Melanoma

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Melanoma is a form of skin cancer that originates from specialized cells in the skin called melanocytes. Environmental, biochemical, molecular and genetic factors are all involved in the genesis of melanoma. Although the incidence of melanoma continues to rise worldwide, no current effective treatment is available for metastatic disease. Thus, development of new and efficacious strategies to treat this aggressive disease is urgently needed. Understanding the molecular and cellular basis of melanoma initiation, progression and metastasis is critical to identify new targets for novel therapeutic approaches that would improve survival and offer hope to patients coping with this aggressive neoplasm.

Introduction

Melanoma is the most serious form of skin cancer, which arises from the pigment-producing cells called melanocytes. Embryologically, melanocytes originate from pluripotent cells of the neural crest. During embryogenesis these specialized cells migrate to the skin, hair follicles, eye and inner ear where they differentiate into mature melanocytes capable of producing pigment (Goding, 2007). Melanocytes can also be found in other organs such as choroids, oral cavity, nasopharynx and leptomeninges. Within the skin, melanocytes are localized at the basement membrane, in close contact with neighbouring keratinocytes that direct their behaviour and growth through a complex network of growth factors and cell adhesion molecules (Haass et al., 2005).

Melanocytes synthesize and distribute the pigment melanin, which imparts skin colour. Melanocytes contain a specialized intracellular organelle, the melanosome. The broad spectrum of skin pigmentation seen among humans depends on many factors including the rate of synthesis of two types of melanin, pheomelanin and eumelanin and the rate of transfer of melanosomes to keratinocytes (Yamaguchi et al., 2007). Melanin in melanosomes provides protective coloration against the damaging effects of ultraviolet (UV) radiation.

See also: Regeneration of Mammalian Skin

The incidence of melanoma continues to rise more rapidly than any other malignancy, with the exception of lung cancer in women (Markovic et al., 2007). The world health organization (WHO) estimates that more than 130,000 cases of melanoma are diagnosed annually worldwide. The incidence of melanoma varies with age, sex, race and ethnicity. The highest incidence is found in Australia, New Zealand, North America and northern Europe. In the United States, melanoma is the sixth most frequent cancer among men and the seventh among women. A recent study of Surveillance Epidemiology and End Results (SEER) data concluded that melanoma incidence is increasing among young women in the United States (Purdue et al., 2008). Melanoma is the most frequent cancer in women 25–29 years old and the second most frequent cancer in women between 30 and 34 years old. It is estimated that the probability of developing melanoma among the general population is approximately 1 in 100. Thus, malignant melanoma represents a major public health concern.

Although the aetiology of melanoma is multifactorial, excessive UV light exposure (UVB 290–320 nm) appears to be an important contributing factor (Leiter and Garbe, 2008). In experimental animal models of melanoma, UV radiation in the longer wavelength (UVA at 320–400 nm) has also been implicated. Approximately 10% of all melanomas arise due to genetic predisposition. Fair skin, red hair and light colour eyes are considered phenotypic characteristics associated with increased risk of melanoma. In addition, individuals with a family history of melanoma, large number of melanocytic or dysplastic naevi, or tendency to freckle, are at increased risk of developing melanomas over their lifetime.

This review summarizes the cellular and molecular events associated with melanomagenesis, and briefly discusses the influence of the microenvironment on disease progression and therapeutic outcome.

Pathobiology of Melanoma

Transformation of melanocytes into melanoma is a step-wise process involving the interaction of environmental,
genetic and host factors. Under normal tissue homeostasis, keratinocytes in the skin keep melanocytes under tight control, regulating their proliferation and survival. Deregulated expression or activity of molecules that control cell cycle progression, growth factor-mediated signalling and adhesion to their surrounding microenvironment allows melanocytes to escape the tight control exerted by the neighbouring keratinocytes.

Melanocyte transformation into melanoma starts with an initial phase of proliferation leading to the development of benign nevi, an early hyperplastic melanocytic lesion, followed by anomalous growth and dysplasia. Clinically dysplastic nevi have typical features such as irregular borders, asymmetry, uneven coloration and increased diameter. Nevi are usually benign lesions but sometimes can progress to a radial growth phase (RGP) melanoma. During RGP, proliferation and invasion of melanoma cells are restricted to the epidermis. RGP cells may form small nests but do not have the capacity to metastasize. In the vertical growth phase (VGP), tumour cells acquire the ability to grow vertically and invade into the dermis and subcutaneous tissue. VGP cells exhibit most of the hallmarks of transformed cells; they have the ability to efficiently form colonies when grown in soft agar and are able to form tumours when injected into immunodeficient mice. In the final step, tumour cells acquire the ability to metastasize to distant organs; this process constitutes the most advanced stage in tumourigenesis. Although this model of linear progression is well accepted, not all melanomas go through each of all these phases. In some cases, RGP, VGP or metastatic melanomas may develop directly from melanocytes, without going through each of the earlier-described steps (Figure 1).

Clinically, melanoma can be divided into four subtypes including superficial spreading melanoma, nodular melanoma, acral melanoma and lentigomaligna melanoma (Elder, 2006). Adequate surgical resection of RGP melanomas leads to cure in 90% of cases, indicating that these lesions have not yet developed competence for tumourigenic growth and metastasis. VGP primary melanomas, however, contain multiple genetic abnormalities and have metastatic competence, growing invasively and independently of exogenous growth factors. The prognosis of patients with early melanoma depends on a number of clinical and histopathological factors, including tumour thickness, mitotic index and occurrence of ulceration (Markovic et al., 2007). Current diagnostic methods for melanoma are based on histopathological examination. No good molecular markers are available to distinguish among different melanoma subtypes or to predict progression of the disease or clinical outcome. Recently, Bastian et al. have demonstrated that somatic mutations and genome-wide copy number could be used to distinguish among the different subtypes of melanoma with 70% accuracy (Curtin et al., 2005). Hopefully, future research will lead to the identification of biomarkers with diagnostic, prognostic and therapeutic significance that could allow for patient-specific treatment selection matched to a particular molecular profile.

![Figure 1](melanoma-development-and-progression.jpg)

**Figure 1** Melanoma development and progression. Melanoma progression is usually regarded as a stepwise process in which normal mature melanocytes become transformed and progress into malignancy. Transformation of melanocytes into melanoma is dependent on genetic and environmental factors, in particular UV radiation. Acquisition of malignancy and metastatic potential can be influenced by the tumour microenvironment, composed of nontransformed cells including fibroblasts, endothelial cells and immune cells. Growth factors and ECM-dependent signalling mediates crosstalk between the tumour cells and the cells in the microenvironment. In some instances advanced melanomas can develop directly from normal melanocytes without going through each of the stages depicted in the model.
Molecular and Cellular Basis of Melanoma

Mutations associated with familial melanoma

The occurrence of melanoma is influenced by genetic as well as environmental factors. Melanoma, as other neoplasias, arises due to the accrual of mutations in genes that are critical for proliferation and survival. See also: Cancer

Familial melanoma represents approximately 10% of melanomas. Germline mutations in two genes that have critical roles controlling cell cycle progression, CDKN2A, on chromosome 9p21, and cyclin-dependent kinase 4 (CDK4), on chromosome 12q13, have been associated with familial melanoma. Inactivating mutations of the CDKN2A gene are the most frequent cause of inherited susceptibility to melanoma. Additionally, polymorphisms in the melanocortin-1 receptor (MC1R) gene, which is generally associated with red hair, fair skin and increased freckling, confer increased susceptibility to melanoma. See also: Cell Cycle; Melanoma: Genetics

CDKN2A locus

Also known as the familial melanoma locus, CDKN2A has a complex genomic organization (Chin, 2003). The CDKN2A locus encodes two different proteins, the cyclin-dependent inhibitors p16INK4a and ARF (also known as p14 in humans) (Gil and Peters, 2006). In human melanoma, inactivation of p16INK4a/ARF is a common genetic lesion. The tumour suppressor p16INK4a can be inactivated by point mutations, deletions and promoter methylation. p16INK4a is a CDK inhibitor, which binds and inhibits the activity of the CDK4 and CDK6. CDK4 is a G1 CDK that phosphorylates and inactivates the retinoblastoma protein (pRB), allowing cells to pass through the restriction point and progress through the cell cycle. The tumour suppressor pRB interacts with the E2F family of deoxyribonucleic acid (DNA)-binding transcription factors (E2F) and through this interaction sequesters and thus inhibits binding of E2F to the promoter of its target genes. Phosphorylation (and inactivation) of pRB leads to the release of E2F and subsequent binding of the transcription factor to the promoter of genes required for S phase entry and cell cycle progression (e.g. cyclin A). Albeit genetic inactivation of pRB is not associated with familial melanoma, individuals who carry germline mutations in this gene, such as retinoblastoma patients, have increased risk of developing melanoma (Fletcher et al., 2004). See also: Cell Cycle: Regulation by Cyclins; Tumor Suppressor Genes

ARF is the product of an alternative reading frame on the CDKN2A locus. Although mutations in CDKN2A frequently affects both p16INK4a and ARF, somatic and germline mutations that affect only ARF have been found in cell lines and tumour samples (Sharpless and Chin, 2003). The tumour suppressor ARF binds to and inhibits MDM2 (murine double minute 2)-dependent ubiquitination and degradation of the tumour suppressor p53; therefore inactivation of ARF leads to p53 degradation. The CDKN2A locus, and its two gene products p16INK4a and ARF, regulates the RB and p53 pathways influencing both proliferation and survival in melanoma.

Cyclin-dependent kinase 4

Germline mutations in cdk4 have also been identified in families known to have increased risk of melanoma. Mutations in Cdk4/ (Arg24Cys; R24C) prevent binding of p16INK4a CDK inhibitors and render CDK4 insensitive to these inhibitors. Mutations in CDK4 are also frequently found in sporadic melanomas. In addition to mutations in CDK4 found in human melanoma, a knockin mouse model expressing a CDK4 R24C mutant allele form of CDK4 exhibits increased susceptibility to melanoma formation after carcinogen treatment (Sotillo et al., 2001), providing additional support for the role of CDK4 in melanogenesis.

Melanocortin-1 receptor

The MC1R is a seven transmembrane G protein-coupled receptor expressed on the surface of melanocytes. The MC1R plays an important role in pigmentation; UV radiation stimulates secretion of the MC1R ligand, melanocyte-stimulating hormone (MSH). The MC1R gene, located on chromosome 16q24.3, is highly polymorphic and these genetic variations are partially responsible for the differences in skin pigmentation in humans. Genetic variations in the MC1R receptor can affect its signalling capability. Certain genetic variations reduce the ability of MC1R to stimulate the production of eumelanin, resulting in mostly pheomelanin synthesis and decreased protection against UV radiation and increased risk of melanoma. Additionally, variations in the MC1R gene have been proposed to affect the penetrance of mutations in the CDKN2A gene (Box et al., 2001); recently, MC1R variants have been associated with BRAF mutations (see later) in nonchronic sun-damaged melanomas in Caucasian populations (Landi et al., 2006). See also: G Protein-coupled Receptors

Somatic mutations and dysregulated signalling pathways in melanoma

Most of the genetic alterations associated with melanoma development are not inherited but rather result from sporadic mutations. The majority of melanoma-related oncogenes are activated through somatic mutations, leading to deregulation of important cellular signal transduction pathways, critical alterations in the melanoma cell cycle machinery, and melanoma–microenvironment interactions that are essential for tumor progression (Figure 2).

Important contributions and new insights into dysregulated signalling in melanoma have recently been fostered by new technologies, including large-scale sequence analysis of candidate genes or their hot-spots, analyses of gene
copy number by comparative genome hybridization (CGH) and from large-scale gene expression profiling.

**MAPK pathway**

An important milestone was the recent discovery of mutations in the protein kinase BRAF in approximately 60% of melanomas and common nevi (Davies et al., 2002). Substitution of valine for glutamic acid in codon 600 (V600E) accounts for 80% of BRAF mutations. Mutations in BRAF lead to constitutive activation of the mitogen-activated protein kinase (MAPK) pathway resulting in increased proliferation and survival.

The RAF/MAPK pathway (Woodgett, 2006) is activated by several membrane receptors, including receptor tyrosine kinases (RTKs), G-coupled receptors and extracellular matrix (ECM) receptors or integrins (Figure 2). Stimulation of cell surface receptors leads to the activation and membrane translocation of the small G protein RAS. Activation of RAS stimulates the RAF family of serine/threonine kinases, which includes ARAF, BRAF and CRAF (or RAF-1). Activated Raf phosphorylates the MAPK kinase MEK (MAP kinase/ERK kinase), which subsequently phosphorylates the MAPKs, extracellular-regulated kinases 1 and 2 (ERK1/2). Phosphorylation of ERK promotes its nuclear translocation where it can regulate gene expression through phosphorylation of target substrates. Through MAPK activation, BRAFV600E regulates the expression and function of cell cycle regulators including cyclin D1, p16INK4A, p21cip/kip, p27kip1 and the transcription factors microphthalmia-associated transcription factor (MITF) and nuclear factor κB (NF-κB) (Figure 2). See also: Protein Kinases: Physiological Roles in Cell Signalling

Activation of the MAPK pathway can also be associated with mutations in the NRAS oncogene. Approximately 10–20% of cutaneous melanomas harbour mutations in NRAS, most commonly at codon 61 due to substitution of leucine for glutamic acid (Q61L). Interestingly, mutations in BRAF and NRAS are mutually exclusive, suggesting
that they have functionally comparable roles activating the MAPK pathway and thus promoting melanomagenesis. Additionally, MAPK activation can also be stimulated by continuous activation of growth factor-mediated signalling (see later). It is important to note that there are a few cases of melanomas that despite having wild-type forms of BRAF and NRAS, also exhibit high levels of MAPK activity, further underscoring the importance of this signalling pathway for melanomagenesis.

**PTEN/PI3K/AKT signalling**

The phosphotyridinositide 3-kinase (PI3K) pathway is deregulated in many cancers including melanoma. PI3K is a heterodimeric lipid kinase, composed of two subunits: the regulatory subunit (p85) and the catalytic subunit (p110). RTKs and RAS activate PI3K; activated PI3K generates lipids second messengers, phosphatidylinositol (3, 4, 5)P3 (PIP3), inducing translocation of downstream effectors such as AKT (also called protein kinase B (PKB)) to the plasma membrane where it gets phosphorylated and further activated. The AKT family has three members: AKT1, 2 and 3. AKT3 appears to be the predominant AKT isoform associated with melanoma initiation and progression (Stahl et al., 2004). Recent studies indicate that AKT signalling is deregulated in approximately 50% of melanomas (Stahl et al., 2004). Aberrant PI3K/AKT signalling in melanoma can result from AKT gene amplification, AKT overexpression or inhibition of negative regulators such as the tumour suppressor phosphatase and tensin homologue (PTEN) (Stahl et al., 2003). PTEN is a lipid and protein phosphatase, which negatively regulates PI3K-mediated signalling. **PTEN** deletion or mutation is found in 60% of melanoma cell lines and 10% of tumour samples (Lopez-Bergami et al., 2008); **PTEN** silencing can also be achieved through promoter methylation (Mirmohammadsadegh et al., 2006). PTEN, PI3K, PIP3 and AKT are key mediators of intracellular signalling pathways that regulate important cellular processes such as proliferation, growth, differentiation, survival, motility, invasion, metabolism and intracellular transport. Alterations in this signalling pathway can contribute to melanoma initiation and progression. Recently, Cheung et al. have shown that AKT3 overexpression can cooperate with BRAFV600E to transform human melanocytes by phosphorylating BRAF and attenuating MAPK signalling to levels that promote cell proliferation and transformation (Cheung et al., 2008). Furthermore, a recent study by Dai et al. using tissue microarray (TMA) and immunohistochemistry showed that levels of activated AKT increased with tumour stage and inversely correlated with overall patient survival (Dai et al., 2005). Mutations in BRAF and PTEN are simultaneously present in 20% of melanomas.

**Growth factor-mediated signalling**

The expression of multiple growth factors and growth factor receptors is dysregulated in melanoma. Dysregulated growth factor-mediated signalling in melanoma cells may be induced through different mechanisms including gene amplification, activating mutations and overexpression of growth factors and/or their receptors. Melanoma cells express an assortment of growth factors and cytokines, which stimulate proliferation, survival, migration, invasion and metastasis. Some of the growth factors produced by melanoma cells such as basic fibroblast growth factor (bFGF), transforming growth factor β (TGF-β) and platelet-derived growth factor (PDGF-A and -B), stimulate proliferation of melanoma cells in an autocrine manner (Lazar-Molnar et al., 2000). In addition, some of the melanoma-derived growth factors stimulate neighbour cells in the surrounding microenvironment, promoting favourable conditions that further enhance tumour progression. Melanoma-secreted growth factors stimulate angiogenesis and stroma formation by inducing proliferation and activation of fibroblasts and endothelial cells. Additionally, melanoma-secreted PDGF stimulates neighbouring fibroblasts to produce ECM proteins such as collagen, fibronectin and laminin (Smalley et al., 2005). Tumour-associated fibroblasts can promote and sustain tumourigenesis by not only contributing to ECM synthesis, but also secreting paracrine growth factors such as bFGF, IGF-1 and TGFβ into the tumour microenvironment. Melanomas also produce and secrete TGFβ. The TGFβ receptors are serine/threonine kinases that upon ligand binding induce phosphorylation of the SMAD family of transcription factors. TGFβ signalling induces tumourigenesis and metastasis acting on tumour cells as well as on cells of the tumour microenvironment. TGFβ promotes growth inhibition of epithelial cells and melanocytes, but melanoma cells themselves are resistant to these effects, likely through the expression of repressors of TGFβ/SMAD signalling (Hussein, 2005). TGFβ promotes deposition of ECM, survival, angiogenesis and transition to more aggressive phenotypes. The **MET proto-oncogene** encodes the hepatocyte growth factor/scatter factor (HGF/SCF) receptor, a tyrosine kinase that is involved in melanocyte growth and melanoma development. c-MET has been associated with invasive growth and metastatic potential in various cancers (Lesko and Majka, 2008). Melanomas secrete HGF, which can then induce sustained autocrine activation of c-MET. Binding of HGF to the RTK induces c-MET auto-phosphorylation creating a docking site for PI3K, or Grb-SOS (son of sevenless) adaptors, leading to MAPK activation and mitogenesis. Met can also interact with SRC, the transcription factor STAT-3 (signal transducers and activators of transcription 3), and the adaptors SHC and GAB1 (Grb2 associated binder 1). Through these interactions, MET regulates multiple cellular functions including growth, cell motility and migration, invasion, morphogenesis and differentiation. HGF/MET signalling has been implicated in melanoma progression. In early melanomas, HGF induces downregulation of E-cadherin expression and induction of metalloproteases (MMPs) (Li et al., 2001). Recently, overexpression in tumour
samples has been correlated with poor prognosis (Cruz et al., 2003).

The receptor tyrosine kinase KIT (also known as CD117/SCF (stem cell factor) receptor) and its ligand SCF are essential regulators of growth, differentiation, migration and proliferation in melanocytes (Lennartsson et al., 2005). The role of KIT signalling in melanoma is not completely understood. In melanoma, increased c-KIT activity may be caused by overexpression, activating mutations or autocrine loops. Some studies indicate loss of KIT receptor expression during tumour progression (Huang et al., 1998). In some melanoma cell lines, overexpression of KIT leads to apoptosis (Huang et al., 1996). Bastian et al. have identified activating KIT mutations in a subset of melanomas (Curtin et al., 2006). Recently, we have identified a novel subset of melanoma cell lines with high expression of both KIT and CDK4. This subgroup of melanomas lack KIT mutations, but have high KIT signalling activity and do not rely on BRAF for growth and survival (Smalley et al., 2008).

The significance of growth factor-mediated signalling and its role in melanocyte transformation and the development of the malignant phenotype has been demonstrated in experimental models where overexpression of bFGF, HGF, SCF and endothelin-3 together with UV radiation led to melanocyte transformation and the formation of invasive and in situ-like tumours (Berking et al., 2004). Importantly, signalling through RTKs and G-coupled receptor is known to activate intracellular pathways such as MAPK, PI3K, protein kinase C and JAK( Janus Kinase)-STAT all of which play critical roles in cell differentiation, proliferation, survival and migration thus influencing melanoma development.

**Extracellular matrix and adhesion interplay**

In the skin, melanocyte behaviour and homeostasis is tightly controlled by neighbouring keratinocytes. Under normal conditions, keratinocytes exercise tight control of melanocyte proliferation through paracrine growth factors and intercellular communication via cell–cell adhesion and cell–ECM adhesion. Deregulated proliferation takes place when melanocytes break away from the control imposed by keratinocytes through downregulation of cell adhesion molecules such as E-cadherin, P-cadherin, desmoglein and connexins and upregulation of ECM receptors or integrins allowing the transformed cells to detach from the basement membrane and migrate to other locations (Haass et al., 2005). Melanoma is composed of the tumour cells and the supporting stroma, which includes fibroblasts, endothelial cells, immune cells, soluble molecules and the ECM. Several studies support the view that in addition to the genetic events required for melanomagenesis, interactions between the tumour cells and its adjacent microenvironment could strongly influence the transformation process. Alterations in adhesion receptors are fundamental for this process. See also: Extracellular Matrix; Integrin Superfamily

Cadherins are transmembrane proteins that promote calcium-dependent intercellular adhesion. The extracellular domain of cadherins mediates homotypic interactions with similar cadherins in adjoining cells. The cytoplasmic domain of E-cadherin links to the cytoskeleton through interactions with cytoplasmic protein complexes that include β-catenin. Melanoma cells break away from the control imposed by keratinocytes through downregulation of E-cadherin and upregulation of N-cadherin. This cadherin switch, usually observed during the transition from RGP to VGP, allows melanoma cells to interact with other N-cadherin-expressing cells such as fibroblasts and endothelial cells. N-cadherin-mediated cell adhesion increases cell motility and survival. Reexpression of E-cadherin in melanoma cells restores keratinocyte control over proliferation, precludes invasion and reduces tumourigenicity in vivo (Hsu et al., 2002). E-cadherin can also prevent tumour progression by downregulating β-catenin-mediated signalling as β-catenin induces proliferation by promoting transcription of growth-regulatory and survival genes such as cyclin D1, c-MYC and MITF (Li et al., 2004).

Invasion by malignant cells requires altered cellular interactions with the ECM. Integrins are a family of cell surface molecules that mediate adhesion between cells and the ECM. Expression of cell surface molecules, including integrins, changes with progression from RGP to VGP primary melanoma and to metastatic melanoma. Integrins are heterodimeric receptors, composed of two subunits that associate to bind specific components of the ECM. Integrin-mediated adhesion to the ECM leads to cytoskeleton reorganization and activation of multiple signalling pathways. Integrins lack intrinsic kinase activity and consequently depend on intracellular kinases and adaptor molecules, such as integrin-linked kinase (ILK), focal adhesion kinase (p125FAK), small Rho-GTPases and SRC-family kinases among others, for signalling. Through these interactions, integrins are able to activate signalling cascades such as MAPK and PI3K, and, consequently, integrin-mediated signalling affects cell growth, migration, invasion, angiogenesis and survival. See also: Signal Transduction: Overview

Expression of zvβ3 integrin is controlled by the RAF-MEK pathway (Woods et al., 2001) and is associated with progression of melanoma cells from RGP to VGP. Overexpression of β3 in RGP melanoma leads to a tumourigenic and invasive phenotype, and inhibition of this integrin in metastatic cells inhibits the invasive phenotype (Hsu et al., 1998).

Crosstalk among the different signalling pathways activated by integrins and RTKs is important for the regulation of melanocyte proliferation and melanoma tumour progression.

**Targeted Therapy**

Melanoma is a highly aggressive disease that is notoriously refractory to currently available therapies. The best
management for melanoma continues to be early detection and surgical resection. If detected early, treatment is highly effective; however, the prognosis is generally poor for patients with advanced disease. Currently, the only US Food and Drug Administration (FDA)-approved chemotherapeutic agent for metastatic melanoma is dacarbazine (DTIC), an alkylating agent associated with temporary objective response rates below 10% (Tawbi and Kirkwood, 2007). The orally available DTIC analogue, temozolomide, a drug with good oral bioavailability, CNS penetration and low toxicity, is frequently used off-label to treat melanoma. In addition, biotherapies such as interferon α (IFNα) and interleukin 2 (IL-2) are commonly used as adjuvants, however response rates are low and toxicity is generally high.

The reported increase in melanoma incidence as well as the high toxicity and low efficacy of currently available pharmacological treatments underline the need to develop novel treatment approaches to manage this aggressive disease. We hope that increasing knowledge of the molecular biology of melanoma will lead to the development of effective therapies targeting signalling pathways dysregulated in melanoma. The failure of cytotoxic regimens added to the fact that the incidence of melanoma continues to rise, emphasizes the urgency to develop effective therapeutic approaches to treat this deadly disease.

Considering the high frequency of BRAF mutations associated with melanoma, targeting the MAPK pathway appears to be a rational approach. One of the first agents evaluated in clinical trials for melanoma was the multi-kinase inhibitor Sorafenib (BAY 43-9006). When used as single agent, Sorafenib showed little antimelanoma activity; however, when combined with chemotherapeutic agents such as paclitaxel and carboplatin, it led to partial responses in a phase I clinical trial (Flaherty et al., 2008). Recently, other more potent and specific RAF/MEK inhibitors such as ARRY-142886 (AZD6244) (Yeh et al., 2007) and PLX4720 (Tsai et al., 2008) have been developed and are undergoing clinical trials.

In addition to MAPK, PI3K signalling is often deregulated in melanoma. Agents that target the PI3K and its downstream effectors are currently under development. For example, CCI-779, a small molecule inhibitor of the mammalian target of rapamycin (mTOR), already approved for use in renal cell carcinoma and shown to be well tolerated (Samlowski and Vogelzang, 2007), has entered clinical trials for melanoma either as a single agent or in combination with cytotoxic drugs (Margolin et al., 2005; Thallinger et al., 2007).

Alternative targets for melanoma include those involved in survival signals, such as the NF-κB pathway and the antiapoptotic BCL-2, which is generally highly expressed in melanoma cells. Pre-clinical and clinical studies using anti-BCL-2 strategies (Oblimersen) in combination with chemotherapeutic agents have shown some benefits in melanoma.

Cell cycle regulatory proteins constitute an additional target in melanoma. Although broad selectivity cdk inhibitors (e.g. flavopiridol) have not shown significant antimelanoma activity, the use of this class of small molecule inhibitors could be beneficial in patients whose tumours have mutations, gene amplifications or overexpression of cell cycle proteins such as cyclin D, cdk4 or cdk2.

The tumour vasculature may also be a good target for therapeutic intervention. Antiangiogenic factors such as bevacizumab (anti-VEGF antibody) and the VEGFR inhibitor AG013736, have shown antimelanoma activity in xenograft models, but not major effects in clinical trials when used as monotherapy. However, combining antiangiogenic agents with other kinase inhibitors, such as those inhibiting the MAPK pathway, may still show some benefit. Other deregulated pathways such as those activated by growth factors and their receptors or integrins, also constitute attractive targets for melanoma therapy.

Overall, increasing evidence strongly suggests that targeting a single pathway will not be sufficient to eradicate melanoma; thus, targeting multiple pathways, in particular those important for melanoma growth and survival, may offer a better therapeutic approach. Understanding the molecular and genetic basis of melanoma is critical not only for identifying therapeutic targets and designing better drugs, but also for adequately selecting patient populations that would most likely benefit from a particular therapeutic regimen.

Conclusions

Malignant melanoma constitutes a significant public health problem and a scientific and medical challenge. Although significant progress has recently been made understanding the biology and molecular mechanisms underlying melanomagenesis, no current effective treatment is available for metastatic disease. Melanoma is notoriously resistant to cytotoxic therapies. The development of effective therapeutic approaches faces many challenges, including the lack of good experimental models that closely resemble the in vivo behaviour of the tumour cells, the lack of adequate biomarkers that could be used to accurately diagnose the disease and predict clinical outcome, and the high degree of heterogeneity seen in tumours. A better understanding of the molecular and genetic mechanisms regulating important cellular processes such as proliferation, signal transduction and, survival is needed to optimize our diagnostic, prognostic and therapeutic strategies. The advent of new technologies such as DNA microarray, small interfering ribonucleic acid (siRNA) and whole-genome sequencing will hopefully enable us to use molecular profiles to not only design personalized therapies but also to estimate the probability of developing resistance to therapy and disease recurrence.

References


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