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Role of genetic variations on MHC class I antigen-processing genes in human cancer and viral-mediated diseases☆

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ABSTRACT

Cytotoxic T lymphocytes constantly monitor peptide-MHC class I complexes on the cell surface to eliminate transformed and virally infected cells expressing peptides derived from abnormal proteins. The generation of antigenic peptides and their loading on MHC class I molecules is a multistep process involving different molecules that constitute the so-called antigen processing and presentation machinery (APM). To avoid immune-mediated elimination, human tumors and pathogens have adopted different strategies including loss of MHC class I expression and dysregulation of APM genes and proteins. Here, we summarize recent knowledge on genetic variations in APM genes and their association with cancer development and viral-mediated diseases.

1. MHC class I antigen processing pathway

The generation of antigenic peptides is central in the regulation of immune responses. Cytotoxic T lymphocytes (CTLs) recognize and eliminate transformed and infected cells expressing on the cell surface peptide bound to MHC class I molecules derived from aberrant proteins. To avoid immune-mediated elimination, tumors and viruses adopt different strategies, including the loss of their antigenicity through the reduced expression of MHC class I or dysregulation of the antigen processing machinery (APM) components leading to the formation of antigenic peptides.

Antigenic peptides are generated from the proteolytic degradation of endogenous proteins in the cytosol and endoplasmic reticulum (ER) by the concerted action of the proteasome and additional peptidases (Fig. 1) (Shastri et al., 2005). Proteasome is a multimeric complex containing a catalytic core and regulatory particles (Sijts and Kloetzel, 2011). Inflammatory cytokines, including type I and type II interferon (IFN), induce expression of catalytic subunits, named low molecular weight protein (LMP) 2, LMP7, and LMP10, which replace the 20 S proteasome's subunits to form the immunoproteasome. This shift results in the increased generation of peptides with basic and hydrophobic residues at C-terminal, providing the optimal anchor residues for stable binding to MHC class I molecules (Gaczynska et al., 1993). Peptides released by the proteasome (ranging from 4 to 25 residues) are rapidly broken down by cytosolic proteases (tripeptidyl peptidase II, insulin-degrading enzyme, Nardilysin and thimet oligopeptidase) (Geier et al., 1999; Parmentier et al., 2010; Kessler et al., 2011), before being actively transported into the ER by the transporter associated with antigen processing (TAP), an heterodimeric complex composed of two members of the ATP-binding cassette transporter family, TAP1 and TAP2 (Lehnert and Tampe, 2017). TAP proteins form a transmembrane pore in the ER membrane whose opening and closing depend on ATP binding and hydrolysis, respectively (Gorbulev et al., 2001). TAP efficiently transports peptides of 8–12 residues with hydrophobic or basic C-terminal (Schumacher et al., 1994; Momburg et al., 1994). Peptides that do not fit the MHC class I binding groove are further trimmed in the ER lumen by ER aminopeptidases, ERAP1 and ERAP2 (Fruci et al., 2014). These enzymes have complementary functions by selecting substrates according to their N-terminal residues and internal sequence. ERAP1 prefers large hydrophobic residues, whereas ERAP2 trims positively charged residues (Saveanu et al., 2005). They preferentially trim peptides up to 8 or 9 amino acids, to produce the mature MHC class I-binding peptide (Chang et al., 2005). In the ER, nascent MHC class I heavy chains are chaperoned by the calnexin-calreticulin system. MHC class I heavy chains assemble with β2-microglobulin (β2m) to form heterodimers that are recruited by calreticulin in the peptide loading complex (PLC), a transient multisubunit complex that coordinates peptide translocation into the ER and peptide loading into MHC class I molecules (Blees et al., 2017). The structure of PLC, as recently determined by cryo-electron microscopy, consists of MHC class

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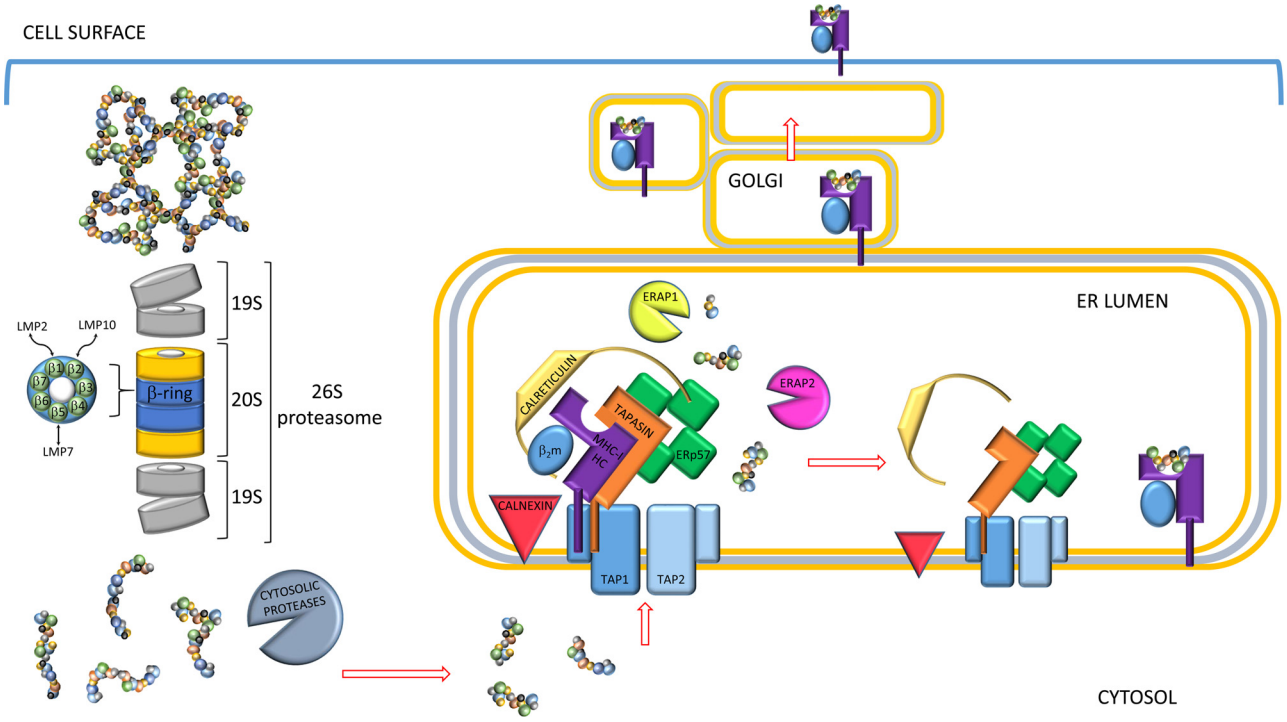

Fig. 1. Schematic diagram of MHC Class I antigen processing and presentation pathway. Proteins targeted to the proteasome (immunoproteasome if contains the catalytic subunits LMP2, LMP7, and LMP10) through ubiquitination are cleaved into peptides and further trimmed by cytosolic proteases. A fraction of these peptides are then transported into the ER through the TAP subunits. After initial association with calnexin, empty MHC class I heavy-chain/β2-microglobulin (MHC-I HC/β2m) enters a multimeric peptide loading complex (PLC) comprising of TAP subunits, tapasin, calreticulin and ERp57. Peptides too long for binding MHC class I are further trimmed by ER aminopeptidases ERAP1 and ERAP2. Once loaded with peptide, MHC class I molecules are released from the PLC and exported via the trans-Golgi to the cell surface for presentation to circulating CTLs and NK cells.

I molecules and a set of accessory proteins including TAP1, TAP2, tapasin, calreticulin and the thiol oxidoreductase ERp57 (Blees et al., 2017). After the peptide binding, stable pMHC class I complexes travel to the cell surface through the Golgi apparatus to be recognized by dedicated receptors on CTLs and NK cells (Kelly and Trowsdale, 2017).

Defects in the function and expression of each component of the APM, ultimately result in altered repertoire of antigenic peptides presented to CTLs and NK cells and different vulnerability to tumor development (Leone et al., 2013) and viral infections diseases (Schuren et al., 2016). Herein we summarise recent knowledge on the genetic variations in APM genes known to be associated with cancer and viral-mediated diseases.

2. Genetic variations in APM genes and their predisposition to cancer

Genetic variations of several APM genes are risk factors for many types of cancer (Table 1).

A recent meta-analysis identified two polymorphisms of LMP2 and LMP7 significantly associated with cancer risk in Asian population (Wu et al., 2017). LMP2-60 showed a higher susceptibility to gynecological cancers, whereas LMP7-145 was associated to an increased risk of gastrointestinal and gynecological cancers (Wu et al., 2017). LMP2-60 and LMP10-151 have been considered risk factors for hematological malignancies (Ozbas-Gerceker et al., 2013aa,b; Bruzzoni-Giovanelli et al., 2015). The prevalence of LMP2-60 AA genotype (Arg/Arg) was significantly higher in acute myeloid leukemia patients and lower in multiple myeloma patients, as compared to control groups (Ozbas-Gerceker et al., 2013aa,b), whereas LMP10-151 was significantly associated with the risk of developing chronic myeloid leukemia (Bruzzoni-Giovanelli et al., 2015). LMP7-145 Lys variant has been correlated with a reduced transcript stability and significantly associated with an increased risk of ovarian, gastric and colorectal carcinomas (Fellerhoff et al., 2011; Song et al., 2014; Ma et al., 2015). Furthermore, LMP7-145 along with TAP2-379, has been considered a risk factor for Human papillomavirus (HPV)16-associated esophageal carcinoma (Cao et al., 2005).

A further evidence of the key role of APM components in susceptibility to HPV16-associated diseases is indicated by the different distribution of SNPs of TAP1, TAP2 and tapasin (TAP1-458, TAP1-518, TAP1-637, TAP2-386, TAP2-577 and tapasin-59) in cervical carcinoma patients as compared to control groups, although no functional data have been reported (Deshpande et al., 2008). Moreover, TAP1-648, located at a residue close to C-terminal to the functional signature motif LSGGQ, typical of all ATP-binding cassette transporter family members (Logan et al., 1994; Li et al., 1996; Derand et al., 2002), has been associated with reduced expression of surface MHC class I in human colon cancer (Yang et al., 2005). Functional analysis revealed that the TAP1-648 Gln variant is associate with a reduced peptide translocation activity as compared to the TAP1-648 Arg variant (Yang et al., 2005). Furthermore, other authors identified two TAP1 SNPs, TAP1-333 and TAP1-637, associated with high-grade cervical intraepithelial carcinoma that remained significant even in women who were positive for high-risk HPV types (Einstein et al., 2009).

TAP1 and TAP2 polymorphisms have been investigated in patients with hematological malignancies. The TAP1-333 G allele and the TAP2-565 GA genotype were associated with multiple myeloma and chronic lymphoid leukemia, respectively, whereas the TAP2-665 GG genotype was considered a risk factor for both hematological malignancies (Ozbas-Gerceker et al., 2013ba,b).

A SNP localized to the 5′ UTR of tapasin was associated with overall survival of colorectal cancer patients (Shao et al., 2013). The functional consequences of this variant were not investigated so far, although its strategic location within histone marks (H3K27Ac, H3K9Ac and H3K4me3) and among binding sites for transcription factors (interferon regulatory transcription factor 1 (IRF-1), IRF-2 and IRF-7) suggests its

Table 1
Single nucleotide polymorphisms (SNPs) in APM genes associated with cancer.

Gene	Name	SNP	Intron/ Exon	Nucleotide change	AA position*	Major/Minor allele (AA)	Tumor**	Reference
LMP2	LMP2-60	rs17587	Exon 3	G/A	60	Arg/His	AML,MM	18,19
LMP7	LMP7-145	rs2071543	Exon 2	C/A	49	Gln/Lys	CRC,OC,GC,EC,CC	18,21-24,25, 29-33
LMP10	LMP10-151	rs14178	Exon 4	C/T	151	Gly/Gly	CML	20
TAP1	TAP1-333	rs1057141	Exon 4	A/G	393	Ile/Val	CIC,MM	30,31
	TAP1-458	rs41550019	Exon 6	G/T	518	Val/Leu	CC	25
	TAP1-518	rs41561219	Exon 7	G/A	578	Val/Ile	CC	25
	TAP1-637	rs1135216	Exon 10	A/G	697	Asp/Gly	CC,CIC	25,30
	TAP1-648	rs1057149	Exon 10	G/A	708	Arg/Gln	CRC	29
TAP2	TAP2-379	rs1800454	Exon 6	G/A	379	Val/Ile	EC,CC	24,35
	TAP2-386	rs2228397	Exon 6	G/T	386	Gly/Gly	CC	25
	TAP2-565	rs2228396	Exon 9	G/A	565	Ala/Thr	CLL	31
	TAP2-577	rs2228391	Exon 9	A/G	577	Met/Val	CC	25
	TAP2-651	rs4148876	Exon 12	C/T	651	Arg/Cys	CC	33,35
	TAP2-665	rs241447	Exon 12	A/G	665	Thr/Ala	CLL,MM	31
Tapasin	Tapasin-5UTR	rs3106189	5' UTR	G/A	–	–	CRC	32
	Tapasin-59	rs45583737	Exon 2	G/T	59	Asp/Tyr	CC	25
ERAP1	ERAP1-56	rs3734016	Exon 2	G/A	56	Glu/Lys	CC	35
	ERAP1-127	rs26653	Exon 2	G/C	127	Arg/Pro	CC, NSCLC	33,34,36
	ERAP1-276	rs26618	Exon 5	A/G	276	Ile/Met	CC, NSCLC	34,36
	ERAP1-528	rs30187	Exon 11	A/G	528	Lys/Arg	CC, NSCLC	34,36
	ERAP1-575	rs10050860	Exon 12	G/A	575	Asp/Asn	CC	35
	ERAP1-730	rs27044	Exon 15	C/G	730	Gln/Glu	CC, NSCLC	33,36

* Amino acid position as referred to NCBI sequences (LMP2: NM_002800.4, LMP7: NM_148919.3, TAP1: NM_000593.5, TAP2: NM_000544.3, Tapasin: NM_003190.4, ERAP1: NM_001040458.1, ERAP2: NM_001130140.2).

** AML, Acute Myeloid Leukemia; CML, Chronic Myeloid Leukemia MM, Multiple Myeloma; CRC, Colorectal Cancer; OC, Ovarian Cancer; GC, Gastric Cancer; EC, Esophageal Cancer; CC, Cervical Carcinoma; CIC, Cervical Intraepithelial Carcinoma; CLL, Chronic Lymphoid Leukemia; NSCLC, Non Small Cell Lung Cancer.

role in transcriptional gene regulation.

Several ERAP1 functional variants have been associated with cancer. Mehta and colleagues identified two ERAP1 SNPs, ERAP1-127 and ERAP1-730, significantly associated with increased risk of HPV-induced cervical cancer (Mehta et al., 2007). They estimated that 12% of all cervical carcinoma cases are attributable to the occurrence of the haplotype combination consisting of four SNPs, the minor alleles at ERAP1-127 and ERAP1-730 loci (Pro and Glu, respectively) and the major alleles at the TAP2-651 and LMP7-145 loci (Arg and Gln, respectively) (Mehta et al., 2007). The same authors showed that genotype distributions at the ERAP1-56, ERAP1-127, ERAP1-276 and ERAP1-528 were significantly associated with the presence of lymph node metastases and decreased overall survival in cervical carcinoma patients (Mehta et al., 2009). Multivariate analysis performed on ERAP1-56 and ERAP1-127 genotypes combined with prognostic factors, revealed that the two SNPs are dependent predictors of survival (Mehta et al., 2009). More recently, the same authors showed that one specific haplotype, consisting of ERAP1-575, TAP2-379 and TAP2-651 loci, was significantly associated with cervical carcinoma risk in one of the two Indonesian populations studied, suggesting that the different association depends on the genetic background and differences in HPV type distribution (Mehta et al., 2015).

Recently, genotype and haplotype frequencies of four ERAP1 SNPs, ERAP1-127, ERAP1-276, ERAP1-528 and ERAP1-730, were compared in non-small-cell lung carcinoma patients from two genetically distant populations, Chinese and Poles. A significant association was detected for all SNPs in Chinese but not in Poles patients, suggesting that other genetic and environmental factors contribute to these associations (Yao et al., 2016).

No genetic variation in the other APM genes, including calreticulin, calnexin, ERp57 and β2m, has been associated with cancer development.

3. Genetic variations in APM genes and their predisposition to virus-mediated diseases

Genetic variations in APM genes have been associated with the outcome of several viral infections (Table 2).

A study in 1207 Chinese individuals with different Hepatitis C virus (HCV) infection outcomes revealed that LMP2-60 SNP affects susceptibility to HCV infection and viral clearance (Huang et al., 2014). In particular, subjects carrying LMP2-60 His variant had a decreased risk of HCV chronicity (Huang et al., 2014). LMP7-145 SNP is one of the host factors affecting IFN response in patients with chronic HCV (Sugimoto et al., 2002). The distribution of LMP7-145 Lys variant was higher in patients who responded to IFN therapy than in non-responder, and it was considered an independent factor that affects the outcome of IFN therapy (Sugimoto et al., 2002). Among patients with a low viral load, those carrying the LMP7-145 Lys variant had an even higher ratio of sustained response compared to patients with the LMP7-145 Gln variant (Sugimoto et al., 2002). A stratified analysis between persistent HCV infection patients and control subjects indicated that the combined genotype Gln/Lys + Lys/Lys was associated to an increased susceptibility to HCV infection (Cui et al., 2010).

LMP7-145, TAP1-637 and TAP2-651 were considered a risk factor for Hepatitis B virus (HBV) infection in Chinese population (Xu et al., 2007). The distribution of LMP7-145 and TAP1-637 was statistically associated with outcome of HBV infection in Chinese patients with chronic HBV, as compared to individuals spontaneously recovered from HBV infection and normal controls (Shi et al., 2011).

TAP variants were investigated in the Han population in northeastern China affected by persistent HBV infection (Qiu et al., 2012). The frequency of TAP1-637 Gly and TAP2-687 Gln variants was significantly higher in persistently and chronic HBV-infected patients than in HBV spontaneously recovered subjects (Qiu et al., 2012). A higher frequency of the TAP2-651 Cys was detected between hepatocellular carcinoma cases and HBV spontaneously recovered controls (Qiu et al., 2012). The TAP2-379 Ile variant was significantly associated with increased susceptibility to HCV infection (Huang et al., 2015).

TAP variants have been involved in human immunodeficiency virus (HIV) and Measles infections. In particular, TAP1-333 GG and TAP1-637 GA genotypes were positively associated with HIV-Tubercolosis co-infection (Sunder et al., 2011), suggesting their involvement as risk factors for developing Tubercolosis co-infection in HIV-positive individuals. Measles vaccine non-responders were more likely to be homozygous at TAP2-665 than hyper-responders, while no association

Table 2
Single nucleotide polymorphisms (SNPs) in APM genes associated with viral-mediated diseases.

Gene	Name	SNP	Intron/Exon	Nucleotide change	AA position*	Major/Minor allele (AA)	Virus**	Reference
LMP2	LMP2-60	rs17587	Exon 3	G/A	60	Arg/His	HCV	37
LMP7	LMP7-145	rs2071543	Exon 2	C/A	49	Gln/Lys	HBV,HCV	38-40,41
TAP1	TAP1-333	rs1057141	Exon 4	A/G	393	Ile/Val	HIV-TB	44
	TAP1-637	rs1135216	Exon 10	A/G	697	Asp/Gly	HBV,HIV-TB	40-42,44
TAP2	TAP2-379	rs1800454	Exon 6	G/A	379	Val/Ile	HCV	43
	TAP2-651	rs4148876	Exon 12	C/T	651	Arg/Cys	HBV	40,42
	TAP2-665	rs241447	Exon 12	A/G	665	Thr/Ala	MV	45
	TAP2-687	rs241448	Exon 12	C/T	687	STOP/Gln	HBV	42
Tapasin	Tapasin-260	rs2071888	Exon 4	C/G	260	Thr/Arg	HCV	45
	Tapasin-intr	rs9277972	Intron 3	A/T	–	–	HCV	43
ERAP1	ERAP1-3UTR	rs17481334	3' UTR	G/A	–	–	HCMV	49
ERAP2	ERAP2-392	rs2549782	Exon 7	G/T	392	Lys/Asn	HIV	47,48
	ERAP2-intr	rs2248374	Intron 10	A/G	–	–	HIV	48

* Amino acid position as referred to NCBI sequences (LMP2: NM_002800.4, LMP7: NM_148919.3, TAP1: NM_000593.5, TAP2: NM_000544.3, Tapasin: NM_003190.4, ERAP1: NM_001040458.1, ERAP2: NM_001130140.2 and NR_137637.1 for rs2549782 and rs2248374, respectively).

** HCV, Hepatitis C Virus; HBV, Hepatitis B Virus; TB-HIV, Tuberculosis (TB) and Human Immunodeficiency Virus (HIV) co-infection; MV, Measles Virus; HCMV, Human Cytomegalovirus.

was detected between TAP1 polymorphisms and vaccine response (Hayney et al., 1997).

Tapasin variants also contribute to the outcome of viral infections. The tapasin-260 variant affects the outcome of HCV infection in synergy with polymorphisms at HLA-B locus. The authors found that the tapasin-260 Arg variant was more frequently detected in resolvers than in chronic HCV infected individuals (Ashraf et al., 2013). In another study, the intronic Thr variant of tapasin was associated with an increased risk of HCV chronicity (Huang et al., 2015).

Two studies evaluated the role of ERAP2 SNPs in resistance to HIV-1 infection. In the first study, ERAP2-392 was genotyped in an Italian population of HIV-1-exposed seronegative (ESN) individuals and donors (Cagliani et al., 2010). The distribution of ERAP2-392 GG genotype was significantly deviated from Hardy-Weinberg equilibrium in ESN subjects, but not in controls, suggesting a role in conferring resistance to HIV-1 infection. In the second study, the authors performed a genotype analysis in 104 HIV-1 ESN individuals and 130 controls, and found that haplotype B ERAP2 harbouring the ERAP2-392 T allele and the ERAP2-intron G allele conferred susceptibility to HIV infection (Biasin et al., 2013). Of note, the ERAP2-intron G allele determines the activation of a cryptic splice site in intron 10 and production of an alternative spliced ERAP2 mRNA with an in frame-stop codon, which following a nonsense-mediated decay does not produce the expected truncated protein. The authors confirmed that ERAP2 diplotype status, consisting of the combination of ERAP2-392 Lys allele and ERAP2-intron A allele (encoding full-length ERAP2), conferred protection to HIV infection (Biasin et al., 2013).

Recently, we identified a SNP in the 3′UTR of the ERAP1 gene, which prevents ERAP1 targeting and degradation by HCMV miRUL112-5p (Romania et al., 2017). Specifically, HCMV miRUL112-5p binds the 3′ UTR of ERAP1 A variant, but not the 3′ UTR of ERAP1 G variant and accordingly ERAP1 expression is reduced, both at RNA and protein levels, in HCMV-infected AA but not GG fibroblasts. Consequently, HCMV-infected GG fibroblasts were more efficient in trimming viral antigens and being lysed by HCMV-peptide-specific CTLs. These data indicate that individuals carrying GG genotye are able to resolve HCMV infections more readily than AA individuals.

4. Concluding remarks

In summary, we have discussed an up-to-date summary of the genetic variations of APM genes associated with tumors and viral-infected diseases. Although we do not have information about the functional role for the majority of APM gene variants, the recurrent associations observed with different tumors and viral-infected diseases are indicative of their functional effect. Understanding their physiological functions will be useful to explain their interplay among the other APM components and improve the knowledge of complex human diseases as tumors and viral-mediated diseases. In this sense, the recent associations between functional ERAPs polymorphisms and autoimmune diseases (Reeves et al., 2014; Lopez de Castro et al., 2016) have highlighted the interest in MHC class I antigen-processing pathway, underlining how its modulation can be exploited for therapeutic purposes.

Conflict of interest

The authors declare no potential conflict of interest.

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