Skin Cancer Rodents Models: A Review

Introduction:

Melanoma and non-melanoma skin cancer are the most common type of malignancy in the Caucasian population (1-10). The incidence of both MM and NMSC is on the rise ,with an annual increase in MM of 0.6% among adults over 50 years (11). The incidence of melanoma may be even higher than indicated, as the national cancer registries has reported an underestimation of its incidence in certain countries. Consistent epidemiologic and experimental studies have demonstrated that UV-emitting tanning devices cause melanoma and non-melanoma skin cancer. Non-melanoma skin cancer occurs in all races worldwide, and the most important factor related to the development of these malignancies is skin type. However, other risk factors include UV-B exposure(2), chemical exposure, tanning bed use, human papillomavirus (HPV) infection, immunosuppression, and others. In individuals with fair skin, approximately 75% to 80% of non-melanoma skin cancers are basal cell carcinomas, and up to 25% are squamous cell carcinomas. Heritable defects in DNA repair mechanisms, as seen in xeroderma pigmentosum and Muir-Torre Syndrome, also make afflicted individuals at high risk for cutaneous ‘carcinomas. In India, skin cancers constitute about 1-2% of all the diagnosed cancer (4).

Methodology

The current data was extracted from highly reputed journals on PMC, Pubmed, Scopus
Comment by MAZHAR: Eg total 230 articles and skin cancer, keywords were used, specific
Comment by MAZHAR: Science direct, Wiley online

1.1 Pathophysiology

(Angiogenesis Increased VEGF AND iNOS) Intermittent, recreational sun exposure, more so than cumulative UV radiation is a significant risk factor for the development of basal cell carcinoma. The gene most often altered in basal cell carcinoma is the PTCH gene and the second most common alteration is point mutations in the p53 gene. Unlike the complex relationship between basal cell carcinoma and UV radiation, squamous cell carcinoma is related to the cumulative lifetime dose of UV radiation. Current opinion favors clonal expansion of keratinocytes with a p53 mutation causing precancerous actinic keratosis lesions with slight dysplasia which precede further severe dysplasia and transformation into invasive squamous cell carcinoma.

Molecular pathophysiology

(Inflammation Increased COX-2, PCNA, PGs, MPO Increased CPX 2 and Pgs, Mpo,)

(Immunosuppression Increased IL 10,IL 6 and 12 decreased)

(Skin cancer)

(Skin carcinogen Increased DNA adduct, ros, lipid peroxidation)

(Unregulated proliferation)

(apoptosis)

(DNA damage NER decreased and chromosomal aberration increased)

Extrinsic pathway intrinsic pathway

Inflammation or infection oncogenic activation

(Transcription factors (NF-??, STAT3) activated in tumor cells)

(Chemokines, cytokines, prostaglandins, and COX-2 produced by tumor cells)

(Inflammatory cells recruited)

Mast cell eosinophil neutrophil (Transcription factors (NF-??, STAT3) activated in tumor cells, stromal

cells and inflammatory cells, stromal cells, and inflammatory ells)

(Chemokines, cytokines, prostaglandins and COX-2 produced)

Current status

Treatment of precancerous lesions and cutaneous carcinoma should be tailored toward the individual patient scenario and the best clinical outcome. If presenting as isolated lesions, precancerous actinic keratoses can be treated individually with lesion-directed therapies such as cryotherapy. Often patients may present with numerous lesions and diffuse actinic damage which require field-directed therapy as opposed to individually treating each lesion. This can be done with topical agents (5-fluorouracil, imiquimod, and ingenol mebutate) or with photodynamic therapy after sensitizing the skin with a topical agent. Initial pre-emptive efforts should be made to reduce the patient's risk profile for developing cutaneous carcinoma including optimizing the immunosuppressant regimen in solid organ transplant patients, proper surveillance schedules in patients treated with immunomodulatory therapies, and adequate therapy of precancerous lesions.

Basal cell carcinomas and squamous cell carcinomas, if superficial, can be treated with topical therapies depending on provider preference. However, the standard practice is to surgically treat these lesions with destructive means such as electrodesiccation and curettage or surgical excision. Skin cancers greater than 2 cm in diameter and those located on functionally and cosmetically sensitive sites (head/neck, hands, and feet, genitalia) usually are referred for a special surgical procedure called Mohs micrographic surgery. Some patients with aggressive and recurrent forms of basal cell carcinoma who would not be good surgical candidates are treated with radiation therapy or a systemic medication called Vismodegib which inhibits cellular proliferation.

Melanomas are the most aggressive form of skin cancer; the gold standard of treatment is surgical excision. If caught early, surgical excision can be curative. Later stage tumors portend a poor prognosis and often require adjuvant immunotherapy.

Models

The skin is the largest organ of the body, made up of multiple layers.

Current mouse models of BCC involve activation of some component of the Hh signal transduction pathway. (2015)

The canonical carcinogenesis model that cSCC development is a multistep progression starting from the precancerous actinic keratosis (AK) in which keratinocyte atypia is confined to only PORTION OF THE Epidermis leading to abnormal differentiation and stratum corneum thickening with retained nuclei. Mutation in p53, an important tumor suppressor whose inactivation has been implicated in a variety of tumors, has been implicated in a variety of tumors, identified in UV exposed skin as well as the majority of AK/SCC.

K14-SCF; XPA Mouse model (K 14 promoter stem cell factor xeroderma pigmentosa A complement group): the k-14 –SCF transgenic mice do not spontaneously form melanoma however when expressed in mice lacking the XPA they formed metastatic melanocytic skin tumors after UV exposure in about 30% of animals.

Melanoma animal models are enhanced with regard to tumor penetrance and latency by exposing the mice to additional mutagens such as UV light or DMBA/TPA.

K14-Fyn : Fyn is a potent oncogene in the skin. K-14 transgene develops precancerous lesions and invasive squamous cell carcinomas (SCCs) spontaneously in 5 to 8 weeks.

Patched knockout mouse models of basal cell carcinoma (PTCH) :-PTCH knockout mouse models to investigate BCC as well as for potential use in preclinical research.

Delineating molecular mechanisms of squamous tissue homeostasis and neoplasia: focus on p63: P63, a transcription factor that plays an essential role in the development and maintenance of normal stratified squamous epithelium.

Role of stat3 in skin carcinogenesis: insights gained from relevant mouse models”

Models of skin cancer

Name of model

Name of cell line/mechanism

Dose/medium

No of days for induction

Breed

Melanoma models

(a) models that facilitate the study of melanoma progression and its underlying mechanisms using preexisting malignant cells and (b) allow generation of melanomas through manipulation of specific genetic event

Oncogene induced DNA damage model

Activating ATM/TP53/MDM2 checkpoint pathway

DMBA/TPA induced (Rajmani et al;2011)

AgNOR and PCNA staining

Mutation in hras gene and trp 53

1%

20 to 25 weeks

Wistar rats

UV induced skin cancer (UV B)

TP53 mutation

RAS mutation

transgenic mice used in UV radiation-induced skin cancer studies was a strain of mouse which carried the SV40 T antigen under control of the tyrosine promoter and expressed only in melanocytes

In vivo models of skin cancer

gene

Mouse model

Phenotype

reference

Akt

Akt1 knockout

In the DMBA/TPA model, Akt12/2 mice develop tumors with reduced yield and size

Skeen et al. 2006

Cyclin D1

Cyclin D1 knockout

Cyclin D12/2 mice develop papillomas with increased latency and reduced incidence and yield in the DMBA/TPA mode

Robles et al. 1998

Erk

Erk1 knockout

Erk12/2 mice show reduced skin inflammation and proliferation in response to TPA treatment and are tumor-resistant in the DMBA/TPA model

Bourcier et al. 2006

Fos

c-fos knockout

c-fos-deficient papillomas quickly become dry and hyperkeratinized, and fail to progress to malignancy

Saez et al. 1995

Jnk

Jnk1 and Jnk2 knockouts

In the DMBA/TPA model, Jnk12/2 mice show enhanced tumor susceptibility while Jnk22/2 mice are tumor resistance

Chen et al. 2001; She et al. 2002

Jun

c-jun knockout in the epidermis using K5-Cre

In the K5-SOS-F skin tumor model, c-jun ablation leads to smaller papillomas that show increased differentiation, possibly caused by down-regulation of EGFR

Zenz et al. 2003

Mek

Overexpression of Mek1 in basal keratinocytes and hair follicle ORS using the K14 promoter

Mek2 knockout and conditional Mek1 knockout using K14-Cre

Epidermal hyperplasia and spontaneous skin tumor formation.

In the DMBA/TPA model, Mek1 knockout but not Mek2 knockout impedes tumorigenesis; in a mouse model of oncogenic Ras-driven skin cancer; however, both Mek1 and Mek2 (or at least one copy of each) have to be deleted to impede carcinogen

Feith et al. 2005

Scholl et al. 2009a,b

Myc

K5-Myc transgenic mice

K14-driven Myc overexpression

Spontaneous papilloma and SCC development; mice are also more tumor susceptible in the DMBA/TPA model

Epidermal hyperplasia, enlarged sebaceous glands, spontaneous skin lesions and stem cell loss; DMBA/TPA-treated K14-Myc mice develop tumors with reduced latency and increased yield, but these are predominantly sebaceous adenomas

Rounbehler et al. 2001

Arnold and Watt 2001; Waikel et al. 2001; Honeycutt et al.2010

Pak1

Pak1 knockout

Pak1 deficiency impedes tumor development and progression in a mouse model of KrasG12D-driven skin cancer

Chow et al. 2012

PKC

PKC-h knockout; K5-driven PKC-a overexpression; K14-driven PKC-d or PKC-1 overexpression

In the DMBA/TPA model, PKC-h2/2 and K5- PKC-a mice show enhanced tumor formation; K14-PKC-d and K14-PKC-1 mice, on the other hand, are resistant to papilloma development; K14-PKC-1 mice also show increased de novo carcinoma

Reddig et al. 1999, 2000; Chida et al. 2003; Cataisson et al. 2009

Rac1

Keratinocyte-specific deletion using K5- and K14-Cre

Hair follicle (and epidermal) stem cell loss/ impairment; K5-driven Rac1 ablation leads to tumor-resistance in the DMBA/TPA model, associated with a decrease in keratinocyte prolifera

Keely et al. 1997; Benitah et al. 2005; Chrostek et al. 2006; Wang et al. 2010

The K14-Shh transgenic mice developed cutaneous BCC-like tumors within 4 days of embryonic skin development [11]. Similar spontaneous BCC-like tumors were found in mice over-expressing a mutant variant of SMO (SMO-M2) under the control of the K5 promoter [12]

PTCH1 heterozygous mice (PTCH1+/?) spontaneously develop microscopic BCC and after chronic UV exposure, the PTCH1+/? mice develop rapidly growing BCC-like tumors after 4 months [15].

Skin cancer cell lines as per ATCC

Melanoma cell lines

s.no

Cell line

Cell type

Disease

application

1

A-375-P

Melanocyte

Malignant melanoma

This cell line is useful as a control for A375-MA1 and A375-MA2 to study the mechanisms of metastasis. It has been used with microarray analyses to identify metastasis-specific genes using a functional genomics approach and in proteomics analyses

2.

NRAS-mutant-A375 Isogenic-Luc2 (ATCC® CRL-1619IG-2-LUC2™)

melanocyte

malignant melanoma

BRAF drug resistant melanoma model. Excellent signal/background ratio and stable Luciferase expression make this cell line ideal for in vivo bioluminescence imaging of xenograft animal model to study human cancer and monitor activity of anti-cancer drug. It also can be used in cell-based assays for cancer research

3.

VMM15 (ATCC® CRL-3227™)

Melanocyte

Melanoma, Stage IIIC; malignant

Drug screening

Development of targeted therapy

Development of combination therapy

Tumor vaccine development

4.

VMM917 (ATCC® CRL-3232™)

Melanoma

Melanoma, Stage IV; malignant

Drug screening

Development of targeted therapy

Development of combination therapy

Tumor vaccine development

5.

VMM5A (ATCC® CRL-3226™)

Melanocyte

Melanoma, Stage IIIC; malignant

Drug screening

Development of targeted therapy

Development of combination therapy

Tumor vaccine development

6.

VMM39 (ATCC® CRL-3230™)

Melanocyte

Melanoma, Stage IIIC; malignant

Drug screening

Development of targeted therapy

Development of combination therapy

Tumor vaccine development

7.

A375.S2 (ATCC® CRL-1872™)

Melanoma

malignant melanoma

8.

VMM425 (ATCC® CRL-3231™)

Melanocyte

Melanoma, Stage IV; malignant

Drug screening

Development of targeted therapy

Development of combination therapy

Tumor vaccine development

9.

A375-MA2 (ATCC® CRL-3223™)

malignant melanoma

This cell line is useful to study the mechanisms of metastasis. It has been used with microarray analyses to identify metastasis-specific genes using a functional genomics approach and in proteomics analyses.

10.

VMM1 (ATCC® CRL-3225™)

Melanocyte

Melanoma, Stage IV; malignant

Drug screening

Development of targeted therapy

Development of combination therapy

Tumor vaccine development

11.

KRAS mutant-A375 Isogenic-Luc2 (ATCC® CRL-1619IG-1-LUC2™)

melanocyte

malignant melanoma

BRAF drug-resistant melanoma model. Excellent signal/background ratio and stable Luciferase expression make this cell line ideal for in vivo bioluminescence imaging of xenograft animal model to study human cancer and monitor activity of the anti-cancer drug. It also can be used in cell-based assays for cancer research.

12.

VMM18 (ATCC® CRL-3229™)

Melanocyte

Melanoma, Stage IIIB; malignant

Drug screening

Development of targeted therapy

Development of combination therapy

Tumor vaccine development

13.

SKIN CANCER CELL LINES

s.no

Cell line

Cell type

disease

Application

1

182-PF SK (ATCC® CRL-1532™)

hereditary adenomatosis

2

A-375 [A375] (ATCC® CRL-1619™)

malignant melanoma

This cell line is a suitable transfection host. This cell line is also the ideal control for NRAS mutant-A375 isogenic cell line (ATCC®CRL-1619IG-2™).

3.

A-431 (ATCC® CRL-1555™)

epidermoid carcinoma

This cell line is a suitable transfection host.

4.

A.P. (ATCC® CRL-6295™)

normal

This cell line is neither produced nor fully characterized by ATCC. We do not guarantee that it will maintain a specific morphology, purity, or any other property upon passage.

5.

A2058 (ATCC® CRL-11147™)

melanoma

This cell line is a suitable transfection host

6.

A375-Luc2 (ATCC® CRL-1619-LUC2™)

malignant melanoma

Excellent signal/background ratio and stable luciferase expression make this cell line ideal for in vivo bioluminescence imaging of xenograft animal model to study human melanoma and monitor activity of anti-cancer drug. It also can be used in cell-based assays for cancer research.

7.

A375-MA1 (ATCC® CRL-3222™)

malignant melanoma

This cell line is useful to study the mechanisms of metastasis. It has been used with microarray analyses to identify metastasis-specific genes using a functional genomics approach and in proteomics analyses.

8

A375-MA2 (ATCC® CRL-3223™)

malignant melanoma

This cell line is useful to study the mechanisms of metastasis. It has been used with microarray analyses to identify metastasis-specific genes using a functional genomics approach and in proteomics analyses.

9

A7 [M2A7] (ATCC® CRL-2500™)

melanoma

melanoma

A7 [M2A7] cells are useful as a control for studying filamin systems (cell signal transduction, cell membrane sorting and cytoskeleton-membrane association).

10

Ad Hot (ATCC® CRL-1227™)

Ehlers-Danlos syndrome, type II

11

Am Coo (ATCC® CRL-1286™)

osteogenesis imperfecta (tarda)

12

Amdur II (ATCC® CCL-124™)

Fibroblast

methylmalonic acidemia

13

An Zan (ATCC® CRL-1266™)

Marfan syndrome

14

Ar Ke-2 (ATCC® CRL-1324™)

Ehlers-Danlos syndrome, presumed heterozygote

15

B16-F0 (ATCC® CRL-6322™)

melanoma

This cell line is a suitable transfection host.

16

B16-F1 (ATCC® CRL-6323™)

melanoma

This cell line is a suitable transfection host.

17

B16-F10 (ATCC® CRL-6475™)

melanoma

This line is a suitable transfection host.

18

Ba Pot (ATCC® CRL-1280™)

osteogenesis imperfecta (congenita)

19

Be Ar (ATCC® CRL-1167™)

xeroderma pigmentosum, presumed heterozygote

20

Bi Fin (ATCC® CRL-1219™)

Ehlers-Danlos syndrome

21

BJ (ATCC® CRL-2522™)

Fibroblast

normal

The cells may be used for stable transfection studies.

22

Bo Gin (ATCC® CRL-1180™)

Ehlers-Danlos syndrome, type I (autosomal dominant type)

23

BUD-8 (ATCC® CRL-1554™)

fibroblast

normal

This line is highly sensitive to interferon and can be used in assays of interferon activity.

24

C 211 (ATCC® CCL-123™)

fibroblast

Cri du Chat syndrome

25

C32 (ATCC® CRL-1585™)

melanoma, amelanotic

26

C32 purified DNA, [3 µg] (ATCC® CRL-1585D™)

he C32 cell line is a human skin malignant melanoma cell line

27

C32TG [C32-r16TG] (ATCC® CRL-1579™)

amelanotic melanoma

28

Caki-1 (ATCC® HTB-46™)

clear cell carcinoma

This cell line is a suitable transfection host.

29

CCD 1102 KERTr (ATCC® CRL-2310™)

keratinocyte; human papillomavirus 16 (HPV-16) E6/E7 transform

6E7 sequences were detected by PCR in cells at passage 18. Major Histocompatibility Complex class I or II molecules were not expressed on these cells, but PCR analyses revealed the presence of the genes for directing the synthesis of HLA antigens.

Major Histocompatibility Complex class I or II molecules were not expressed on these cells, but PCR analyses revealed the presence of the genes for directing the synthesis of HLA antigens.

30

CCD 1106 KERTr (ATCC® CRL-2309™)

keratinocyte; human papillomavirus 16 (HPV-16) E6/E7 transformed

31

CCD-1058Sk (ATCC® CRL-2071™)

fibroblast

normal

The future: the Grand Challenges in Global Skin Health initiative

How then do we achieve these goals? There are four key measures to achieve success: (i) research, (ii) education, (iii) clinical application through translation, and (iv) the support of those responsible for the management and delivery of health care at local and national levels. Financial support for basic and translational research is fragmentary on the global stage. While it is true that not all skin diseases are lethal, they contribute signi?cantly to the global disease burden, and the persisting failure to address their management accounts for a huge loss of production and increased medical expenditure. In Europe, the annual cost of occupational dermatitis – including the direct costs of treatment and industrial compensation, as well as the indirect costs of sick leave and loss of productivity – is estimated to be greater than €5 billion.20 In moderate-to-severe psoriasis the annual cost of the disease in the U.S.A., including treatment and loss of productivity, was estimated to be $1125 billion.21 At the other end of the spectrum the cost of inappropriate and ineffective scabies treatment over a 3-month period in resource-poor settings is enough to eliminate household cash reserves.22 Increasing the availability of cost-effective measures would have a major impact on both personal and institutional economies. Education of frontline health workers in the elements of skin disease is also key to successful management. However, competing priorities in medical and nursing training have squeezed the opportunity to address this issue. A new drive to integrate the core skills and knowledge needed to ensure freedom from skin problems into undergraduate and postgraduate teaching for health professionals could provide the answer. Innovation in healthcare delivery has frequently ignored the needs of the whole patient and the populations in which they live. Skin disease has been a casualty in this respect. However, perhaps the most powerful contribution to making skin health a realizable objective over the next 25 years is the recognition, among leaders of governments and non-governmental organizations, that it is a realistic, affordable and achievable goal, integral to future health and research strategies. The recent actions by the World Health Organization in framing a resolution to member states for concerted action on psoriasis23 and in recognizing scabies as a neglected disease24 provide a huge impetus for change. The international dermatological community is committed to this goal and is resolved to see the adoption of these strategies at all levels of research, education and health care. With this objective in mind the International League of Dermatological Societies has embarked on a focused program, the Grand Challenges in Global Skin Health, to tackle these issues. This has started with initiatives in data collection and analysis, aging research and the formation of international alliances in scabies control and the care of those with albinism. Other schemes will follow over the next few years as members of the international dermatological community respond to these challenges that face our patients.

Treatment Challenges

Treatment strategies for skin cancers require careful consideration, and there are many challenges to overcome. However, with increasing treatment choices, in terms of both therapy combinations and sequences, we can achieve better outcomes for patients with fewer recurrences and longer treatment-free periods

References

1. Whiteman DC, Green AC, Olsen CM. The growing burden of invasive melanoma: projections of incidence rates and numbers of new cases in six susceptible populations through 2031. J Invest Dermatol. 2016;136:1161–1171. doi: 10.1016/j.jid.2016.01.035. [PubMed] [CrossRef]
2. De Vries E, Coebergh JW. Cutaneous malignant melanoma in Europe. Eur J Cancer. 2004;40:2355–2366. doi: 10.1016/j.ejca.2004.06.003. [PubMed] [CrossRef]
3. Lasithiotakis K, Kruger-Krasagakis S, Manousaki A, Ioannidou D, Panagiotides I, Tosca A. The incidence of cutaneous melanoma on Crete, Greece. Int J Dermatol. 2006;45:397–401. doi: 10.1111/j.1365-4632.2006.02492.x. [PubMed] [CrossRef]
4. Mansson-Brahme E, Johansson H, Larsson O, Rutqvist LE, Ringborg U. Trends in incidence of cutaneous malignant melanoma in a Swedish population 1976–1994. Acta Oncol. 2002;41:138–146. doi: 10.1080/028418602753669508. [PubMed] [CrossRef]
5. Stang A, Pukkala E, Sankila R, Soderman B, Hakulinen T. Time trend analysis of the skin melanoma incidence of Finland from 1953 through 2003 including 16,414 cases. Int J Cancer. 2006;119:380–384. doi: 10.1002/ijc.21836. [PubMed] [CrossRef]
6. Ulmer MJ, Tonita JM, Hull PR. Trends in invasive cutaneous melanoma in Saskatchewan 1970-1999. J Cutan Med Surg. 2003;7:433–442. doi: 10.1007/s10227-003-0159-0. [PubMed] [CrossRef]
7. Dennis LK. Analysis of the melanoma epidemic, both apparent and real: data from the 1973 through 1994 surveillance, epidemiology, and end results program registry. Arch Dermatol. 1999;135:275–280.[PubMed]
8. Geller AC, Miller DR, Annas GD, Demierre MF, Gilchrest BA, Koh HK. Melanoma incidence and mortality among US whites, 1969–1999. JAMA. 2002;288:1719–1720. doi: 10.1001/jama.288.14.1719.[PubMed] [CrossRef]
9. Hall HI, Miller DR, Rogers JD, Bewerse B. Update on the incidence and mortality from melanoma in the United States. J Am Acad Dermatol. 1999;40:35–42. doi: 10.1016/S0190-9622(99)70562-1. [PubMed] [CrossRef]
10. Perera E, Gnaneswaran N, Staines C, Win AK, Sinclair R. Incidence and prevalence of non-melanoma skin cancer in Australia: a systematic review. Australas J Dermatol. 2015;56:258–267. doi: 10.1111/ajd.12282. [PubMed] [CrossRef]
11. American Cancer Society. Cancer Facts & Figures 2016. http://www.cancer.org/acs/groups/content/@research/documents/document/acspc-047079.pdf. Accessed 2 Aug 2016.