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An Updated Review on Mechanism of Action Involved in Skin Carcinoma and Its Associations with Endogenous Risk Factors

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ABSTRACT

Background: Skin protects the inner organs from injuries and infections. The various structural parts of the skin are the epidermis, the dermis and the skin appendages. Multiple group Skin cancer benign and uncontrollable abnormal growth of cells. Outcome of extracutaneous and cutaneous cells. Cases of skin cancer increased, so it has led to finding its procedure of tumor development by their mechanism and their prevention techniques. **Aim:** The aim of this article is to review an updated mechanism of action which involved in Skin Carcinoma and associations of their endogenous risk factors. **Method:** The selection of data was done by studying combination of review and research papers and those with relevant data were taken into account and those with irrelevant data were excluded from a different databases such as PubMed, NCBI and Web of Science from the year 1985-2020. **Result:** There is a clear association between mechanism of action involved in Skin Carcinoma and associations of endogenous risk factors. **Conclusion:** This brief review about the mechanisms of formation and progression of Skin carcinoma by UV radiation which causes DNA damage and mutations, Loss of cell cycle control and carcinogenesis by mutation, Glycosyltransferases related to skin cancer, Target proteins of N-glycosylation involved in skin cancer, Integrins, CD147, Melanocortin 1 receptor (MC1R), PD-1, EGFR.

INTRODUCTION

The external most barrier of body is the skin. Also, the first protective layer, which is between the atmosphere and our inner body. Skin protects the inner organs from injuries and infections. It contains nerves, which help in sensing the environment [1]. There are two main organizational parts of the derma known as epidermis and dermis. Epidermis is more dermis than the dermis, it is majorly a collection of keratinocytes which helps in terminal differentiation and also in the production of stratum corneum. Epidermis contains melanocytes which is a group of dendritic cells which is found in the basal layer of the epidermis. Second dendritic cells are found majorly in the mid epidermis region. The basal layer of epidermis is surrounded by and consists Merkel cell and keratinocytes. Squamous cell carcinoma is caused in the keratinocytes whereas basal cell carcinoma occurs in the epidermis, and melanoma is caused in the melanocytes and Merkel cell carcinoma occurs in the Merkel cells [2].

Melanoma is a lot frequent in white people. Mostly the risk of occurrence of melanoma is more in Caucasians (2.4%) other than other races [3].

Epidemiological data from Europe [4-7], Canada [8] and the United States [9-11] indicates an uninterrupted and startling fact that there is a sudden rise in the number of patients in the previous few decades. The most patients are from New Zealand then from Australia and followed by the United States of America and then from Europe [12-14]. The progression of melanoma and non-melanoma cancer has increased in past decades. The current scenario of skin cancer is that every three cancer which is diagnosed one of them is skin cancer and one in every five Americans they would have skin cancer [15].

The frequency of SCC and BCC are 18-20 times more than that of melanoma [16]. The progressive potential and death rate of BCC and SCC are less [17-19]. Although it's relatively low malignancy, but the death rate caused by NMSC is far more and with considerable high cost [20,21].

Climatic factors like ozone depletion, exposure to sun and chemicals whereas host factors like genes, colour of skin, HPV and immunity depression [22-24] workers which are working under the sun may be more prone as they get UV exposure more. UV exposure during the vacations and holidays come under the chronic exposure of UV light [25, 26].

Skin cancer is a multiple group of benign and malignant abnormal growth of cells, which are an outcome of both extracutaneous and cutaneous cells [27]**.** The commonest kind of carcinoma human beings is skin carcinoma, the high number of cases has led to finding its procedure of tumour development and their prevention techniques [28]**.** The prevalence of skin cancer is more than all the cancers collectively [29]. The patients of skin cancer are rising day by day, the numbers are increasing by each passing year and the harm is increasing gradually [30]. The best method to stop skin cancer is in its early diagnosis and working on its prevention [31].

Skin cancer is segregated into melanomatous and non-melanomatous cancer, melanoma is caused by the pigmented cells of the skin whereas non melanoma is caused by the tumours of the epithelial cells such as squamous cell carcinoma and basal cell carcinoma [32].

MATERIALS AND METHODS

A literary search was made on different databases like PubMed and Medline by using keywords like "Skin carcinoma", "types of skin carcinoma", "causes of skin carcinoma", "mechanisms skin carcinoma", "melanoma", "non melanoma skin carcinoma". A combination of different review and research papers were searched and those with relevant data were taken into account and those with irrelevant data were excluded. The selection of data was done from year 1999-2020.

Types of skin carcinomas:

Basal cell carcinomas (BCC) originates from the epidermis and it is the most common type of malignancy occurring in cutaneous region of the face. The epidermis has a basal layer in which malignancy of neoplasm of keratinocytes occurs which in other terms is known as BCC. Some studies show that malignant cells are originated from the outer root cover of the hair follicle and the pluripotent cells of the interfollicular epidermis. A connection between the origination of BCC and ultraviolet rays exists because it has been noted that the patients suffering from BCC have previous exposure to sunrays and type of sunrays and ultraviolet rays have a link to higher chances of causing BCC [33].

Squamous cell carcinoma (SCC) originates from the epidermal keratinocytes. It is a result of high exposure of the sun rays. The progression of SCC is directly proportional to the cumulative lifetime exposure of radiation from the sun rays [34].

Melanoma involves the skin but can also start from the eye, meninges and on different mucosal layer. It can be amelanotic and is pigmented excessively. The tiniest of tumours can spread and cause adverse prospects. It causes more than 90% deaths [35-42] [Figure 1].

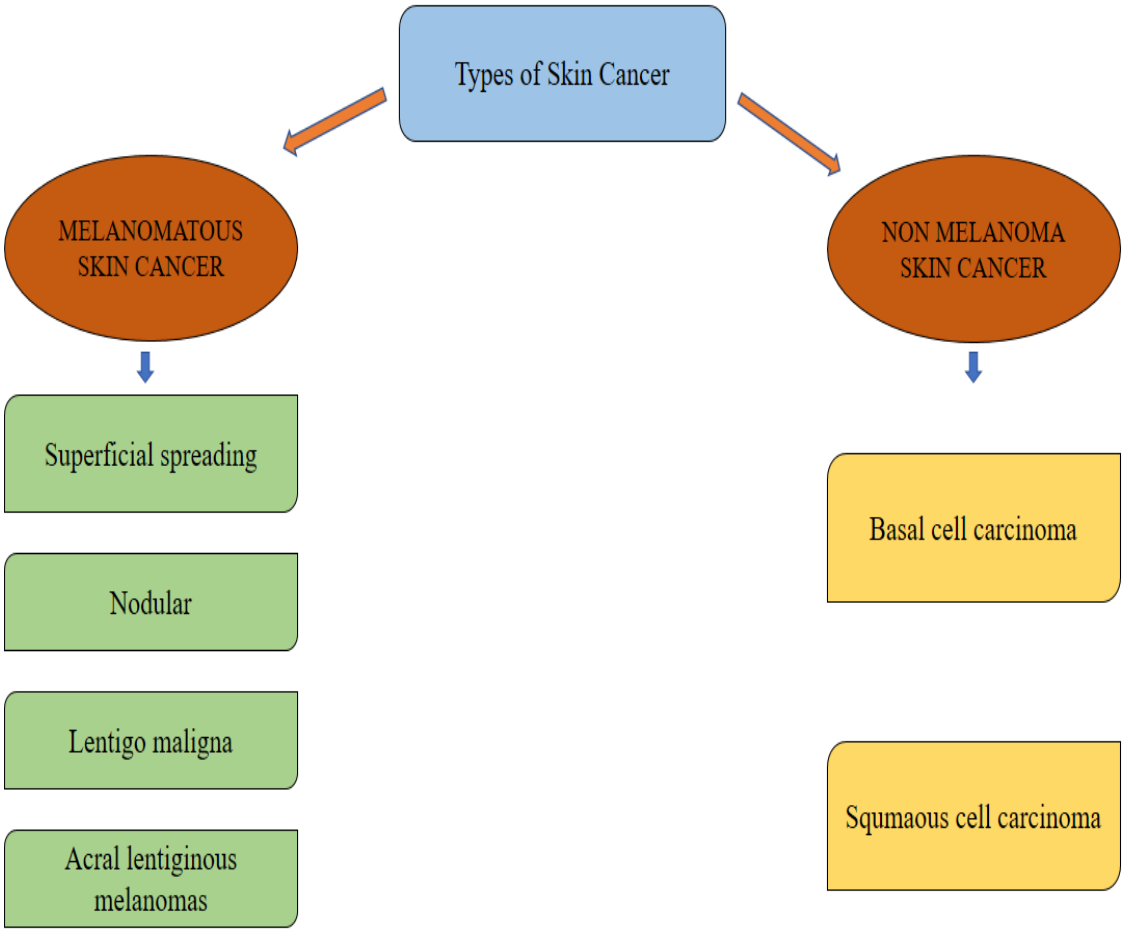

Figure No. 1: Classification on types of skin carcinoma [35-42]

Mechanisms involved in the formation and progression of Skin carcinoma:

Mutation and DNA damage generation by ultraviolet rays

Maximum range of ultraviolet rays which are taken by the DNA is 245-290 nm [43]. A significant biomarker the p53 gene has a distinct pattern in ultraviolet rays causing skin cancer. The risk of melanoma, BCC and SCC increases in the people who have more exposure to the sun rays [44,45]. UV rays create lesions & mutagenic photoproducts in the DNA and forms dimers of the adjacent pyrimidines of DNA. Basically 2 types of dimers are present: first dimer of cyclobutene which is between adjoining thymine and cytosine, and

second dimer is pyrimidine-primidone photoproducts between adjoining pyrimidine residues [46-49]. Hotspots of ultraviolet induced mutation are lesions occurring in the tandem of pyrimidine residues [50]. Additionally, the dimers of pyrimidine can stop the transcription elongation which is on the transcribed strand, and on the transcribed sequences, specifically active genes are mended very fast and the promoter sequences are mended slowly [51,53]. Pyrimidine mono adducts, an adjoining A-T photoproduct and dimers of purine are present in the lesions. These lesions have mutation generation potential or not this is not very clear. Mutations can occur permanently in the DNA sequence if the ultraviolet induced DNA lesions are not cured. The mutation occurring due to the DNA lesions is in the structure of CT and CCTT conversions and is called UV signature mutation. Various type of base modifications, insertion and deletion can surface due to the lesions. To elucidate the kind of mutation caused by the ultraviolet rays the "A rule" was suggested. According to this rule where there was no right base or bases, a residue A was designated by the DNA polymerase. Then DNA replication is done on the strands which have different sets of base pair and mutation is generated. No mutation could occur because of T-T cyclobutene dimers; because A is paired with T, so there is no mutational outcome by insertion of A residues as default adjacent to the dimer. A transition of CCTT occurs in the dimer of C-C cyclobutene; in the places of two G residues in the dimer two, A residues are placed by default. The 5-prime residue base pairs perfectly but the 3-prime C residue is like a non-instructional site in the photoproducts of a pyrimidine and a C residue. A CT mutation is generated due to the placement of A residue along the C residue as a default [54] [Figure 2].

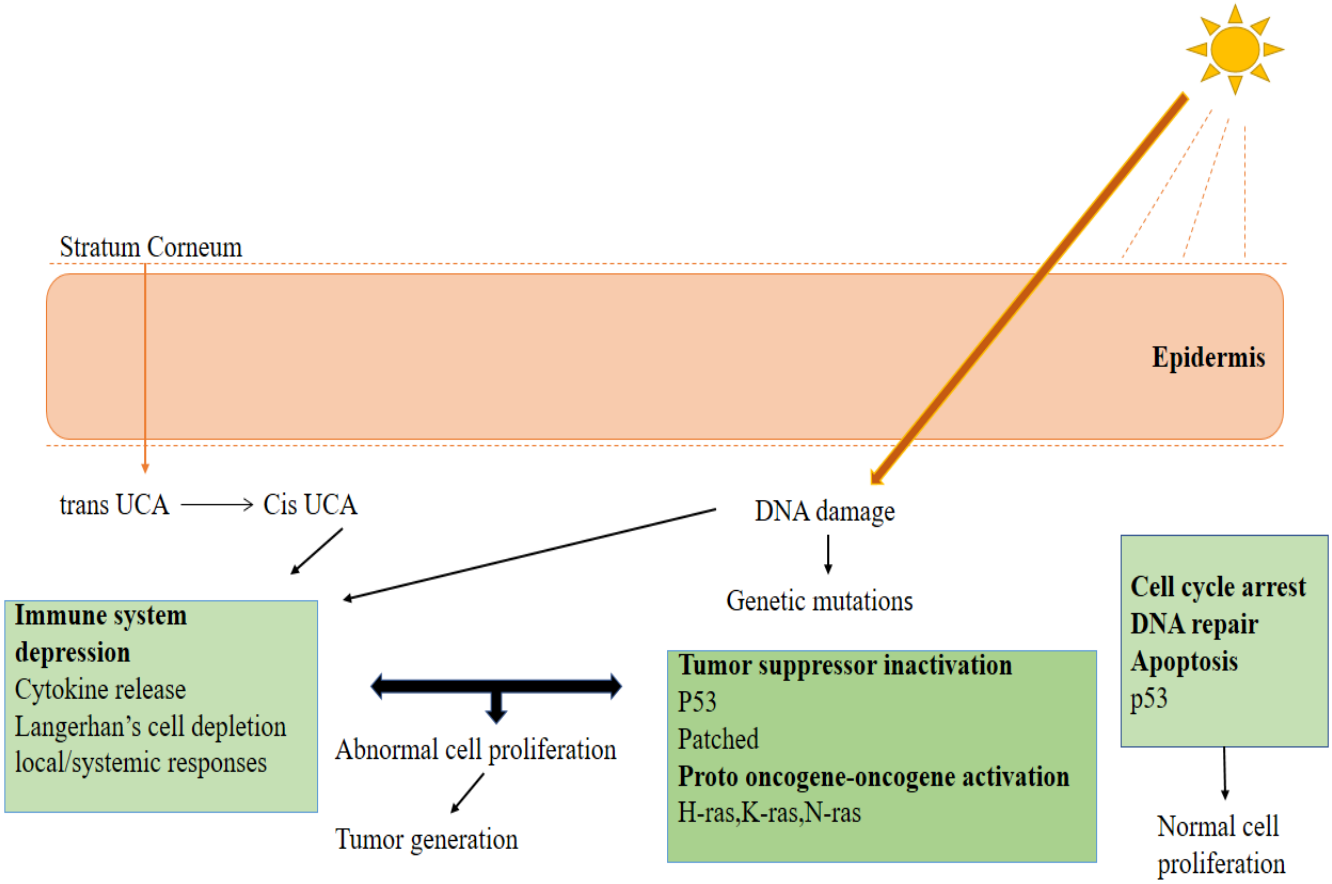

Figure No. 2: Mechanism of action when Skin is exposed to UV light [54]

Reduction in the control of cell cycle and mutation: the cause of cancer generation

UV rays are completely carcinogenic, it can initiate as well as promote cancer formation. DNA polymerase incorporation error, depurination, deamination of 5-methyl cytosine or oxidative damage from free radicals is caused by mutation in DNA which is mainly promoted by ultraviolet radiation [46]. In previous studies in which mice were irradiated with a mix of ultraviolet-A and ultraviolet-B it was found that ultraviolet-A was not alone effective in causing cancer but it enhances the carcinogenesis effect of ultraviolet-B [55,56]. The activity of ultraviolet-B was enhanced when the mice were irradiated with ultraviolet-A after several months of exposure of ultraviolet-B at the starting [57,58]. In further studies, it was found that the ultraviolet-B exposed epidermal cells of mice have more effect on the cell cycle than the ultraviolet-A [59], and indicating dissimilarities in cancer genesis efficiency among ultraviolet-A and ultraviolet-B. Genomic DNA which are mutated can cause cancer by the transformation in the activity of genes which effect cell growth. The stages involved in cancer origination are initiation, promotion and progression. Mutation can be the starting

phenomenon. Mutation can be dormant for a long time till the exposure of promoter. Those promoters could or could not be a cancer generating agent but can help in the starting of progression of tumour formation. Numerous mutations in the different loci of genes when united can affect cancer development. Three to seven events of mutation can change a normal healthy cell into carcer cells according to their life cycle. The main changing mutation is in the tumour suppression genes or the onco-genes which are comprised in the regulation of cell proliferation [50].

Connection of glycosyltransferases to skin carcinoma

It has a crucial part in the alteration of glycans via shifting of different sugar chains to proteins during the biosynthesis of N-glycans. During the formation of N-glycans *N*-acetylglucosaminyltransferase V (GNT-V), *N*-acetylglucosaminyltransferase III (GNT-III), sialyltransferase (ST6GAL1), and α1,6- fucosyltransferase (FUT8) are very important. Abnormal presence of these glycosyltransferases was present in the gastric and small cell lung carcinoma [60-62]. The interaction of different glycosyltransferases leads to differential phenotypes [63]. The details of various glycosyltransferases are explained bellow:

GNT-III - It activates the transference of GlcNAc to the β-mannose residue by the β1,4-coupling and form the cleaved GlcNAc structure [64]. It is abnormally regulated in cancerous cells which includes ovarian cancer and leukaemia [65-66].

GNT‑ V- It helps in the catalysation of the transfer of GlcNAc from UDP-GlcNAc to the 6-OH position of α-Man residue in the α6 arm of core. It was previously found that GNT-V gets activated in the tumour cells and is managed by the RAS-RAF-MAPK [67].

STLGAL1 -Various number of cell lines of melanoma were studied and in those β1,6-branched glycans were found, however glycans having α-2,6 and α-2,3-linked sialic were also present in the melanoma cells [68]. The presence of sialyltransferases were assessed in actinic keratosis, keratoacanthoma, squamous and basal cell cancer. The researchers also observed an excess level of ST3Gal 1 and ST6Gal 1 which are known to be having potential for causing invasion and metastasis [69]. In other studies, it was found that the excision of α2,6 sialic acid by enzymatic de-sialylation or by stably lowering the ST6Gal-1 via shRNA lowers the capability of adhesion and invasion [70].

FUT‑ 8 - Is the specific enzyme which is found to produce 1,6-fucosylated structure which is present on the core of N-glycans belonging to the member of fucosyl transferases, coded by

FUT-8. FUT-8 catalyses the transference of fucose to the N-linked type complex glycopeptides, FUT-8 mediated receptor core fucosylation was found to be activating breast cell invasion and metastasis by encouraging TGF-β-induced epithelial mesenchymal conversion [71].

Ideal proteins of N linked glycosylation which are involved in skin carcinoma

N-glycosylation is the most crucial type of post transcriptional modification, it is irrefutable that different types of protein glycosylation has a vital part in different cellular activities, including protein folding, stability and sorting, protein -protein interaction, etc. More than 700 proteins require multiple glycan structures which includes glycosyltransferases, glycosides and nucleotide sugar transporters [72].

Integrins

It is a widely present trans-membranous hetero-dimeric receptor which is present on different cells who has an 18 α subunit and one of the 8 β-subunits. Its function is connected to the cell-extracellular matrix adhesion. Integrins is a connecting link to hold together the extracellular ligand to the intracellular receptor and stimulate the intracellular signals which accomplish different functions including growth of cell, cell differentiation and existence by picking a sequence of effector molecules like talin, paxillin, ILK, FAK and other GTPases [73]. Cancer development is by the glycosylation of integrins by its heterodimerization, ligand binding, complex formation with other different membranous proteins [74-76] [Figure 3].

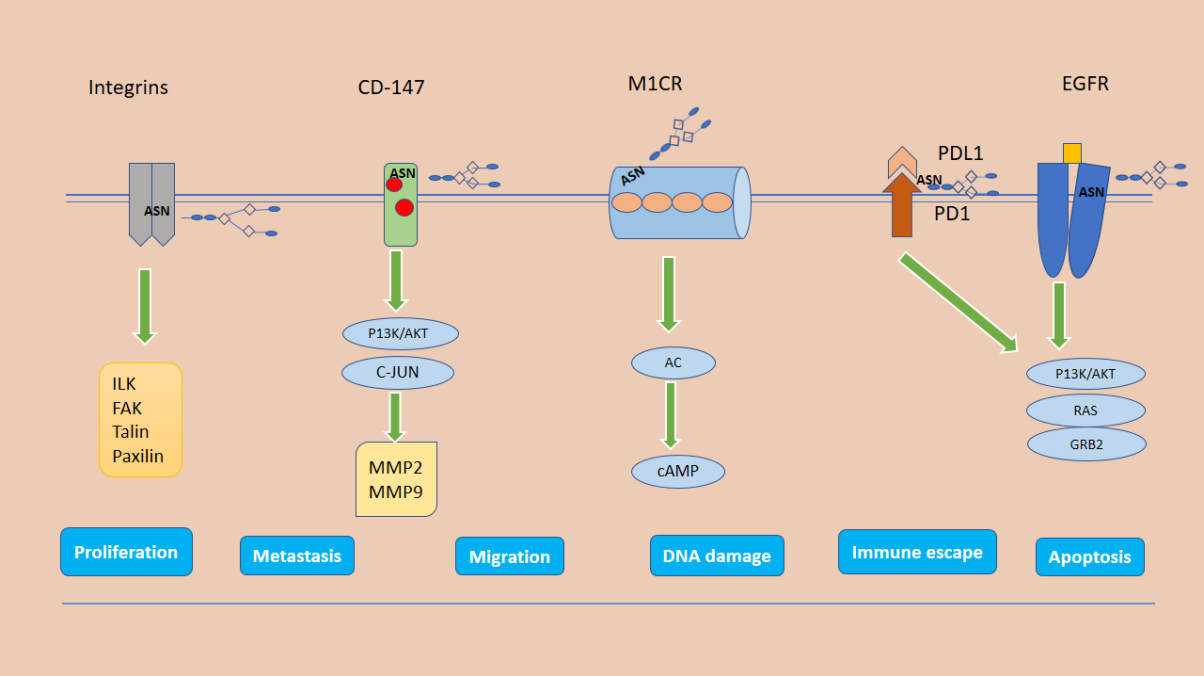

Figure No. 3: Role of Integrins, CD-147, M1CR and EGFR in inducing skin carcinoma [90]

Basigin or CD147

It is a type 1 of trans-membranous glycoprotein of immunoglobulin superfamily called human extracellular matrix metalloproteinase inducer, hBasigin, M6, HAb18G and basigin-1. It is present in tissues and cells like platelets which help in development processes, wound healing, and nutrient transport in the body [77]. CD147 helps in development of melanoma and other carcinomas [78]. It also helps in adhesion of cell matrix by regulation of focal adhesion kinase pathway [79], it inhibits the increasing cellular ROS and also disrupts the intrinsic antioxidant defences in A375 [80]. It being a matrix metalloproteinase inducer boosts the malignant phenotype by hypoxia induced MMP2 initiation [81], and the cleaved CD147 discharged by surface of malignant melanoma cells activates MMP2 which was made by the fibroblasts [82] [Figure 3].

Melanocortin 1 receptor

It is a trans-membranous g protein coupled receptor by which the melanogenesis is regulated and it also has a very significant action in the development, proliferation, and differentiation of melanocytes [83]. The major role of MC1R is stimulation of the adenylate cyclase and hence enhancing the action of tyrosinase enzyme by stimulation of signalling pathway cAMP, which is also found that is the rate restricting step in the production of melanin [84].

The people with MC1R has more risk of melanomas than the wild type of people or subjects whom have a noticeable prospect of clinical diagnostic value [85]. The expression of MC1R shows a higher likelihood of causing melanoma than the normal tissues [86] [Figure 3].

Programmed cell death-1 protein

It is a transmembrane receptor which has 288 amino acid and it has 3 parts namely global extracellular domain, transmembrane domain, and intracellular domain. There is ITIM present in the intracellular domain and in the cytoplasmic end it has ITSM. when the PD-1 on the cell membrane binds with the PD-L1 ligand, SHP-1 and SHP-2 are two phosphates which attach to the ITIM and ITSM respectively and in turn inhibits the activation of T cells. In different tumour tissues and cells PD-1 and PD-L1 is found [87]. The modulation of PD-1 and PD-L1 can produce the suppression of immunity in the surroundings of the tumour, which has been found in different data an important mechanism for tumour immune escape [88,89].

Epidermal growth factor receptor

EGFR is a type of transmembrane which has different functions in physiological and pathological actions like proliferation, differentiation,etc. EGF is a ligand which stimulates the tyrosine kinase receptor. A homo or heterodimer is produced by EGFR when it is autophosphorylated with its family and the subsequent intracellular signal molecules are stimulated which shows all the different physiological functions and then the EGFR gets incorporated into the endosomes. In a lot of human carcinomas including skin carcinoma, it has been seen that EGFR is present and shows its action [90] [figure 3].

DISCUSSION

People diagnosed with skin cancer represents about 40-50% of all the cancers in US. About 4% of these are of melanomas, but they are the cause of equal to half of the deaths caused by skin cancer. In immunotherapy (pembrolizumab) and targeted therapy (vemurafenib) for melanoma the recent progress is made in survival of the patients and some patients fail to show response of those therapy [91]. most number of cases of cutaneous malignant melanoma are due to the harmful ultraviolet rays coming from sunlight. Mainly there are two types of ultraviolet radiations which cause melanoma namely UV-A and UV-B [92]. Main mechanism of skin carcinoma is Oxidative modification of DNA. UVA-induced oxidative damage diminished repair by Melanocytes which as melanin and acts as photosensitizer. ROS

levels increased by Dysplastic nevi which relative to normal melanocytes by supporting a ROS accumulation role in melanoma genesis. The melanoma aetiology involved by its multifactorial which effects on genetic factors as well as familial melanoma, fair skin, xeroderma pigmentosum and atmospheric factors like ultraviolet radiations in sun rays which contribute in their foundation and evolutions [93]. Other factors which are not related to sunrays are occupational vulnerability like usage of those chemicals which can cause or can help in causing melanoma, people working in places where they come in constant contact with radiations like ultraviolet, x-ray, gamma rays etc may interact with the genetic [94]. Multiple inflammation regulatory pathways involve in Melanoma-associated. Immunity also is involved [95].

CONCLUSION

This brief review about the mechanisms of formation and progression of Skin carcinoma by UV radiation which causes DNA damage and mutations, Loss of cell cycle control and carcinogenesis by mutation, Glycosyltransferases related to skin cancer, ideal proteins of N linked glycosylation which are involved in skin carcinoma, Integrins, CD147, Melanocortin 1 receptor (MC1R), PD‑ 1, EGFR. Melanoma is very common in white people than in other ethnic groups. This knowledge about such mechanism which is significance for a new melanoma molecular classification, this is importance for superior prognosing the outcomes, permits in the development of new target molecular therapy for Skin Carcinoma.

Future prospects: Future researches must be involved in studying genetic roles and mutation of genes which alter the metabolism and instigate skin carcinoma in humans.

ABBREVIATIONS:

SCC	squamous cell carcinoma
BCC	basal cell carcinoma
NMSC	non melanoma squamous cell carcinoma
HPV	human papillomavirus
UVA	longwave ultraviolet A
UVB	shortwave ultraviolet B

GNT-V	*N*-acetylglucosaminyltransferase V
GNT-III	*N*-acetylglucosaminyltransferase III
ST6GAL1	sialyltransferase
FUT8	α1,6- fucosyltransferase
ILK	integrin linked kinase
FAK	focal adhesion kinase
CD147	cluster of differentiation 147 or basigin
ROS	reactive oxygen species
MMP2	matrix metalloproteinase-2
MC1R	melanocortin 1 receptor
PD1	programmed cell death protein 1
ITIM	immune receptor tyrosine-based inhibitory motif
ITSM	immune receptor tyrosine-based switch motif
SHP1	protein tyrosine phosphatase 1
SHP2	protein tyrosine phosphatase 2
EGFR	Epidermal growth factor receptor
P13K	phosphoinositide 3-kinase
GRB2	growth factor receptor bound protein 2
RAF	rapidly accelerated fibrosarcoma
MAPK	mitogen activated protein kinase

CONFLICT OF INTREST

The author expresses no conflict of interest.

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