information on some antigens despite our careful scrutiny of the published literature; therefore, we will be grateful to any reader who will provide us with any missing information.

The antigen list can also be found at the INT website (http://www.istitutotumori.mi.it).

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