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Research Article

DNA Methylation and Molecular Therapy of High-Risk Human Papilloma Virus Linked with Epstein Barr Virus in the Regulation of Prostate Cancer

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Abstract

Methylation is the process of a change in the composition of the DNA code (or mutation) that leads to the modulation of the DNA and affect the expression of genes in the cell due to altering protein interaction with DNA. HPV (*Human Papilloma Virus)* are a large group of related viruses that causes several types of cancers. Epstein-Barr virus (or EBV) is associated with diseases like multiple sclerosis, Herpes, inflammatory bowel disease, Burkitts lymphoma, nasopharyngeal cancer, gastric cancer, hodgkin lymphoma and hepatitis. Human papillomavirus associated with EBV may be mostly involved in prostate cancer. Most of the HPV16 genome was aligned with genome regions from 140685 to 149003 of EBV genome based on the pairwise sequence alignment. There are 15 genes that are involved in prostate cancer in the present study. Methylation frequency is higher in genes like CDKN2A, RASSF1, CDH1, DAPK1, APC, RARB, TIMP3, ESR1, PTGS2, CDH13, HIC1, MGMT¸ THBS1, CDH13 and RB1. ESR1 is showing characteristic relationship with prostate cancer. ESR1 is related to several other cancer causing genes like CDKN2A, RASSF1, CDH1, DAPK1, APC, RARB, TIMP3, ESR1, PTGS2, CDH13, HIC1, MGMT¸ THBS1, CDH13 and RB1. The selected molecules like Erlotinib and Vinorelbine have shown good control on mutated E6, E7 of HPV16 and ESR1 proteins.

Keywords: DNA Methylation; ESR1; Prostate Cancer

Introduction

DNA methylation patterns are relatively stable components of the epigenome that are inherited through cell cycles by specific lineage [1]. The patterns maintain gene expression states and stabilize cellular phenotypes especially in multicellular organisms. The process of epigenetics refers to the heritable changes in genome function (or phenotype) that generally occur without changes in the genes of a genotype [2]. Hence, a natural mechanism will be obtained by the identity of a cell during development and differentiation.

Methylation is the process of change in the composition of the DNA code (or mutation) that leads to the modulation of the DNA that affect the expression of genes in the cell due to altering protein interaction with DNA [3]. DNA imprinting occurs due to methylation of a nucleotide cytosine that is inheritable for next generations. Methylation abnormalities can enhance the mutation risk that is linked to CpG islands of glutathione-S-transferase and reactive oxygen species (ROS) damage. Over the past 40 years, many human diseases, especially cancer, has been observed due to changes in DNA methylation process.

HPV (*Human Papilloma Virus)* are a large group of related viruses containing several types that cause warts on the skin and infections in moist surface layers like mucous membranes that leads to several types of cancers [4,5]. Long-lasting infections or

Chronic infections are caused by high-risk HPV types that leads to causing cancer.

Epstein-Barr virus (or EBV) is noted as one of the most common human viruses that spreads through saliva. Diseases that are associated with EBV are multiple sclerosis, Herpes, inflammatory bowel disease, Burkitts lymphoma, nasopharyngeal cancer, gastric cancer, hodgkin lymphoma and hepatitis [6, 7] (Figure 1). Human papillomavirus associated with EBV may be mostly involved in prostate cancer [8].

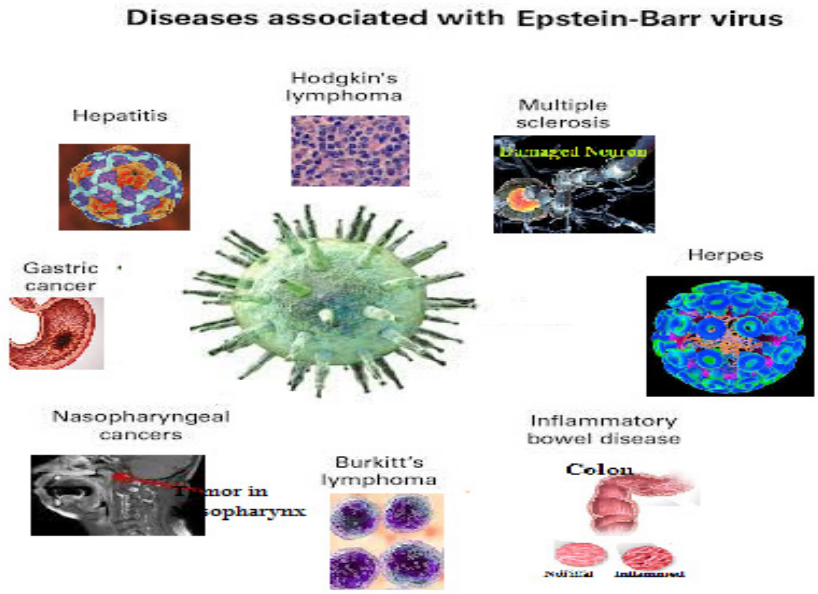

Figure 1: Diseases that are associated with Epstein Barr Virus.

Genes and Proteins involved in DNA demethylation are useful for epigenetic research applications. Many epigenetic studies from embryonic development to tumorigenesis are largely involved in several biological processes like enzyme kinetics, screening inhibitors, RNA processing, selectivity profiling, protein arrays and antibody production [9].

DNA methylation patterns are involved in several interactions process with proteins like DNMT1, PCNA (proliferating cell nuclear antigen), UHRF1, SRA domain, RING finger domains 1, LSD1 (lysine-specific demethylase 1) and H3K9me (Histone H3 lysine 9 methylation) [10].

Materials and Methods

There are about 14 high-risk HPV types including HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. Two viruses' that are linked to prostate cancer are High-risk human papilloma virus found along with Epstein Barr virus. New research are focused that has revealed that both the human papilloma virus and Epstein Barr virus are present together in more than half of the malignant prostate cancers.

Sequence Retrieval

HPV16 from NCBI with accession number NC_001526 showing 7906 bp is showing circular DNA. The sequence is found similar in PAVE database (https://pave.niaid.nih.gov/). Human gammaherpesvirus 4 (Epstein-Barr virus) from NCBI with accession number MT648662 showing 171700 bp is showing linear DNA. EBV is regulated by several epigenetic modification by DNA methylation process of ESR1 via upregulation of HPV16 encoded E6 protein.

Pubmeth

Pubmeth is a cancer methylation database that is annotated and reviewed based on automated textmining of literature. The database includes reporting of genes that are methylated in several cancer types like prostate cancer. The website for search for PUBMETH is http://pubmeth.biobix.be/search.html. The diseases that are related to prostate cancer have been analyzed using pubmeth database.

KEGG / Kyoto Encyclopedia of Genes & Genomes Pathway Maps

The KEGG (Kyoto Encyclopedia of Genes & Genomes) Pathway database is a collection of graphical diagrams (KEGG pathway maps) and associated with text information (KEGG pathway entries) for metabolism, various other cellular and molecular processes, and human diseases.

String v11.0

STRING v11.0 is a database that is known to predicted protein-protein interactions based on physical and functional associations from databases. The search site for multiple protein interactions is https://string-db.org/cgi/input?sessionId=byDwXWOC0ymQ&input_page_active_form=multiple_identifiers.

Retrieval of Ligands and Proteins

The receptor was retrieved from string database and the ligands were retrieved from Drugbank (Table 1).

S.No	Name	Drugbank
1	**Erlotinib**	DB00530
2	**Vinorelbine**	DB00361

Table 1: Drugs for prostate Cancer (from DrugBank)

iGEMDOCKv2.1

iGEMDOCK v2.1 is a graphical environment that is used for recognizing pharmacological interactions and for conducting virtual screening for ligands with selected proteins. The tool is available at http://gemdock.life.nctu.edu.tw/dock/download.php.

Results and Discussion

Most of the HPV16 genome was aligned with genome regions from 140685 to 149003 of EBV genome based on the pairwise sequence alignment. The FGENESV0 gene prediction for HPV16 from PAVE database was predicted to contain 7 genes with total length of 7906 bp (Table 2). Based on identification of genes by BLASTp, the query sequence showed as E6, E7, E1, E2, L2 and L1. The E6 and E7 genes are lethal and carry disease along with EBV.

Gene No	Region	Score	Amino acid length	Identification
1	83 - 559	477	158 aa	E6 protein
2	562 - 858	297	98 aa	E7 protein
3	865 - 2814	1950	649 aa	E1 protein
4	2756 - 3853	1098	365 aa	E2 protein
5	3850 - 4101	252	83 aa	E5 protein
6	4237 - 5658	1422	473 aa	L2 protein
7	5561 - 7156	1596	531 aa	L1 protein

Table 2: Gene identification for HPV16 virus.

There are 15 genes that are involved in prostate cancer. The information has been retrieved from pubmeth (Table 3).

Methylated Gene	Name as on Pubmeth
CDKN2A	Cyclin-dependent kinase inhibitor 2A, isoform 4 (p14ARF) (p19ARF)
RASSF1	Ras association domain-containing protein 1
MGMT	Methylated-DNA--protein-cysteine methyltransferase (EC 2.1.1.63) (6-O- methylguanine-DNA methyltransferase) (MGMT) (O-6-methylguanine-DNA- alkyltransferase)
CDH1	Epithelial-cadherin precursor (E-cadherin) (Uvomorulin) (Cadherin-1) (CAM 120/80) (CD324 antigen
DAPK1	Death-associated protein kinase 1 (EC 2.7.11.1) (DAP kinase 1)
APC	Adenomatous polyposis coli protein (Protein APC)
GSTP1	Glutathione S-transferase P (EC 2.5.1.18) (GST class-pi) (GSTP1-1)
RARB	Retinoic acid receptor beta (RAR-beta) (RAR-epsilon) (HBV-activated protein)
TIMP3	Metalloproteinase inhibitor 3 precursor (TIMP-3) (Tissue inhibitor of metalloproteinases 3) (Protein MIG-5)
ESR1	Estrogen receptor (ER) (Estradiol receptor) (ER-alpha)
PTGS2	Prostaglandin G/H synthase 2 precursor (EC 1.14.99.1) (Cyclooxygenase- 2) (COX-2) (Prostaglandin-endoperoxide synthase 2) (Prostaglandin H2 synthase 2) (PGH synthase 2) (PGHS-2) (PHS II)
THBS1	Thrombospondin-1 precursor

CDH13	Cadherin-13 precursor (Truncated-cadherin) (T-cadherin) (T-cad) (Heart-cadherin) (H-cadherin) (P105)
HIC1	Hyper methylated in cancer 1 protein (Hic-1) (Zinc finger and BTB domain-containing protein 29)
RB1	Retinoblastoma-associated protein (PP110) (P105-RB) (RB)

Table 3: Genes related to prostate cancer with methylation and its summary Pubmeth.

(Table 4) Has shown that ESR1 is showing characteristic relationship with prostate cancer.

Gene	Number of references	Number of references in prostate cancer	Number of samples	Methylation frequency	Details for methylation in prostate cancer
CDKN2A	205	7	482	35	no subtype specified (4); carcinoma (2); adenocarcinoma (1)
RASSF1	125	7	584	60	no subtype specified (6); adenocarcinoma (1)
MGMT	86	1	32	25	adenocarcinoma (1)
CDH1	81	2	125	32	no subtype specified (2)
DAPK1	68	2	182	22	no subtype specified (2)
APC	65	5	506	70	no subtype specified (3)
RARB	48	6	469	50	no subtype specified (4) adenocarcinoma (1) carcinoma (1)
TIMP3	34	2	161	16	no subtype specified (2)
ESR1	24	1	38	95	no subtype specified (1)
PTGS2	20	3	305	45	no subtype specified (2) adenocarcinoma (1)
THBS1	19	1	179	25	adenocarcinoma (1)
CDH13	17	2	280	46	adenocarcinoma (1) no subtype specified (1)
HIC1	17	1	0	0	no subtype specified (1)
RB1	15	1	32	6	adenocarcinoma (1)

Table 4: Methylated frequency and details of prostate cancer genes using Pubmeth.

(Table 5) Has shown that Methylation frequency is higher in genes like CDKN2A, RASSF1, CDH1, DAPK1, APC, RARB, TIMP3, ESR1, PTGS2, CDH13, HIC1, MGMT, THBS1, CDH13 and RB1.

S.No	Related Disease	**Top Affiliating Genes** (text searches by Pubmeth)
1	No subtype specified	CDKN2A, RASSF1, CDH1, DAPK1, APC, RARB, TIMP3, ESR1, PTGS2, CDH13, HIC1
2	carcinoma	CDKN2A, RARB
3	adenocarcinoma	CDKN2A, RASSF1, MGMT¸ RARB, PTGS2, THBS1, CDH13, RB1

Table 5: Diseases related to Prostate Cancer.

(Figure 2) Have shown that ESR1 is related to several diseases related to prostate cancer.

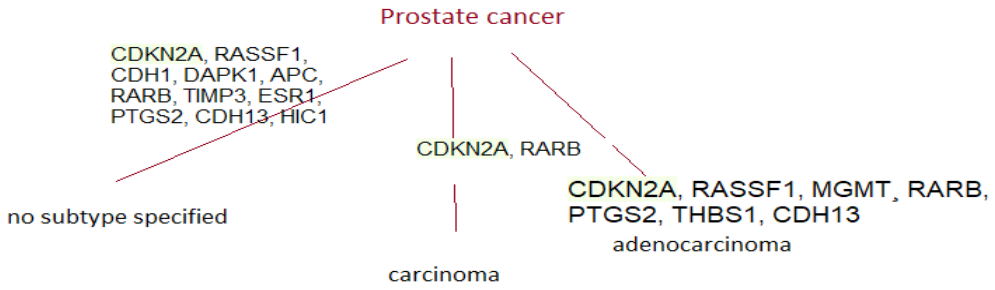

Figure 2: Graphical network of the top 3 diseases related to prostate Cancer.

(Figure 3) Shows superimposition of HPV16 genes like E6, E7 and human gene like ESR1 that relates to prostate cancer is showing structural similarities.

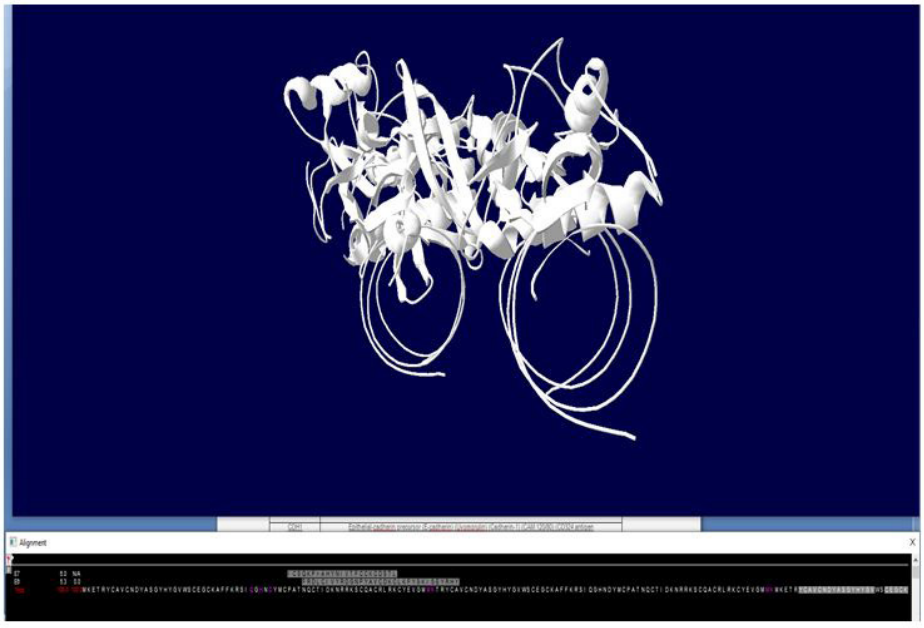

Figure 3: Magic fit analysis from SPDBV showing superimposition.

(Figure 4) Has shown that ESR1 is related to several other cancer causing genes like CDKN2A, RASSF1, CDH1, DAPK1, APC, RARB, TIMP3, ESR1, PTGS2, CDH13, HIC1, MGMT¸ THBS1, CDH13 and RB1.

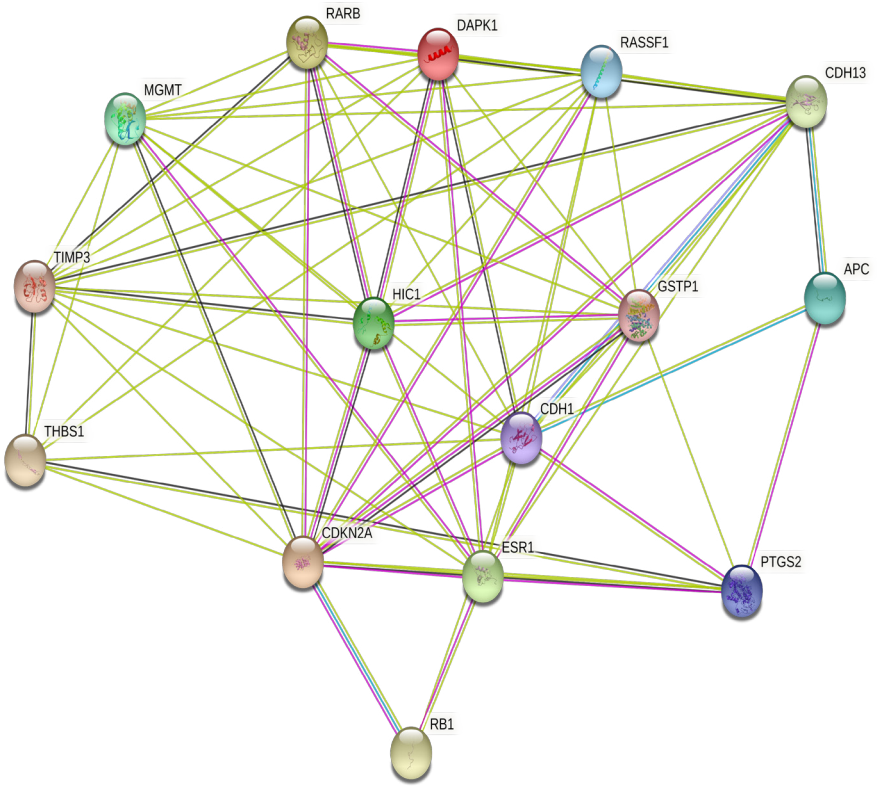

Figure 4: Protein-Protein interaction analysis.

The selected molecules like Erlotinib and Vinorelbine have shown good control on mutated E6, E7 of HPV16 and ESR1 proteins (Table 6, 7).

Drug	**Energy values in Kcal/mol**		
	E6 (HPV16)	**E7 (HPV16)**	**ESR1**
Erlotinib	-86.2318	-76.77	-84.23
Vinorelbine	**-112.89**	**-94.9**	**-109.47**

Table 6: Docking results of drug molecules with E6, E7 of HPV16 and ESR1 proteins**.**

Drug	Active site and docking poses		
	E6 (HPV16)	E7 (HPV16)	ESR1 (Human)
Erlotinib	H-S-ARG-63 H-M-MET-42 H-S-CYS-59 V-M-SER-58 V-S-SER-58 V-M-CYS-59 V-S-GLN-60 V-S-GLN-60	H-M-PHE-54 V-M-PHE-54 V-S-ASP-56 V-S-LEU-107 V-S-LYS-115 V-M-PRO-116 V-S-PRO-116 V-M-LEU-117	H-M-MET-42 H-M-ARG-56 H-M-SER-58 H-S-ARG-63 V-M-SER-58 V-S-SER-58 V-M-CYS-59 V-S-GLN-60 V-S-ARG-63
Vinorelbine	H-M-GLU-69 V-M-TYR-68 V-S-TYR-68 V-M-GLU-69 V-S-GLU-69 V-M-GLY-71 V-M-MET-72 V-M-MET-73 V-M-LYS-74 V-M-LYS-74	H-M-CYS-68 H-M-ARG-66 H-S-SER-95 V-S-ASN-53 V-M-ARG-66 V-S-ARG-66 V-M-LEU-67 V-M-PRO-92 V-S-PRO-92 V-M-PRO-92 V-S-PRO-92 V-S-SER-95 V-S-GLN-96	H-M-SER-34 H-S-ASN-39 H-M-TYR-41 V-M-SER-34 V-M-ILE-35 V-M-GLY-37 V-M-HIS-38 V-M-ASN-39 V-S-ASN-39 V-M-TYR-41 V-S-TYR-41 V-M-MET-42

Table 7: Active site and docking poses of drug molecules with E6, E7 of HPV16 and ESR1 proteins.

(Figure 5) Has shown control mechanism of prostate cancer via ESR1 gene.

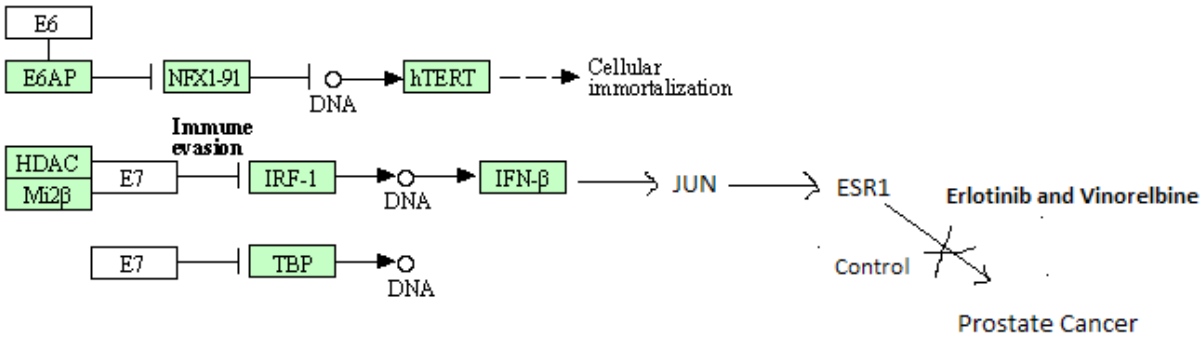

Figure 5: Control mechanism for Prostate cancer.

DNA methylation process is an epigenetic modifications present in mammals [11]. DNA methyl transferases are mainly responsible for the establishment and maintenance of the methylation pattern in the genome. DNA methylation is a reversible process that makes scientists interesting to study therapy approaches. The present study has shown that vinorelbine may be more active drug component compared to erlotinib with high-risk human papilloma virus that is linked with Epstein Barr virus in the regulation of prostate cancer.

Conclusion

Human papilloma virus 16 has shown 7 genes of which E6 and E7 are shown virulent based on previous literature. The present study has shown vinorelbine may be more active drug component compared to erlotinib and high-risk human papilloma virus linked with Epstein Barr virus in the regulation of prostate cancer.

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Conflicts of Interest: There is no known conflict of interest associated with the publication.

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