Clemson University
TigerPrints

Publications School of Nursing

10-2014

The Role of Melanocortin 1 Receptor in Cutaneous Malignant Melanoma

Mary B. Steck
Clemson University, steck@clemson.edu

Follow this and additional works at: https://tigerprints.clemson.edu/nursing_pubs

Part of the Nursing Commons

Recommended Citation
Please use publisher's recommended citation. http://brn.sagepub.com/content/16/4/421.full.pdf

This Article is brought to you for free and open access by the School of Nursing at TigerPrints. It has been accepted for inclusion in Publications by an authorized administrator of TigerPrints. For more information, please contact kokeefe@clemson.edu.

Abstract

Cutaneous malignant melanoma (CMM) is an epidemic cancer in the United States. Survival rates for invasive CMM have not decreased in past decades despite numerous clinical trials and various combinations of chemotherapy agents effectively used for other cancers. Recent exploration of a predisposing CMM gene, melanocortin 1 receptor (MC1R), associated with red hair phenotype in white individuals, has been investigated for its role in the mitogen-activated protein kinase (MAPK) pathway. This limited review will discuss the incidence, history, and risk factors for CMM. Familial CMM will be identified, along with a brief review of melanocyte development and melanogenesis. MC1R structure and function will be discussed, including MC1R's role in the MAPK pathway. The alternative network biology approach for CMM will be introduced, along with histology and cytogenetic techniques used to identify CMM mutations. Finally individualized therapy for CMM will be touched upon along with recommendations for future research.

Incidence

Skin is the largest organ in humans, so it is not surprising that skin cancer is the most commonly occurring cancer in the United States (U.S.). Two common types of skin cancer, basal cell and squamous cell, are highly curable. Melanoma, the third most common and most lethal skin cancer, is considered an epidemic cancer, curable only in its initial stages (Gerstenblith, Goldstein, Tucker & Fraser, 2007; Blokx, van Dijk & Ruiter, 2010). Cutaneous malignant melanoma (CMM) is the fifth most common cancer among men and the sixth most common among women in the United States. Compared to all other cancers, the incidence of CMM among white individuals in the U.S. increased dramatically during the years 1975-2001. Incidence increased from 8.7 cases per 100,000 persons, to 22.6 cases per 100,000 persons, an increase of more than 150% (Gerstenblith, et al., 2007). Since 1930, the incidence has increased more than 2000 % (American Cancer Society [ACS], 2011). The National Cancer Institute (NCI) estimates for 2008 were 62,480 new cases and 8,420 deaths from CMM (National Cancer Institute [NCI], 2010). The American Cancer Society (ACS) predicted that over 76,000 Americans would develop CMM in 2011 alone. Incidence of CMM progressively increases with age and is one of the more commonly found types of cancer in the 20-35 year-old age group (Houghton & Polsky, 2002). Lifetime incidence of developing melanoma has increased to 1 out of every 57 Americans (ACS, 2011).

History

Writings of Hippocrates in the 5th century B.C, refer to “black cancer” and “fatal black tumors with metastasis”. In 1806, the French inventor of the stethoscope, Rêne Laennec, first described melanoma as a disease. He termed the disease, “melanosis”, from the Greek word for “black” (Ibrahim & Haluska, 2009; Chin, 2003). Currently, melanoma can be classified into four types of melanoma: CMM (superficial spreading melanoma), nodular melanoma, lentigo maligna melanoma and acral lentiginous melanoma. About 90% of CMM and nodular melanomas arise on the skin, such as sun-exposed limbs, trunk and facial areas. Lentigo maligna melanoma takes years to develop from a pre-existing lentigo and is subsequently found in older persons. Darker-skinned persons typically present with acral lentigo

melanoma in non-sun exposed sites; mucous membranes, nail beds, palms and soles of the feet (Melanoma Center, 2010). Only 3-5% of melanoma arises in the ocular uveal tract and rarely in non-cutaneous epithelial surfaces; the sinus and oropharnyx mucous membranes, esophagus, rectum and vagina (Houghton & Polsky, 2002). For this article's purposes, CMM, the most common type of melanoma that represents over 70% of all malignant melanoma cases, will be considered.

Pathogenesis

CMM pathogenesis results from interactions of the environment with host/genetic factors. Sun exposure as an environmental risk contributing to CMM development is widely accepted by the public; though debate still exists concerning which length of exposure, intermittent intense ultraviolet (UV) or chronic UV exposure is related to this increased risk (Chin, 2003). An additional factor related to sun exposure is to consider what type of UV radiation contributes to CMM, the longer wavelength UVA radiation (320- 400 nm) or the shorter UVB radiation (280-320 nm). UVB is considered the most carcinogenic waveband, inducing erythema or sunburn. UVB absorption can result in DNA damage that can become mutations if not repaired. DNA damage results in two types of lesions, photo products between adjacent pyrimidines, or pyridimine dimers formed between adjacent thymines (T) or cytosines (C). Pyridmidine dimers are more carcinogeneic than photo products, three times as frequent and repaired less. These DNA lesions can lead to C →T or CC→TT transitions. UVB wavelengths also cause C→A and G (guanine) →T transversions and breaks in DNA. As a result, UVB wavelengths are 1000 times more effective at causing sunburn that UVA radiation. UVA radiation found in tanning salons, with its longer wavelengths penetrate deeper into the skin and is also able to mutate DNA. Damage to DNA through UVA radiation can be induced by absorbing non-DNA oxygen radicals, leading to breaks and mutations (Jhappen, Noonan, & Merlino, 2003). General consensus among researchers is that intense intermittent sun exposure at any age is a more important environmental risk factor for CMM development than an individual's sun exposure over their lifetime. Recent data from the U.S. Nurses' Health Study revealed that more than 10 lifetime-blistering sunburns increased the relative risk of CMM by 3-9 fold

(Miller & Tsao, 2010). CMM incidence is also influenced geographically by an individual's proximity to the equator. The incidence of CMM is two to three times greater in the southern U.S. as compared to northern U.S. regions. Migrants with darker skin from higher CMM incidence areas in the southern U.S. are found to retain their high-risk status when they move to a lower CMM incidence region in the northern U.S. (Houghton & Polsky, 2002).

Risk Factors

Skin cancer is primarily a disease among the white population. Major host factors associated with melanoma include increased numbers of nondyplastic and dysplastic nevi, fair hair color, light eye color, many freckles and inability to tan. Atypical nevi are visible markers for increased risk of developing CMM. White individuals have an average of 15-35 cutaneous benign nevi while individuals with more than 100 atypical nevi have an increased chance of developing CMM (Hocker, Singh & Tsao, 2008). Having a previous melanoma or nonmelanoma skin cancer also increases the risk for melanoma development (Rhodes, 2006; Gerstenblith, et al., 2007). About 5 to 12% of CMM develops in individuals who have at least one affected first-degree relative (parent, sibling, or child), strongly suggesting that an individual's family history of malignant cutaneous melanoma may include genetic risk factors. In familial CMM (FCMM), compared with nonfamilial CMM, age at diagnosis is typically earlier, lesions are generally thinner (less than 1 mm in depth), and there is a higher frequency of multiple primary melanomas (Figure 1) The lesions of FCMM individuals are histologically similar and the clinical course is not significantly different from nonfamiliar CMM (Gerstenblith, et al.). Thus, FCMM appears to be a complex interaction of environmental, host and genetic factors. (Figure 2)

Melanogenesis

CMM is derived from melanocytic nevi, commonly referred to as moles, which are benign clusters of pigment-synthesizing skin cells, melanocytes. Melanocytes make up one to two percent of the epidermal cell population, whereas keratinocytes, make up over 95% of the total epidermal cell

population (Jhappan et al., 2003). Melanocytes are derived from neural crest progenitor cells that migrate to the epidermis during early human development (Ibrahim & Haluska, 2009). Each melanocyte transfers melanin-containing organelles, termed melanosomes, through its dendrite tips to approximately 36 basal and suprabasal keratinocytes, thereby forming the epidermal melanin unit. The function of melanocytes is to synthesize, store and transfer melanin pigments to surrounding epithelial cells. Melanin can absorb UV photons and free radicals induced by UV wavelengths before they interact with other cellular components. Melanosomes scattered throughout the epidermis provide a highly protective screen designed to absorb and scatter damaging UV radiation (Jhappen et al.).

The melanin in melanosomes is produced when a positive skin cell regulator, melanocortin 1 receptor (MC1R), a guanine-protein-coupled receptor (GCPR) with seven transmembrane domains, is activated by its ligand peptide, α-melanocyte stimulating hormone (α-MSH). The G (guanine- nucleotide binding) family of proteins in the skin cell's cytoplasm bind to MC1R, transmitting its signals to adenyly cyclase. This enzyme then catalyzes the conversion of cytoplasmic ATP (adenosine triphosphate) to cAMP (cyclic adenosine monophosphate). The increased levels of cAMP activate protein-kinase A (PKA), which in turn translocates into the nucleus of the cell to phosphorylate CREB (cAMP response-element binding protein) (Herraiz, Jiménez-Cervantes, Zanna & Garcia-Borrón, 2009). The phosphorylated CREB then upregulates expression of microphthalmia-associated transcription factor (MITF), a helix-loop-helix transcription factor. MITF binds to the promoters of E box consensus sequences, dopachrome tautomerase, tyrosinase-related protein 1 (TYRP 1) and the rate-limiting enzyme, tyrosinase, which synthesize melanin production in the melanosomes (Herraiz et al., Hocker et al.,2008; Jhappan et al., 2003,) (Figure 3). Melanin has two distinctive types, red/yellow pheomelanin, present in red hair and freckled individuals, and black/brown eumelanin, present in individuals with dark skin and hair (Jhappan et al.; Palmer et al., 2000). Pheomelanin has a decreased UV-light protective capacity and is believed to produce metabolites that are cytotoxic and mutagenic. MC1R mutations are known to shift

the balance of pheomelanin and eumelanin depending on their regulatory functions and associations with other melanoma-predisposed genes (Chin, 2003).

MC1R Gene

The MC1R gene may be identified by numerous names. MC1R's full names are melanocyte-stimulating hormone receptor, melanocortin receptor, or melanocortin receptor 1. Alternative, shorter abbreviations besides MC1R include MSH-R, and MC1-R. MC1R is an intronless, low-penetrance gene, containing only one highly polymorphic exon. MC1R is one of a family of five different melanocortin receptors, located on the positive strand of chromosome 16p24.3, with a genomic size of 3099 with the genomic sequence, chromosome 16:88,511,788-88,514,886 (USCS Genome Browser, 2010; Ibrahim &Haluska, 2009) (Figure 3).

This 317 amino acid encoding-protein helps regulate melanocytic activities; nonfunctional MC1R has been linked with increased sensitivity to UV's cytotoxic effects while loss-of-function mutations prevent sufficient production of eumelanin (Jhappan et al., 2003). To date, no MC1R gain-of-function mutations for humans have been recorded. Over 75 nonsynonymous variations of MC1R exist that determine the variations in pigment and resultant human skin phenotypes. Seven of these variants with significantly diverse allele frequencies in Caucasians impair the function of MC1R by reducing the stimulation of cAMP production and the resultant proteins; it appears that dark pigmented individuals possess fewer MC1R variants than light pigmented individuals. Three of these MC1R variants, Arg151Cys, Arg160Trp, and Asp294His, have been identified as red-hair color variants due to their diminished in vitro receptor function (Ibrahim & Haluska, 2009). Carrying a single red-hair color variant is known to reduce the ability of the epidermis to respond to damage caused by UV light (Chin, 2003).

Interaction of MC1R with Melanoma-Predisposing Genes

Melanocyte proliferation, differentiation and migration are key events in normal human development. Regulation of these events can be irreversibly altered at the genetic level by a mutated

developing melanoma cell. Other melanoma-predisposing genes in addition to MC1R, such as CDKN2A (cyclin-dependent kinase inhibitor 2A) on chromosome 9p21, encodes for two predisposing melanotic tumor-suppressing genes, p16 and p14. These tumor-suppressing genes along with CDK4 (cyclin-dependent kinase 4) on chromosome 12q14, have been identified based on their varying degrees of penetrance in germline melanoma (Ibrahim & Haluska, 2009). In fact, two familial pedigree studies in separate countries showed that MC1R variants are associated with increasing penetrance of CDKN2A mutations from 50 to 84%, accompanied with a decrease in mean age onset of FCCM from 58 to 37 years of age (Box, 2001). Another study revealed an increase from 18 to 35% in CDKN2A penetrance with one MC1Rvariant and 55% increase in CDKN2A penetrance with a different MC1R variant (van der Velen, 2001). Clinical genetic testing is available for a CDKN2A gene, specifically the p16 gene. The test is used to identify FCCM predisposition for preventive measures (Chin, 2003).

MAPK Pathway

CMM genes are unique and critically positioned within different and sometimes interacting signaling networks of the cell cycle. Rather to refer the disruption of regulatory function by mutations in individual melanoma-encoded genes, it may be better to consider MC1R's relationship to other genes within activated/suppressed pathways or networks (Hocker et al., 2008). The constitutively activated MAPK (mitogen-activated protein kinase) pathway in melanoma is involved in cell growth regulation. In melanocytes, the MAPK pathway is weakly stimulated by α-MSH signaling with MC1R. This signaling is insufficient to activate melanoctye proliferation. However, more than 90% of melanoma tumors are known to have continuous hyperactive CMM cells in the MAPK pathway. Current thought is that a hyperactive MAPK pathway is due to activating oncogenic mutations. A vast majority of benign and malignant melanomas carrying these hyperactive mutations are found in one of two key MAPK oncogenes, BRAF (v-raf murine sarcoma viral oncogene homolog B1) or NRAS (neuroblastoma RAS viral oncogene homolog) (Hocker et al.; Smalley, 2010).

Mutations in CMM

MAPK-activating mutations were first reported in NRAS; they occur in 15-20% of all CMM. The common mutation in NRAS is a point mutation of leucine changed to a glutamine. However, most mutations reported for CMM are in BRAF, the serine-threonine kinase located downstream of NRAS. Recent genome-based high-throughput sequencing efforts have identified that at least 60% of all CMM hold at least 50 distinct mutations in BRAF (Smalley, 2010). Development of CMM due to the unrepaired DNA damage from intermittent sun exposure has the highest rates of BRAF mutation. MC1R polymorphisms may increase this tendency toward BRAF mutation development. Although these BRAF mutations don't bear the typical C>T (cytosine to thymidine) signature of other known UV radiation-induced mutations, research findings suggest that MC1R polymorphisms with intermittent sun exposure result in BRAF mutations (Sekulic et al., 2008).

BRAF's somatic missense mutations have been identified in the kinase domain. A single substitution, V600E BRAF, in the kinase domain accounts for 80% of mutations with 10-fold greater kinase activity than wild-type BRAF. A T1796A transversion at position 600 substitutes a glutamate for a valine. This single base pair change makes kinase constitutively active, affecting downstream pathway events (Panka, Atkins, & Mier, 2006). However, a majority of benign nevi were also found to possess the same V600E BRAF mutation, eliminating this mutation as a solo initiating event in CMM. A zebrafish model showed that BRAF activation led only to benign nevi development; progression to CMM in the zebrafish required concurrent p53 inactivation. Thus, full potential of an oncogenic BRAF may be reached if it is combined with other genetic components (Hocker et al., 2008; Fecher, Amaravadi & Flaherty, 2008).

Hypotheses, other than NRAS or BRAF mutations, may be considered to explain a constitutive MAPK signaling theory in invasive melanoma. These include: an increased coupling of RAS (rat sarcoma viral oncongene homolog) to a c-KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene

homolog) upregulated expression, an overexpression of wild-type RAS protein, fibroblast growth factor constitutive expression, upregulated growth factor receptors signaling errors such as found in c-MET(met proto-oncogene receptor) or reduced expression of the negative regulators of ERK (extracellular signal-regulated kinase) (Fecher et al., 2008). CMM lacking activating mutations in NRAS or BRAF also may have genetic alterations in other downstream components of the MAPK pathway. Researchers and investigators have attempted to establish a correlation between BRAF's mutational status and CMM progression but have not consistently shown a significant association. Future research remains to be conducted regarding BRAF's role in CMM. BRAF appears to be the apparent key to melanoma tumorigenesis and is a crucial therapeutic target for CMM treatments (Hocker et al., 2008).

CMM in Network Biology

The complexity of signaling pathways in CMM could benefit from a network biology approach of explanation. Interactions between CMM signaling molecules are viewed as links between interconnected nodes; the total of all these nodes make up a CMM cell signaling network. The robustness associated with a CMM network approach can survive removal of one node from the network without impairing its functionality. Attacking a CMM network with a treatment therapy targeting inhibition of the MAPK pathway would not result in a network failure; there exists additional network connections that would allow the mutated melanoma cell to circumvent the inhibited MAPK pathway. However, if the CMM melanoma network was attacked from its most centrally connected points, called hubs, the CMM melanoma network would fail due to cellular apoptosis or tumor regression. The present challenge for CMM therapy is to identify the key signaling hubs in the network to ensure that a mutated cell survival network would fail. Treating CMM using the network approach would probably require combination therapies to inhibit multiple signaling pathways simultaneously. Genetic screening would be required to identify pair wise combinations of signal transduction inhibitors for use in treating invasive CMM. Using a synthetic lethal approach would also allow identification of the pairs of signaling hubs that CMM therapy needs to target (Smalley, 2010). Unfortunately, the network biology approach for CMM is in its

initial phases; a consensus network for CMM is not available to date. Currently, treatment for CMM is based on the histology of CMM's solid tumors.

Histology of CMM

Histologically, there are five classifications to describe the progression from benign nevi to metastatic CMM. The first classification includes acquired and congenital nevi without any dysplastic changes. The dysplastic nevi may then progress to structural and architectural atypia. These first two stages are characterized by disruption of the epidermal melanin unit, resulting in increasing numbers of melanocytes in relation to the number of keratinocytes. Radial-growth phase melanoma, the third classification, references to dysplastic nevi in the epidermis, still dependent on exogenous growth factors. Surgical excision of melanoma at this phase is usually curative. At the fourth classification, vertical-growth phase melanoma has escaped control of the keratinocytes, invades the epidermal layer, and penetrates into the dermis down through to the basement membrane of this skin layer, resulting in a two to four millimeter thickness of melanoma. At this stage, the melanoma, usually a solitary tumor, acquires the potential to metastasize to other organs, preferably the lungs, liver and brain. Final histological classifications results in a poor clinical outcomes despite current treatments (Chin, 2003) (Figure 4).

Cytogenetics

Besides histology, there is an increasing role for cytogenetics in the treatment of CMM. Currently cytogenetic techniques have increased researchers' understanding of CMM tumor pathogenesis and have been used on a limited clinical basis. Allelic imbalance (AI) analysis, to detect loss of heterozygosity, uses a polymerase chain reaction (PCR) based technique to detect copy number alteration of microsatellites. Comparative genomic hybridization (CGH) is used to compare the CMM tumor from normal reference DNA. CGH has been used extensively in research, but has little clinical application. Since the 1980's, fluorescence in situ hybridization (FISH) has been used to study CMM tumors, specifically to visualize copy number changes and translocations. However, FISH continues to have

difficulty obtaining enough nuclei from small CMM tumors and is unable to link its information with histological information (Blokx et al., 2010).

Using MC1R and other specific CMM predisposing genes, the multiplex ligation-dependent probe amplification method (MLPA) and high-resolution melting analysis (HRMA) are two methods that have been used for both research and diagnostic purposes. MLPA is based on annealing of 45 probes with a target-specific sequence. PCR primers are used along with electrophoresis to separate and quantify PCR product to indicate DNA copy number. MLPA is a good alternative for AI analysis and FISH because no wild-type DNA is needed and multiple probes can be tested in a single experiment. HRMA uses the DNA's dissociate behavior when DNA is heated to detect single base pair mutations. The HRMA technique combines copy number detection with presence of hot-spot mutations. Both of these new techniques have good sensitivity, are cost-effective and timely for use in the clinical setting. They can be used to determine which treatment modality should be employed to deregulate a signaling pathway such as MAPK (Bloks et al., 2010).

Treatment

Despite decades of chemotherapy clinical trials and interventions, invasive malignant melanoma continues to have a poor outcome. No overall survival rate has been shown for nonspecific chemotherapy, immunotherapy with interferon, and radiation or retinoid therapies. Cancer vaccines have been proposed, but due to the heterogeneity of CMM, they have not received much attention. Melanoma stem cells, also known as tumor-initiating cells, were thought to have attributes of "normal" stem cells. However, current therapies with chemotherapy showed that only the daughter cells died, with the melanoma stem cell surviving, resulting in tumor relapse (Sekulic et al., 2008). Until 2011, the only Food and Drug Administration (FDA) approved therapies for advanced CMM were high dose interleukin 2 (IL-2) and dacarbazine (Scheier, Amaria, Lewis & Gonzalez, 2011). Using current genomic technology may hold the key for improved treatment outcomes for CMM patients. Molecular markers from melanoma tumors that undergo improved cytogenetic techniques that can lead to individualized therapy.

Inhibiting the MAPK signaling pathway at all of its levels is being investigated in a number of clinical trials.

Inhibiting BRAF V600E mutation kinase activity in the MAPK pathway, by blocking cell proliferation and signals in the pathway, is the target for the newest therapy for advanced CMM, approved by the FDA in August, 2011. Vemurafenib (brand name Zelboraf) has the indication for treating metastatic or unresectable melanoma possessing the BRAF V600E mutation, when the mutation is detected by a FDA-approved test, the cobas 4800 BRAF V600 Mutation Test. When compared in patient clinical trials with dacarbazine, vemurafenib showed statistically significant improvement in patient survival rates over dacarbazine or placebo. However, BRAF inhibitors introduced into patients with a mutated RAS protein can lead to oncogenesis, by activating CRAF and signaling for a hyperactive MAPK pathway. In this way vemurafenib and other BRAF inhibitors have the potential to induce tumorigenesis in other molecular pathways (Scheier, Amaria, Lewis & Gonzalez, 2011) (Figure 6).

Summary

CMM is not a singular, homogenous disease. Development of CMM involves a combination of risk factors and signaling pathways to initiate melanogenesis. With the advent of better cytogenic techniques, a well-researched network pathway and identification of key oncogenic alleles, researchers can apply significant findings from the bench to the clinical arena, ultimately discovering effective individualized therapies to stop progression and metastasis of invasive CMM. Until then, individuals need to be aware of their individual risk factors and take appropriate preventive measures to control risk factors. These preventative measures include limiting sun exposure, the routine use of sun protective measures and yearly visit to their dermatologist for a full body skin exam.

References

American Cancer Society (2011). 2011 Cancer Facts and Figures. Retrieved from http://www.cancer.org/Research/Cancer/FactsFigures/CancerFactsFigures/cancer-facts-figures-2011.

Blokx, W A., Van Dijk, M.C. & Ruiter, D.J. (2010). Molecular Cytogenetics of Cutaneous Melanocytic Lesions - Diagnostic, Prognostic and Therapeutic Aspects. *Histopathology*, 56, 121-132.

Box, N.F. (2001). MC1R Genotype Modifies Risk of Melanoma in Families Segregating CDKN2A Mutations. *American Journal of Human Genetics*, 69, 765-773.

Chin, L. (2003). The Genetics of Malignant Melanoma: Lessons from Mouse and Man. *Nature Reviews/Cancer*, 3, 559-570.

Chin, L., Garraway, L.A. & Fisher, D.E. (2006). Malignant Melanoma: Genetics and Therapeutics in The Genomic Era. *Genes Development*, 20, 2149-2182.

Fecher, L.A., Amaravadi, R.K. & Flaherty, K.T. (2008). The MAPK Pathway in Melanoma. *Current Opinions in Oncology*, 20, 183-189.

Fecher, L., Cummings, S.D., Keefe, M.J. & Alani, R.M. (2007). Toward a Molecular Classification of Melanoma. *Journal of Clinical Oncology*, 25(12), 1606-1620.

Gerstenblith, M.R., Goldstein, A.M., Tucker, M.A., & Fraser, M.C. (2007). Genetic Testing for Melanoma Predisposition: Current Challenges. *Cancer Nursing*, *30*(6), 452-459.

Herraiz, C., Jimênez-Cervantes, C., Zanna, P. & García-Borrón, J.C. (2009). Melanocortin 1 Receptor Mutations Impact Differentially on Signaling to the cAMP and the ERK Mitogen-Activated Protein Kinase Pathways. *Federation of European Biochemical Societies*, 583, 3269-3274.

Hocker, T.L., Singh, M.K. & Tsao, H. (2008). Melanoma Genetics and Therapeutic Approaches in the 21st Century: Moving from the Benchside to the Bedside. *The Society for Investigative Dermatology*, 128, 2575-2595.

Houghton, A.N. & Polsky, D. (2002). Focus on Melanoma. *Cancer Cell*, 2, 275-278.

Ibrahim, N. & Haluska, F.G. (2009). Molecular Pathogenesis of Cutaneous Melanocytic Neoplasms. *Annual Review of Pathology: Mechanisms of Disease*, 4, 551-579.

Jhappan, C., Noonan, F.P. & Merlino, G. (2003). Ultraviolet Radiation and Cutaneous Malignant Melanoma. *Oncogene*, 22, 3099-3112.

Melanoma Center (2010, January). Melanoma Basics: Types of Melanoma. Retrieved from http://www.melanomacenter.org/basics/types/html.

Miller, A.J. & Tsao, H. (2010). New Insights into Pigmentary Pathways and Skin Cancer. *British Journal of Dermatology*, 162, 22-28.

National Cancer Institute (2008). Melanoma. Retrieved from http://cancer.gov/cancertopics/types/melanoma.htm.

Palmer, J.S., Duffy, D.L., Box, N.F., Aitken, J.F., Gorman, L.E., Green, A.C. et al. (2000). Melanocortin-1 Receptor Polymorphisms and Risk of Melanoma: Is the Association Explained Solely by Pigmentation Phenotype? *American Journal of Human Genetics*, 66, 176-186.

Panka, D.J., Atkins, M.B. & Mier, J.W. (2006). Targeting the Mitogen-Activated Protein Kinase Pathway in the Treatment of Malignant Melanoma. *Clinical Cancer Research*, 12(7), 2371s-2375s.

Rhodes, A. (2006). Cutaneous Melanoma and Intervention Strategies to Reduce Tumor-Related Mortality: What We Know, What We Don't Know, and What We think We Know That Isn't So. *Dermatologic Therapy, 19*, 50-69.

Scheier, B., Amaria, R., Lewis, K., & Gonzalez, R. (2011). Novel Therapies in Melanoma. *Immunotherapy, 3*(12), 1461-1469.

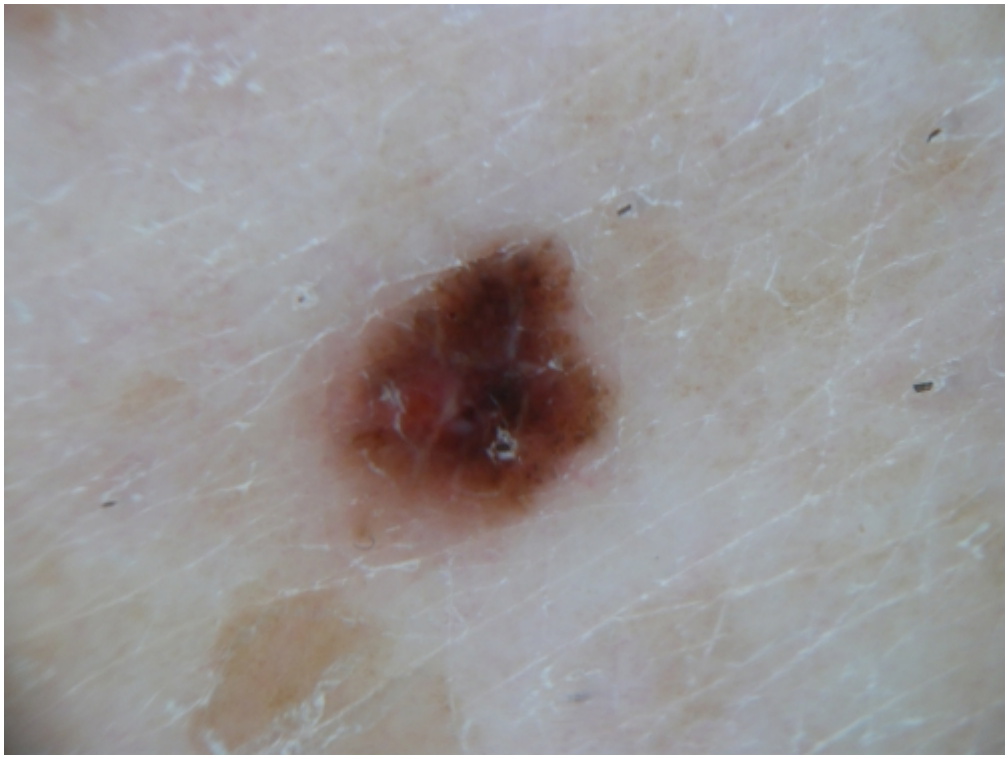
Sekulic, A., Haluska Jr., P., Miller, A.M., de Lamo, J.G., Ejadi, S., Pulido, J.S. et al. (2008). Malignant Melanoma in the 21st Century: The Emerging Molecular Landscape. *Mayo Clinic Proceedings*, 83(7), 825-246.

Smalley, K.S. (2010). Understanding Melanoma Signaling Networks as the Basis for Molecular Target Therapy. *Journal of Investigative Dermatology*, 130, 28-37.

University of California Santa Cruz Genome Browser (2010). Human Gene MC1R (uc002fpe.2) Description and Page Index. Retrieved from http://genome.ucsc.edu/cgibin/hgGene?hgg_gene=uc002fpe.2&hgg_prot=Q01726&hgg_chrom=chr16&hgg_start=88511787&hgg_end=88514886&hgg_type=knownGene&db=hg18&hgsid=157623846.

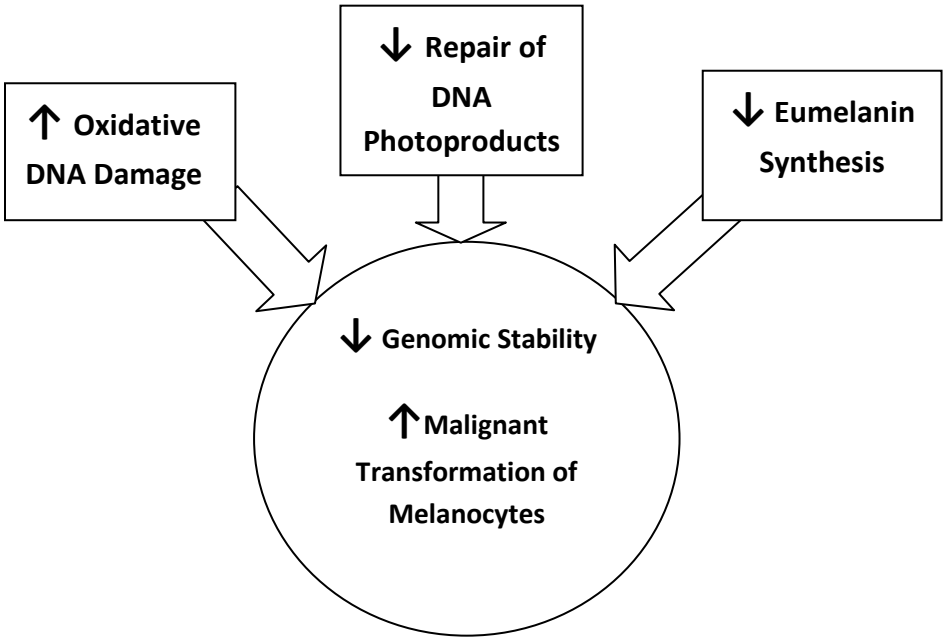
van der Velen, P.A. (2001). Melanocortin-1 Receptor Variant R151C Modifies Melanoma Risk in Dutch Families with Melanoma. *American Journal of Human Genetics*, 69, 774 -7.

Figure 1



Thin invasive melanoma. Retrieved from
http://www.dermpedia.org/image/thin-melanoma

Figure 2



Activating Factors for Melanogenesis

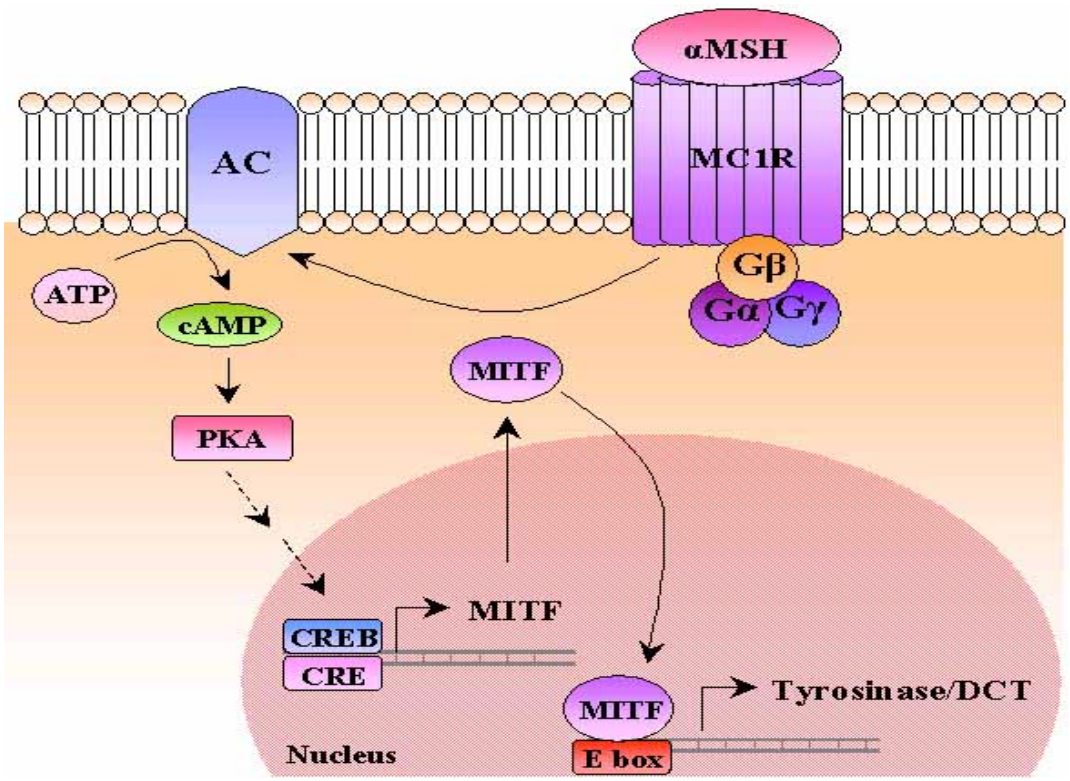
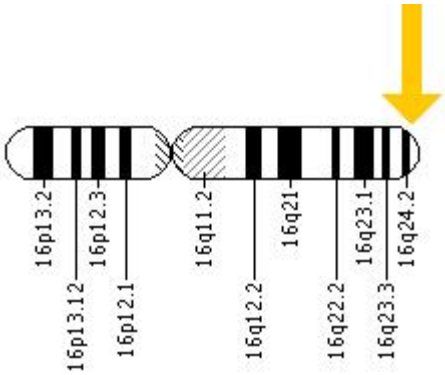


Figure 3

MSH-MC1R Regulation of Pigmentary Genes. Taken from Chin, L. The Genetics of Malignant Melanoma: Lessons From Mouse and Man, p. 563.

Figure 4



MC1R gene location - chromosome 16p24.3

Retrieved from http://ghr.nlm.nih.gov/dynamicImages/chromomap/MC1R.jpeg

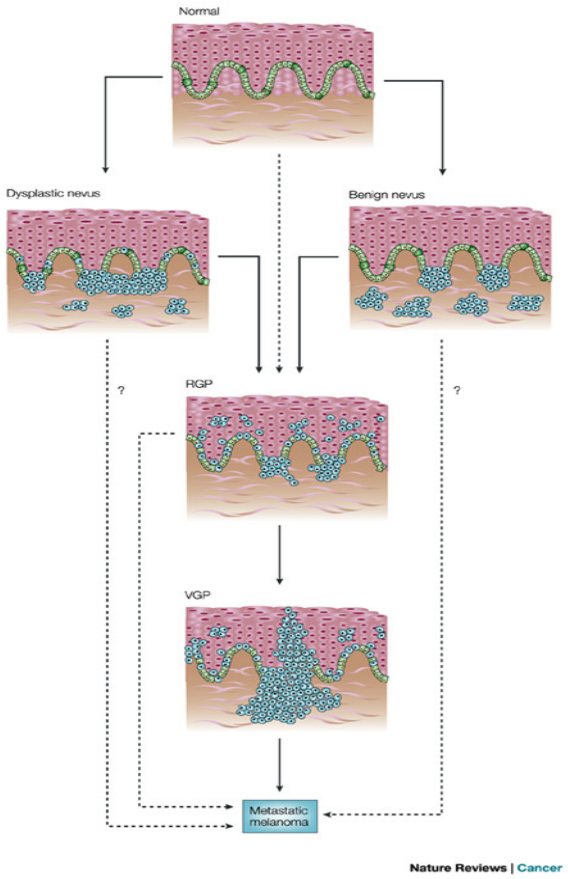
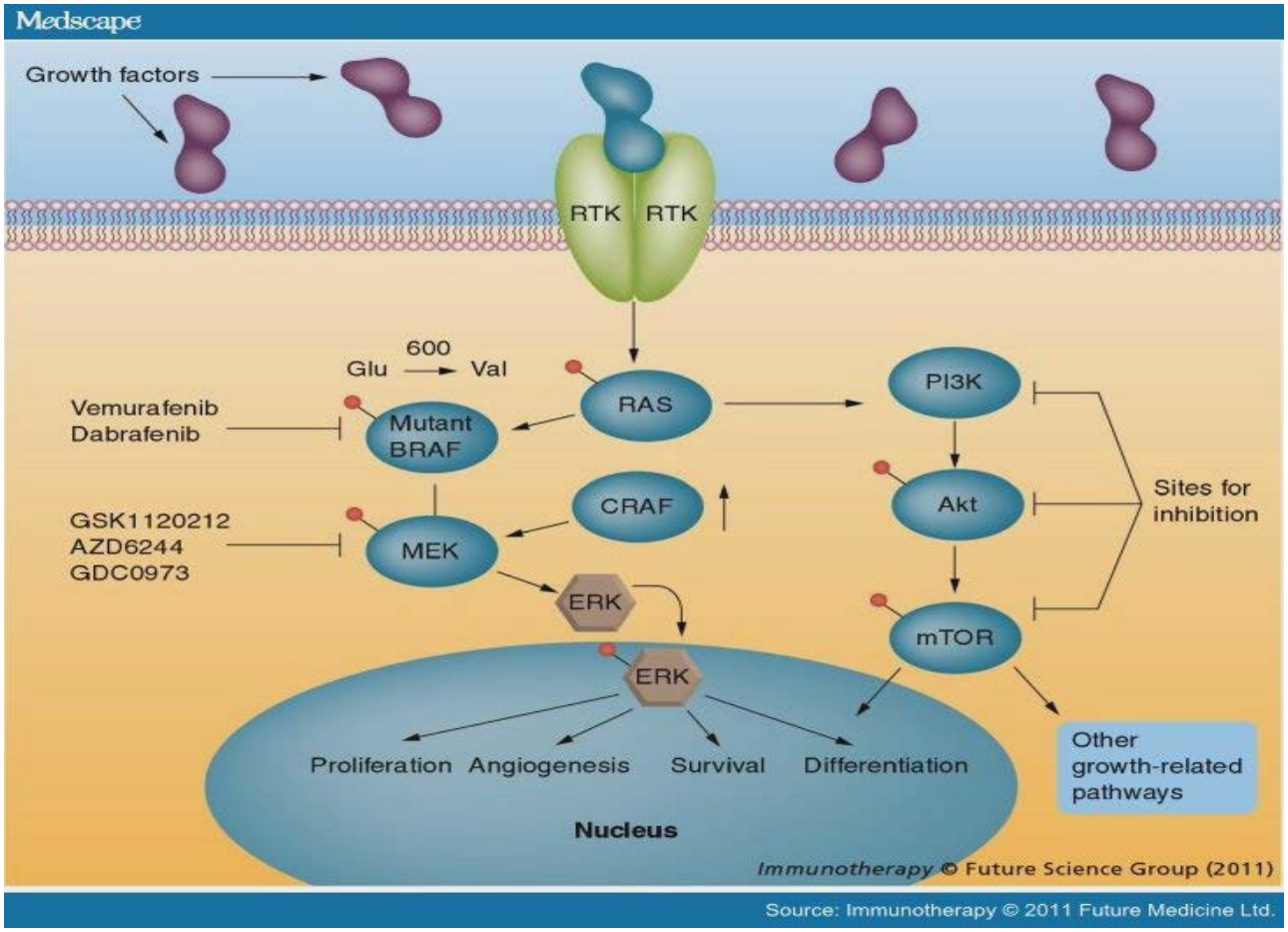


Figure 5

Histology Classification of CMM

Retrieved from http://www.nature.com/nrc/journal/v3/n 8/images/nrc1145-i1.jpg

Figure 6



Targeted therapy for BRAF V600 mutation in advanced CMM by vermafenib.