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A short review on cervical cancer cell lines characterization and their corresponding human leukocyte antigen (HLA) type expression

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Abstract. – Cervical cancer is one of the leading causes of death in women worldwide. Extensive research is ongoing to develop efficient diagnostics and therapeutic approaches for cervical cancer, which rely on the preliminary studies based on cervical cell lines. It is essential to characterize these cell lines to ensure the suitability of the cells for each study. In this review, the human leukocyte antigen (HLA) molecule expressed on each cervical cancer line is presented. HLA characterization of the cervical cancer cell lines is essential to increase the specificity of treatment towards certain type of cervical cancer, allowing accurate therapy. HLA characterization is also important for the generation of novel diagnostics and/or therapeutics molecules, especially for HLA-based strategies.

Key Words:
Cervical cancer, CaSki, SiHa, Hela, Me180, INBL, Human leukocyte antigen.

Introduction

Cervical cancer originates from the cervix and is categorized based on its histological classifications [adenocarcinoma (AC), squamous cell carcinoma (SCC), and adenosquamous carcinoma][1]. Harald zur Hausen first detected the human papillomavirus from cervical cancer and concluded that HPV types 16 and 18 have a high risk in cancer development, which earned the discovery a Noble Prize in 2008[2,3]. Cervical carcinoma is the fourth most prevalent cancer among women worldwide[4] and second most common cancer in middle-and low-income countries. It is estimated that in the year 2040 the fatality rate of cervical cancer will spike by almost 50%[5].

Human papillomavirus is a sexually transmittable infection-causing pathogen and is the primary cause of cervical cancer[6]. Human papillomavirus is a double-stranded DNA virus that is non-enveloped, small, circular, and about 50-55 nm diameter. This virus belongs to the Papillomaviridae family[7]. The five main HPV genera are α-papillomavirus, β-papillomavirus, γ-papillomavirus, mu-papillomavirus, and nu-papillomavirus[8,9]. The HPV types are categorized based on the ORF nucleotide sequence that codes for the capsid protein L1[10].

Healthy cells are driven towards oncogenesis by two primary HPV viral oncoproteins, E6 and E7. Both proteins are in charge of replicating the viral genome, which induces cervical cancer hallmarks like angiogenesis, unconstrained cell division, metastasis, and uncontrolled telomerase activity. In the absence of E6 and E7 proteins, cancer cells deteriorate or experience apoptosis, indicating that those oncoproteins are vital for the persistence of HPV-mediated cancer[11,12].

Cervical cancer can be successfully treated and prevented, if diagnosed early[13]. Pap smear is the primary screening method due to its ability to detect early changes in cervical epithelial cells before they develop into invasive cervical cancer[14]. With an increased interest in precision and personalized medicine, immunotherapy becomes the primary focus for cancer diagnosis and treatment.

The development of immunotherapies towards cancer is based on the understanding of tumor escape mechanism, immune system manipulation for anticancer immune response and controlling the tumor escape pathways. Multiple sections of the immune system have been manipulated and investigated for therapeutic approaches, such as cancer vaccines, oncolytic viruses, adoptive cell therapy and immune checkpoint inhibitors[15]. The primary limitation of immunotherapies is

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the antagonistic immune activation and inflammatory response against the host's normal cells/tissues[16]. These immunotherapies have a fundamental mechanism where an immune response is activated by T cells by recognizing neoantigens presented by the major histocompatibility complex (MHC) on tumor cell membrane. A set of highly variable genes presented in almost all the vertebrates is known as MHC, which regulates histocompatibility between individuals. MHC was initially discovered in mice due to tumor rejection and is known as human leukocyte antigen (HLA) in humans[17].

Human MHC can be characterized into three types, which are class I, class II, and class III[18]. The genes encoding for the 'classical' HLA antigens (HLA-A, HLA-B, and HLA-C) are present in the class I region. Commonly, class I antigen exists on most of the body cells, except for trophoblasts and erythrocytes, at a different density. The minor genes in the class I region are HLA-E, HLA-F, and HLA-G[19]. All nucleated cells exhibit MHC class I molecules[20]. The molecules of HLA class II are heterodimers made up of α and β chains. As various exons encode different domains of the protein, the exon-intron arrangement of class II genes is similar to that of class I genes[21]. The HLA class III complex is found in between class I and class II HLA regions. Unlike HLA class I and II, HLA class III encodes for more minor polymorphic antigens. Only two out of several presented genes in the HLA class III molecules have an absolute function in the human immune system. Even though class III HLA genes have a low degree of genetic variability compared to other HLA classes, they are crucial in converting genes and gene copy number changes during meiosis[22]. The existence of HLA class I molecule on all nucleated cells[20] means that cervical cancer cells also exhibit HLA class I molecules on their cell surface and present tumor antigens to T cells to activate appropriate immune response towards cancer cells.

There are various types of cervical cancer cell lines available and a few of them are shown in Table I[23-42].

Cell lines play a key role in the provision of preliminary data for diagnostics and therapeutics of cervical cancer. Given the significance of these cell lines, it is important to characterize the cell lines to ensure that a suitable cell line is selected for a study. This review focuses on the type of HLA molecule expressed in each cervical cancer cell line. Characterizing the cervical cancer cell lines and their corresponding HLA types is crucial for the diagnosis and therapy of cervical cancer. The specificity of treatment towards a certain type of cervical cancer can be improved by targeting the right HLA type on cancer cells. An example of the importance of HLA is the determination of antigenic peptides to develop antigen specific therapy. Different HLA would present different antigenic peptide despite originating from the same antigen/target protein. Therefore, characterizing cervical cancer cell lines with their respective HLA type is vital. HLA characterization is also important for the generation of novel diagnostics and/or therapeutics molecules in cervical cancer because of the recent advancement in personalized and precision medicine.

Table I. Types of cervical cancer cell lines.

Cervical cancer cell line	HPV type
CaSki	HPV 16[23-30]
SiHa	HPV 16[23-25,27-33]
HeLa	HPV 18[23-25,28,30,34,35]
ME-180	HPV 68[27,28,33,36]
C-4I	HPV 18[28,30,37,38]
INBL	HPV 18[39-41]
C-33A	HPV negative[25,28-30,32,33,36]
HaCaT	HPV negative[24,42]

Cervical Cancer Cell Lines and Their Respective HLA(s)

CaSki Cell Line-Associated HLA

Mora-García et al[43] showed the association of HLA-A*0201 with the CaSki cell (Figure 1) by testing it with hydralazine (H) and valproic acid (VA) compounds[43]. When the expression

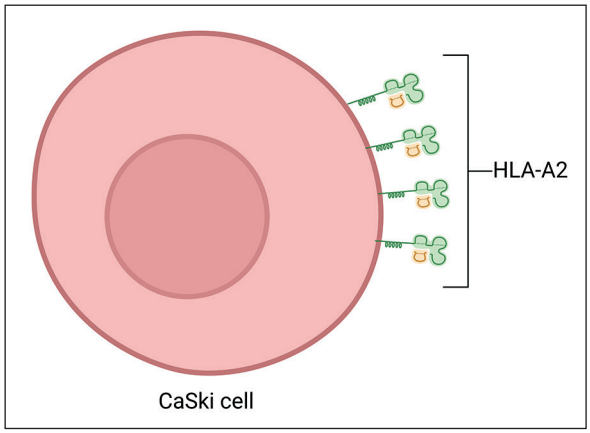

Figure 1. HLA-A2 presented on CaSki cervical cell line (Created in BioRender.com).

of HLA-A2 alleles were analyzed by PA2.1, and W6/32 MAbs, the cells treated with VA, H/VA, IFN-γ and H/VA/ IFN-γ displayed an increase of HLA-A2 by one-fold when compared with hydralazine alone. The antigenic peptides (TLGIVCPIC and YMLDLQPETT) that mainly bind to HLA-A*0201 were tested in CaSki cells for effector T cells to recognize cervical cancer for immune response. It was concluded that both peptides were able to activate cytotoxic T lymphocytes and resulted in CaSki cell lysis[43]. In another study[44], sublines obtained from the volunteers were able to lyse (20-45% lysis) HPV 16 E7 HLA-A*0201 positive CaSki cell line when the cytotoxicity against antigen-expressing target cells was tested using the keratinocytes presenting E7 protein. The capacity of improved synthetic lipopeptide vaccine to activate effector T cells was investigated by generating CTL using healthy HLA-A*0201+ donor PBMC with peptides. It was found that T2 cells transduced with E786–93 peptides were lysed together with increased IFN-γ production when CTL was induced with P1, P2, and P3 peptides. However, no lysis was observed in T2 cells alone. While analyzing specific CTLs' ability to lyse endogenously expressed HPV-E7 tumor cells, CaSki cells (HPV E7+, HLA-A*0201+) were used as target cells, and an efficient lysis in CaSki cells was detected[45]. Nosaka et al[46] investigated the heat shock protein (HSP) 105 expression in cervical cancer as a target. In this study, the efficacy of the HLA-A2 restricted HSP105 peptide-specific effector T cell clone was evaluated against cervical cancer cell lines (CaSki, HeLa, SiHa), human liver cancer cell line (HepG2) and human lymphoblastoid cell line (T2) were used as target cells, meanwhile human normal lung cells derived fibroblast was used as a control target. The result indicated CaSki, SiHa and HeLa cells have higher expression of HSP 105 while HepG2 cells have lower HSP 105 expression and T2 is an antigen processing deficient cell. Through flowcytometry it was found that only CaSki, HepG2 and fibroblast cells exhibited HLA-A2 while HeLa and SiHa did not express HLA-A2[46].

SiHa Cell Line-Associated HLA

The activation of specific CD8+T cells in human blood donors by HPV16 L1E7 chimeric virus-like particles (CVLP) was investigated for its immunotherapeutic potential. The HLA typing of the blood donors were determined. Analysis of SiHa cells showed presence of HLA-A*24, HLA-B*40, HLA-C*03[47]. HLA expression was determined by flowcytometry for HLA-A3, HLA-A11, and HLA-A24. The analysis of HLA expression levels was normalized to expression levels of CaSki HLA-A*0201. The results showed HLA-A24 expression being highly expressed in the SiHa cell line (Figure 2), followed by HLA-A3 expressions and lastly HLA-A11 expression[48].

HeLa Cell Line-Associated HLA

In a study to determine TABPR and class I MHC interaction, the expression of HLA-68 associated with WT-TAPBPR transduced HeLa, and non-transduced HeLa cells were investigated. The cytofluorometric analysis showed that both transduced and non-transduced HeLa cells showed association with high expression of HLA-68[49]. Espmark et al[50] conducted a study to determine HLA distribution in several solid tumor cell lines. It was found that the HeLa cell line is associated with HLA-A3, HLA-A28, HLA-BW35, HLA-BW15, HLA-CW2 and HLA-CW3[50]. A genomic study[51] carried out in 1998 revealed that the HeLa cell line is associated with HLA-A68 (A2 subtype) (Figure 3) and HLA-B75 (B15 subtype), but not with HLA-B35.

Me180 Cell Line-Associated HLA

With the aim of finding more successful immunotherapy for cervical cancer treatment, Zehbe et al[52] evaluated class II MHC antigen components' processing and presenting pathways[52]. LFMDSLNFVCPWC epitope presented by class II MHC molecules on the ME180 tumor cell was detected

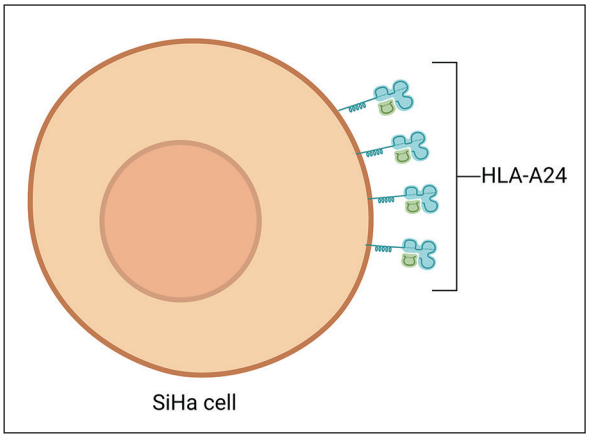

Figure 2. HLA-A24 presented on SiHa cervical cell line (Created in BioRender.com).

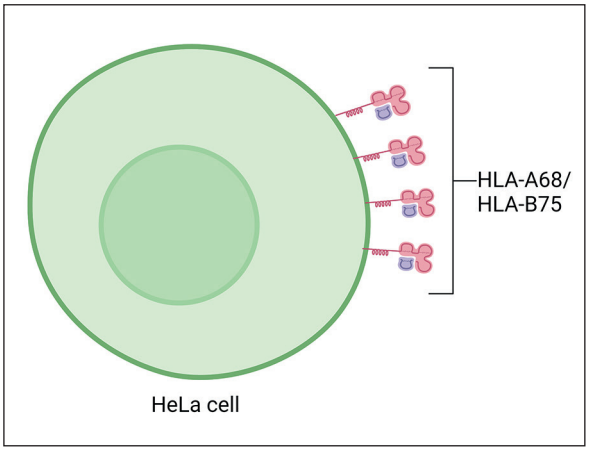

Figure 3. HLA-A68 and HLA-B75 presented on HeLa cervical cell line (Created in BioRender.com).

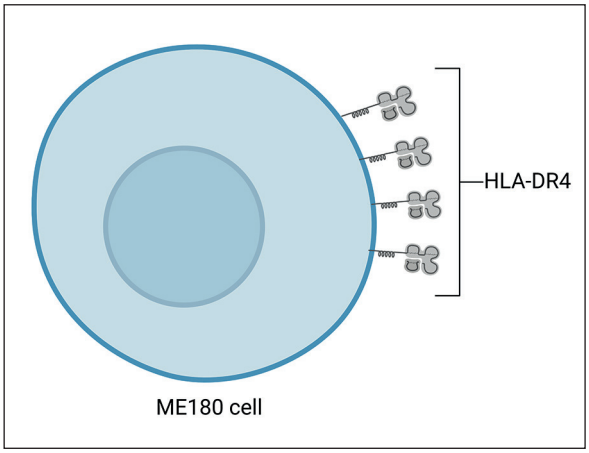

Figure 4. HLA-DR4 presented on ME180 cervical cell line (Created in BioRender.com).

by CCA1 (HLA-DR4- matched T cell clone), derived from tumor-infiltrating lymphocytes[52]. The binding ability of peptides LFMDTLSFVCPLC and LFMDSLNFVCPWC (HPV59 and HPV68, respectively) to HLA-DR4 was tested for T cell recognition. An adequate amount of TNF-α was found to be secreted by CCA1, tumor infiltering lymphocytes when both peptides were added to autologous B cells. When a monoclonal antibody directed against TCR VB14+ was preincubated with tumor-infiltrating lymphocytes, peptide recognition was significantly decreased. This shows that notable T cell population mediating HPV-specific and HLA-DR restricted T cell recognition. The preincubated tumor-infiltrating lymphocytes with anti-TCR VB14 monoclonal antibody caused a clear TNF-α secretion reduction in response to ME180 cervical cancer cells. In conclusion, the CD4+ TIL line CCA1 and, in particular, T cells expressing the TCR VB14 chain describe a peptide epitope given by HPV 59 (or HPV 68) offered by HLA-DR4 (Figure 4) molecules[53].

INBL Cell Line-Associated HLA

A study conducted by García et al[54] used the INBL cell line to identify and isolate peptides of human cervical cancer exhibited by HLA alleles. INBL was considered to have HLA-A11 HLA-Aw33, HLA-B39, HLA-B48, HLA-Bw6, HLA-Cw3 and HLA-Cw4 haplotypes. It was found that the INBL cell line was able to activate T cells from a donor who was positive for HPV18 and matched for HLA-Cw4 (Figure 5)[54].

There is no literature available that mentions the HLA type of the C-4I cell line.

Conclusions

Cervical cancer is one of the topmost fatality-causing illnesses among women, and the primary cause of this illness is the persistent infection by human papillomavirus (HPV). E6 and E7 proteins of this virus transform a normal cell into cancerous. CaSki, HeLa, SiHa, and ME180 are the major cervical cancer cells available, and they are frequently experimented for cervical cancer diagnosis and treatment. The HLA type associated with the cervical cancer cell line is an essential aspect of the immune response against cancer. As such, HLA characterization of the available cervical cancer lines will be able to provide an essential platform for the preliminary development of cervical cancer immunotherapy.

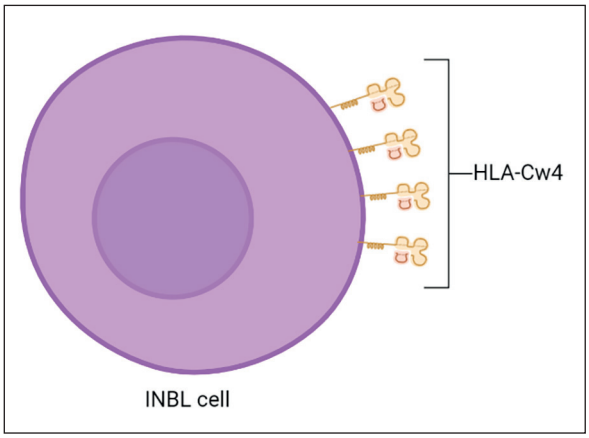

Figure 5. HLA-Cw4 presented on INBL cervical cell line (Created in BioRender.com).

Conflict of Interest
The Authors declare that they have no conflict of interests.

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Data Availability Statement
Data sharing is not applicable to this article, as no datasets were generated or analyzed during the current study.

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