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In Silico DNA Methylation Epigenetic Studies and Molecular Therapy in Human Skin Carcinoma

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Abstract

Skin cancer appears are the most life-threatening disease among all types of cancers in the present decades, especially in white population, due to carcinogens, ageing and ultraviolet irradiation. The studies on altered DNA methylation are a very important epigenetic mechanism in understanding of development of skin cancer. The genes like CDKN2A, RASSF1, MGMT, CDH1, DAPK1, RARB and ESR1 are showing characteristic relationship with skin cancer based on Pubmeth database. RARB is shown relationship with several diseases like cutaneous melanoma and malignant melanoma in skin cancer with high DNA Methylation frequency. The tissue-specific pattern of mRNA expression from BioGPS is shown more for CDH1 and least for RASSF1. The selected genes are related to several other cancer causing genes like TP53. The selected molecules like Ensulizole, Curcumin and Beta carotene have shown control of mutated RARB protein causing skin diseases. The Curcumin has shown best in control of RARB protein. Hence Curcumin is the best option molecular therapy in control of skin cancer followed by Ensulizole and Beta carotene.

Keywords: Skin cancer; DNA methylation; Molecular therapy

Introduction

Epigenetic modifications play an important role in gene regulating and expression to study putative pathways and possible role in carcinogenesis [1]. Skin cancers are presently the most common types of cancer that is increasing at an alarming rate and has reached epidemic proportions around the globe [2,3].

The mortality rate melanoma is increasing in the present decades that occur due to intense and intermittent exposure in ultraviolet sun light [2]. The pathogenesis of skin cancers may be also due to complex genotypic, phenotypic, and environmental factors. DNA damage and genetic mutations causes immunosuppressant that leads to occurrence of skin carcinomas [4].

Carcinogens, ageing and Ultraviolet irradiation are the factors that induce epigenetic alterations that lead for the development of skin cancer [5,6]. Modifications of epigenetic molecular mechanisms within the cells through epigallocatechin-3-gallate (EGCG) may alter the cancer risk that can be controlled by dietary phytochemicals available in medicinal plants [7]. Methylguanine Methyl Transferase (MGMT), Mismatch Repair (MMR) and Base Excision Repair (BER).

Drug Bank database queried using TMZ (Temozolomide) with id DB00853 was depend on three DNA repair systems like Mismatch Repair (MMR), Methyl Guanine Methyl Transferase (MGMT) and Base Excision Repair (BER) that include gene networks like MRC1, MSH6,ATP9B, MSH3, EXO1, MLH1, TDG, PMS2, RAD1,MSH2, RAD9A, FEN1, NTHL1, HUS1, PARP1, PARP2, PARP3, PNKP, POLL, APEX1, USP47 and APEX2. The genes like CDKN2A,EGFR, PTEN, HRAS, KRAS, TP53 and CDH1 are highly involved in skin cancer according to Web Gestalt. The genes like CDH1, EGFR, CDKN2A, HRAS, PTEN, KRAS, and TP53 are responsible to skin cancer according to ClueGC. The present experimentation was conducted for involvement of the genes that are highly responsible for the development of skin cancers [8].

Epigenetic disorders like cancers play a major role that is highly characterized in epigenetic mechanism in DNA methylation. Reversible nature of DNA methylation aberrations can be controlled by cancer diagnosis, prognosis and therapy approaches that will hold effective interventions in the present decades [9].

Materials and Methods

Pubmeth

Pubmeth is a cancer methylation database (http://pubmeth.biobix.be/search.html) that is annotated and reviewed based on automated text mining of literature. The database includes

DNA methylated genes that are in several cancer types like skin cancer. The disease genes that are related to skin cancer have been analyzed using pub meth database.

Genecards

GeneCards (https://www.genecards.org/) is a web source that contains annotated and predicted human genes for the analysis of genetic, genomic, proteomic, transcriptomic, clinical and functional studies.

BioGPS

BioGPS (http://biogps.org/dataset/tag/skin/) provides information about tissue-specific pattern of mRNA expression of several cancer types.

String v11.0

STRING v11.0 (https://string-db.org/) is a database that is known to predicted protein-protein interactions based on physical and functional associations from databases. The query multiple proteins submitted are CDKN2A, RASSF1, MGMT, CDH1, DAPK1, RARB and ESR1.

Retrieval/ Design of ligands and proteins

Skin cancer related drugs are retrieved from Drug Bank (https://go.drugbank.com/structures/search/small_molecule_drugs/structure) (Table 1). The drugs like Ensulizole, Curcumin and Beta carotene were selected in the present study.

S. No	Name	Drug Bank Id
1	Ensulizole	DB11115
2	Curcumin	DB11672
3	Beta carotene	DB06755

Table 1: Selected Drugs for Skin Cancer (from Drug Bank).

The mutated protein of tumor suppressor gene RARB (PDB id: 1hra) is retrieved from PDB database (https://www.rcsb.org/)

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

Skin cancer is increasing with an alarming rate and pose major role in public health concern [4]. Most of the common types of cancer in white populations are related to skin cancers [10].

The information has been retrieved from Genecards (https://www.genecards.org/) (Table 2).

Methylated Gene	Name as on GeneCards	Entrez Gene Summary
CDKN2A	Cyclin Dependent Kinase Inhibitor 2A	Tumor suppressor gene.
RASSF1	Ras Association Domain Family Member 1	inhibit the accumulation of protein like cyclin D1, and thus induce cell cycle arrest
MGMT	O-6-Methylguanine-DNA Methyltransferase	Methylation of the genes promoter is associated with cancer types like colorectal cancer, lung cancer, lymphoma and glioblastoma.
CDH1	Cadherin 1	A mutation in the gene leads to gastric, breast, colorectal, thyroid and ovarian cancer.
DAPK1	Death Associated Protein Kinase 1	positive mediator of gamma-interferon induced programmed cell death; a tumor suppressor candidate
RARB	Retinoic Acid Receptor Beta	a hepatocellular carcinoma where it flanks a hepatitis B virus integration site
ESR1	Estrogen Receptor 1	Plays a key role in breast cancer, endometrial cancer, and osteoporosis.

Table 2: Genes related to Skin cancer (Above 20 references in Pubmeth with methylation) and its summary from Genecards.

Table 2 has shown that CDKN2A, RASSF1, MGMT, CDH1, DAPK1, RARB and ESR1 are showing characteristic relationship with skin cancer.

Gene	Number of references	Number of references in skin cancer	Number of samples	Methylation frequency	Details for DNA methylation In Skin cancer
CDKN2A	205	3	65	11	squamous cell carcinoma (2); melanoma (1)
RASSF1	125	2	64	36	squamous cell carcinoma (1); malignant melanoma (1)
MGMT	86	4	146	25	malignant melanoma (2); cutaneous melanoma (1); squamous cell carcinoma (1); melanoma (1)
CDH1	81	2	42	14	squamous cell carcinoma (2); invasive (1)
DAPK1	68	1	9	22	melanoma (1)
RARB	48	3	133	61	malignant melanoma (3); cutaneous melanoma (1)
ESR1	24	1	107	51	melanoma (1)

Table 3: Methylated frequency and details in skin cancer genes using Pubmeth.

Table 3 has shown that DNA Methylation frequency above 50 is shown for CDKN2A, RASSF1, MGMT, CDH1, DAPK1, RARB and ESR1.

S. No	Related Disease	Top Affiliating Genes (text searches by Pubmeth)
1	Squamous cell carcinoma	CDKN2A, RASSF1, MGMT, CDH1
2	Melanoma	CDKN2A, MGMT, DAPK1, ESR1
3	Malignant melanoma	RASSF1, MGMT, RARB
4	Cutaneous melanoma	MGMT, RARB
5	Invasive	CDH1

Table 4: Diseases related to Skin Cancer.

Table 4 and Figure 1 have shown that RARB is related to several diseases related to Cutaneous melanoma and Malignant melanoma in skin cancer with high DNA Methylation frequency.

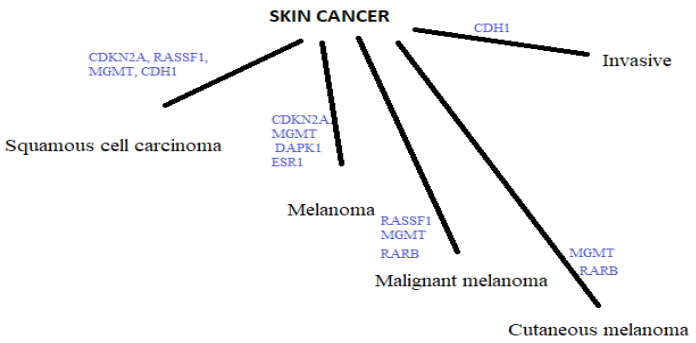

Figure 1: Graphical network of the top 5 diseases related to Skin Cancer.

Gene	Tissue-specific pattern of mRNA expression from GeneAtlas U133A, gcrma
CDKN2A	22.9
RASSF1	2.5
MGMT	7.90
CDH1	69.35
DAPK1	7.4
RARB	4.7
ESR1	3.1

Table 5: DNA Methylated frequency and details in skin cancer genes using BioGPS.

Table 5 has shown that tissue-specific pattern of mRNA expression from BioGPS is more for CDH1 and least for RASSF1. The data provided that all the genes have mechanisms of same genes generating differentiated phenotypes in the tissues and provide important information about gene function.

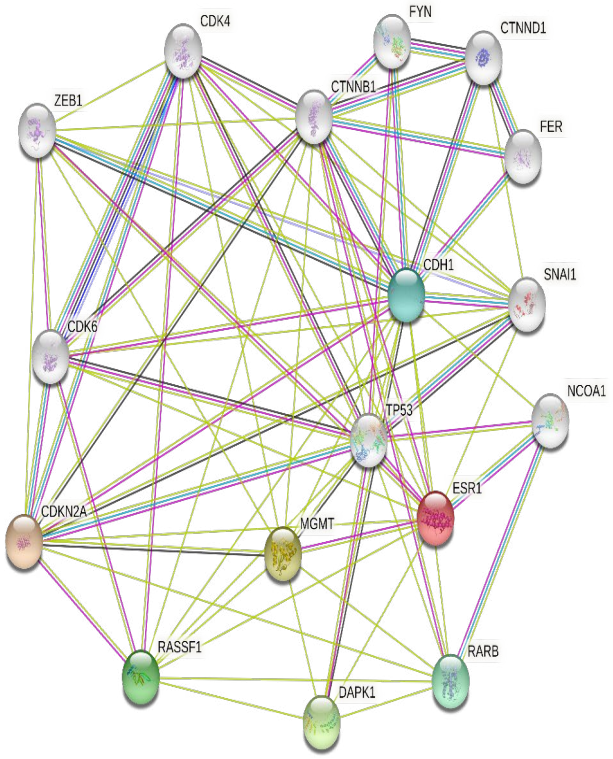

Figure 2: Protein-Protein interaction analysis fir skin cancer.

Figure 2 has shown that all the selected genes are related to several other cancer causing genes like TP53.

As DNA methylation frequency is shown more for RARB (PDB id: 1hra), docking studies for screening of better molecule in the selected has been analyzed for the molecular therapy.

S.No	Name of Drug	RARB	
		Total energy in Kcal/mol	Active site
1	Ensulizole	-76.02	E-S-ARG-34;H-S-ARG-34;H-M-HIS-45;H-M-ARG-59;V-M-HIS-45;V-S-ARG-46;V-M-CYS-60
2	Curcumin	-82.15	H-S-TYR-5;H-S-ASP-13;H-M-SER-15;H-S-ARG-57;V-S-MET-1;V-S-TYR-5;V-M-ASP-13;V-M-LYS-14;V-S-LYS-14;V-M-SER-15;V-M-LYS-54;V-M-VAL-55;V-S-ARG-57
3	Beta carotene	-73.11	V-M-MET-40;V-M-ILE-41;V-S-ILE-41;V-S-ARG-57;V-S-ARG-59;V-M-CYS-60;V-S-GLN-61

Table 6: Activity of drugs against CDH1 gene as molecular therapy for Skin cancer.

The selected molecules like Ensulizole, Curcumin and Beta carotene have shown control of mutated RARB protein. The Curcumin has shown best in control of RARB protein. Hence Curcumin is the best option molecular therapy in control of skin cancer followed by Ensulizole and Beta carotene (Table 6). Figure 3 has shown the docking poses and active site of drugs against RARB proteins respectively.

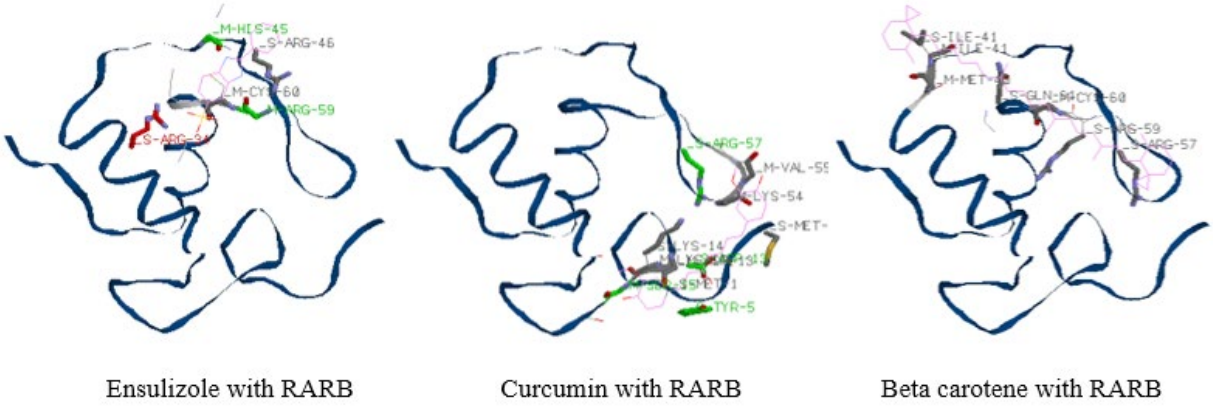

Figure 3: Docking of selected drug molecules with RARB protein.

In the present decades, due to climatic and metabolic changes in humans, skin cancer appears are most life-threatening disease among all types of cancers. Most of the possibility for skin cancers may be due to upregulating RARB gene [1-14]. β-Carotene is one of the form of carotenoids that can treat ultraviolet-induced skin cancer [1]. Skin cancers like melanoma or squamous cell carcinoma can be controlled by ensulizole or 2-Phenylbenzimidazole-5-sulfonic acid [11]. Curcumin was shown effective with aggressive skin cancer cell line SRB12-p9 [13]. Based on the screening studies, Curcumin has shown better activity against skin cancer.

Conclusion

Skin cancer appears are most life-threatening disease among all types of cancers in the present decades due to carcinogens, ageing and ultraviolet irradiation. Based on the present studies Curcumin has shown better activity against RARB related to skin cancer.

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