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The Role of Genetics in the Pathogenesis of Periocular Cutaneous Neoplasms: Implications for Targeted Therapy

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Recent discoveries in genetics and gene expression have revolutionized the ability to diagnose, treat, and prognosticate various forms of cancer. Cancer is essentially a genetic disease characterized by genomic instability. The mutations that predispose an individual to cancer formation are either germline (inherited) or somatic (acquired). Few tumors are considered to be bona fide hereditary tumors and most develop from mutations caused by inherent defects in the DNA reparative apparatus, derangements in DNA replication, or carcinogens.¹

There are two main classes of genes that, when mutated, contribute to the pathogenesis of cancer. Oncogenes, or cancer promoting genes, when mutated can be perpetually “turned on” as in the case of *RAS*, the oncogene in cutaneous melanoma.² The tumor suppressor genes represent the second class of genes that negatively regulate cell growth and promote cell death. When these “gatekeeper” genes are inactivated, there is uncontrolled cell proliferation. The patched (*PTCH*) gene is an example of such a gatekeeper gene that is inactivated in both sporadic and hereditary basal cell carcinomas.³ Furthermore, the elucidation of key signaling pathways, such as the sonic hedgehog signaling pathway in basal cell carcinoma and the protein kinase pathway in cutaneous melanoma, is facilitating the advent of targeted therapies for these malignancies.⁴ The purpose of this paper is to provide a review of the genetic background of various cutaneous neoplasms that are found in the periocular region and discuss the ramifications on current and future targeted therapies.

Basal Cell Carcinoma

Basal cell carcinoma (BCC) is the most common human malignancy, accounting for approximately 90% of eyelid cancers in the United States.⁵ Although many risk factors for BCC have been identified including fair skin type, ultraviolet (UV) exposure, immunosuppression, ionizing radiation, and advanced age, the underlying mechanism is genetic alteration.⁴

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Sonic Hedgehog (Shh)

It has been known since 1996 that a mutation in the *patched 1* gene (*PTCH1*) located at chromosome 9q22.3 was linked to basal cell nevus syndrome, or Gorlin Syndrome.^{6,7} *PTCH1* is involved in the sonic hedgehog signaling pathway, which was first discovered in *Drosophila melanogaster*, and found to be critical to the proper formation of segments of the fruit fly during embryogenesis.⁸ This signaling pathway begins at the primary cilium, which is present on most cells during interphase.⁹ *PTCH1*, a 12-transmembrane domain protein, normally functions to block Shh signaling by antagonizing the activity of Smoothened (SMO), a seven domain transmembrane protein, preventing its migration into the cilium.⁹ The downstream events involving a family of zinc-finger transcription factors called GLI play a key role in mediating the Shh signal.⁸ If the tumor suppressive action of *PTCH1* is inactivated, there is subsequent dysregulation of the Shh pathway with a resulting predisposition to developing BCC (Figure 1). The *PTCH1* gene mutation is also seen in up to 70% of sporadic cases of BCC. Basal cell carcinomas overexpress the transcription factors GLI1 and GLI2, which indicates that the Shh pathway is constitutively active in BCC.¹⁰ Aside from tumorigenesis, the Shh pathway activation is known to play a role in mammalian visual system development. Shh is expressed in the retinal ganglion cells and has been known to play a role in precursor cell proliferation, photoreceptor differentiation, and normal cellular organization in the rodent retina.¹¹ Moreover, in patients with Gorlin syndrome, focal areas of dysplasia involving retinal cells in the outer nuclear layer have been reported.¹¹

Vismodegib (GDC-0449), an oral inhibitor of the Hedgehog pathway which works by antagonizing SMO (Figure 1), was approved by the US Food and Drug Administration (FDA) in January 2012 for treatment of metastatic and locally advanced BCC.¹² A multicenter phase 2 clinical trial of vismodegib was conducted on 104 patients from February 2009 through November 2010. Of the 33 patients that were enrolled with metastatic BCC, 30% were found to have a response. In 63 patients with locally advanced basal cell carcinoma, the response rate was 43%, with complete responses in 13 patients (21%). Locally advanced BCC was defined as at least 1 lesion 10mm or more in longest dimension and considered unresectable for one of the following reasons: the patient had recurrence after 2 or more surgical procedures or surgery was expected to result in substantial morbidity or deformity.¹³ Disease progression was noted in 18% of patients with metastatic disease. An additional phase 2 trial was conducted in 41 patients with Gorlin syndrome. Vismodegib was associated with a decrease in the number of new and existing surgically eligible BCCs compared to placebo. Surgically eligible BCCs were defined as BCCs with a diameter of 3mm or greater on the nose or periorbital skin, 5mm or greater elsewhere on the face, or 9mm or greater on the trunk or limbs. The effect of this medication against BCC was associated with a decrease in hedgehog signaling with a 90% decrease in GLI1 messenger RNA in biopsy specimens treated for 1 month. Histologic examination revealed no detectable BCC in biopsies from clinically regressed areas in 83% of samples.¹⁴ The tumors were observed to recur when the medication was stopped.¹⁴

The adverse effects profile of vismodegib included toxicities considered to be grade 1 or 2 (mild to moderate). Despite the low-grade toxicities, adherence to the anticancer agent was

compromised by the side effects and the discontinuation rates from loss of taste and muscle cramps were 12% and 27% respectively. Serious adverse events were reported in 25% including death in seven patients.¹³ These seven patients were thought to have coexisting conditions at baseline and the relationship between the study drug and the deaths is unknown.¹³

Cyclopamine is a naturally occurring sterol alkaloid derived from the *Veratrum californicum* plant, which was postulated to inhibit the Shh signaling pathway when cyclopia was reported in offspring of pregnant sheep that ingested small quantities of the plant. Its main mechanism of action occurs by binding and inactivating SMO (Figure 1). Cyclopamine was topically found to be successful in advanced BCC in a phase 1 clinical trial.⁴

Other SMO inhibitors have been investigated which include an antifungal, itraconazole, and arsenic trioxide. These agents inhibit SMO and GLI1 in a distinct mechanism than the other Smoothened antagonists, thus conferring inhibition in drug-resistant SMO mutants (Figure 1).¹⁵

TP53

Mutations in the gene *TP53*, which encodes the protein P53, occur in a wide variety of tumor types and disruption of this pathway occurs in most human cancers. P53 is known as the “guardian of the genome”¹⁶ and functions to sense genotoxic injury and arrest cell division allowing DNA repair prior to replication. It also induces apoptosis in cases of extensive DNA damage to eliminate defective and potentially malignant cells.¹⁶ The germ line mutation of *TP53*, Li-Fraumeni syndrome, does not predispose the patient to BCC, but may be a secondary event occurring after tumor initiation.¹⁶ In fact, mutations of *TP53* are actually found in 44–100% of BCC tumors themselves rather than in the germ line. Moreover, patients using sunscreen had significantly less *TP53* mutations in their tumors compared with those not using sunscreen, further suggesting that *TP53* mutation is a secondary event and not responsible primarily for carcinogenesis.¹⁰

Melanocortin-1 receptor variants. The melanocortin-1 receptor (MC1R) is a key protein regulating skin and hair pigmentation. Human MC1R variants have been found in a large proportion of white individuals. The red hair color variant alleles contribute to fair skin, freckling, and poor tanning response to UV, which in turn leads to decreased capacity to produce eumelanin and reduced skin photoprotectivity.¹⁷ Carriers of any two variant alleles are at increased risk of developing both nodular BCC and superficial BCC. Thus, MC1R variants may be an independent risk factor for the development of BCC. There is ongoing research to see if there is potential merit in pursuing MC1R agonists for skin cancer prevention. There have been no clinical trials as of yet.¹⁸

Squamous Cell Carcinoma

Cutaneous squamous cell carcinoma (SCC) is the second most common eyelid malignancy accounting for 5% of all eyelid malignancies in the United States.¹⁹ Unlike BCC, which has no precursor lesion, SCC can develop from actinic keratosis. Squamous lesions are thought

to occur on chronically sun-exposed sites, suggesting that UV radiation is the leading environmental risk factor.

The development of SCC is thought to involve anti-apoptotic and cell proliferative pathways including *TP53*, *RAS*, and *p16/CDKN2A*.¹

TP53

Inactivation of this tumor suppressive gene is reported to play a crucial role in development of actinic keratosis and SCC. Brash et al²⁰ found that 14 (58%) of 24 invasive SCCs of the skin contain mutations in *TP53*. Inactivation of p53 occurs in precancerous lesions, suggesting that early loss of p53 function contributes to later malignant degeneration. Moreover, UV irradiation in mice with deficient p53 activity leads to decreased apoptotic ability, likely leading to an inability to abort precancerous cells.²¹ Similar to BCC, the germline mutation in *TP53* in Li-Fraumeni syndrome does not increase the risk for SCC.

RAS

Mutations that activate the oncogene *RAS* are among the most common oncogenic lesions in human cancer. The reported frequency of *RAS* mutations in SCC ranges from approximately 10% to nearly 50%.²²

EGFR

Epidermal growth factor receptor is another common oncogene that is implicated in SCC of the head and neck.²³ The results of *EGFR* activation in keratinocytes are increased survival and resistance to apoptosis (Figure 2). Overexpression of EGFR has been implicated in cutaneous carcinoma of the head and neck, glioma, breast carcinoma, bladder cancer, and non-small-cell lung carcinoma.²⁴ Studies have shown that the degree of overexpression of EGFR correlates with the aggressiveness of cutaneous SCC. Strong EGFR overexpression was seen in 79% of 64 patients that had metastases compared with 36% of cases without metastases.²⁵ Furthermore, multivariate analysis by the same group of researchers found that EGFR expression was an independent predictor of metastasis.²⁵ Therefore, inhibitors of EGFR have been investigated for potential treatment of various cancers.

Gefitinib, a tyrosine kinase inhibitor, was used for treatment of solid tumors including non-small-cell carcinoma starting in 2003. It works by selectively inhibiting EGF-stimulated tumor cell growth and has been shown to block autophosphorylation in tumor cell lines in vitro, which in turn, prevents the remodeling of the cytoskeleton, proliferation, and induces a more differentiated phenotype (Figure 2).²⁶ A study was conducted on 22 patients with recurrent or aggressive SCC, defined as lesions that were 2 cm or greater, invaded deep tissue, or were associated with perineural invasion and/or metastasis to lymph nodes. Neoadjuvant treatment with oral gefitinib provided an overall response rate of 45.5% without treatment-related deaths. Fifty-nine percent of patients (13/22) experienced grades 2 and 3 toxicities including diarrhea, fatigue, and acneiform rash.²⁷

Erlotinib is also a tyrosine kinase inhibitor that inhibits tumor cell proliferation and autophosphorylation (Figure 2). Although it was approved by the US FDA in 2004 for

treatment of locally advanced or metastatic non-small-cell lung carcinoma and pancreatic cancer, clinical trials of erlotinib for cutaneous SCC have not yet been completed.²⁸ The most prominent side effects were rash and diarrhea. There have been numerous case reports of treatment of cutaneous squamous cell carcinoma with erlotinib. In a case of a 90-year-old woman with invasive SCC of the orbit, which would have required exenteration, parotidectomy, and neck dissection followed by free flap reconstruction and adjuvant radiation therapy, a decision was made to treat her non-invasively, because of her age and history of significant coronary artery disease. After three months of treatment, she had marked improvement in her clinical examination including visual acuity as well as both proptosis and ocular motility, although residual tumor remained.²⁹

Cetuximab is a monoclonal antibody to EGFR, which has greater specificity than the previously mentioned tyrosine kinase inhibitors but requires intravenous infusion (Figure 2).³⁰ Currently, cetuximab is approved by the US Food and Drug Administration for use in certain types of head and neck cancer in conjunction with radiation therapy. A phase 2 clinical trial of cetuximab as a single-agent therapy for cutaneous SCC included 36 patients with surgically unresectable or metastatic SCC.³⁰ Seventy-two percent of patients had lesions with high *EGFR* expression. Partial or complete response was seen in 69% of 36 patients at a dosage of 400mg/m² loading dose followed by weekly infusions of 250mg/m² for at least 6 weeks.³⁰ Interestingly, tumor EGFR expression levels were not associated with treatment efficacy.³⁰ Seven patients died during the treatment, but were considered to be related to disease progression or general conditions. The most frequent adverse effect was an acne-like rash occurring in 87% of the patients.³⁰

Sebaceous carcinoma

Sebaceous carcinoma comprises 5% of all eyelid malignancies in the United States and approximately 40% of all sebaceous gland carcinomas arise in the ocular adnexal skin.³¹ Muir-Torre syndrome is an autosomal dominant disorder characterized by sebaceous skin tumors, with or without keratoacanthomas, and visceral malignancies. It is considered to be a variant of hereditary nonpolyposis colorectal cancer syndrome (HNPCC). Cutaneous manifestations of Muir-Torre syndrome can occur before, concurrent with, or after the diagnosis of a visceral malignancy.³² Seventy percent of patients with Muir-Torre syndrome are reported to have a germline mutation in one allele of the mismatch repair genes, which encode mismatch repair proteins, essential for the maintenance of genomic integrity. Acquisition of a somatic “second-hit” mutation in a second allele leads to defective mismatch repair function and subsequent accumulation of genetically unstable cells.³² The strength of the association of sebaceous carcinoma with Muir-Torre syndrome is debated. Most studies agree that periocular sebaceous carcinoma is rarely associated with Muir-Torre syndrome.³³

TP53

67% of eyelid sebaceous carcinomas were detected to have point mutations in *TP53* in a study by Kiyosaki et al.³⁴ In other cancers, the *TP53* mutation status has been reported to be a useful prognostic marker or predictor of therapy response. Furthermore, in SCC of the eye and adnexa and BCC, *TP53* mutation analysis has implicated UV radiation as the major

carcinogen involved. However, Kiyosaki et al also found that the point mutations detected in *TP53* in 10 out of 15 cases were not induced by UV stimulus as in SCC and BCC.³⁴ UV-related mutations in *TP53* occur at dipyrimidine sites in 92% of skin tumors. In contrast, internal malignancies contain this particular mutation in *TP53* only 61% of the time, which was consistent with what Kiyosaki et al reported in their sebaceous carcinomas of the eyelid. This suggests that sebaceous carcinomas of the eyelid contain mutations that are distinct from those of other skin cancers and are potentially not stimulated by UV exposure.³⁴ Moreover, the downregulation of *p21* (transcriptional target of p53) expression was associated with lymph node metastases and was thought to be a potential prognostic marker of nodal metastases in sebaceous carcinoma of the eyelid.³⁴

Sonic Hedgehog and Wnt Signaling Pathways

Activation or dysregulation of the Shh and Wnt signaling pathways is suggested to lead to the development of many human malignancies, including BCC. Kim et al. studied 37 cases of eyelid sebaceous gland carcinoma wherein 8 patients showed lymph node or distant metastasis. The group with metastasis showed higher expression levels of Shh and Wnt than did the group without metastasis, implying that activation of the Shh and Wnt signaling pathway is associated with aggressive behavior of the tumor.³⁵

One gene expression profiling study showed dysregulation of the MAPK and JAK/STAT pathways in meibomian gland carcinomas through microarray analysis. Clusters of genes on chromosomes 1, 12, and 19 were also found to be dysregulated.³⁶ This study may be a precursor to future identification of specific markers or therapeutic targets in sebaceous carcinoma of the eyelid.

Cutaneous Malignant Melanoma

Cutaneous malignant melanoma develops from a malignant proliferation of melanocytes and accounts for 5% of all malignant cutaneous tumors and 1% of all eyelid malignancies. These lesions can arise de novo or from pre-existing nevi.³⁷ A family history of melanoma is elucidated in 10% of melanoma patients and increases the risk of melanoma by two-fold.³⁸ On a molecular level, activation of proliferative kinase signaling pathways is thought to be responsible for the transformation of a normal melanocyte into melanoma. These signaling pathways involve *BRAF*, *NRAS*, and *KIT* oncogenes.³⁹ Not only is there activation of these proliferative kinase signaling pathways, but there is also additional dysregulation of apoptotic pathways involving tumor suppressor genes *CDKN2A*, *TP53*, and *PTEN* for the development of melanoma.³⁹ Genomic instability occurs predominantly at the chromosomal level in melanoma. Over 95% of melanomas show multiple gains and losses of chromosomal portions, most frequently involving chromosomes 1, 6, 7, 9, 10, 11, 17, and 20.³⁹

Cyclin-dependent kinase N2A (CDKN2A)

Linkage analysis studies of families with an increased occurrence of melanoma led to putative loci on chromosome 9p21. Within the 9p21 region, the *CDKN2A* gene was established as a high-risk susceptibility locus in melanoma.⁴⁰ *CDKN2A* inhibits the activity

of cyclin-dependent kinase 4 (CDK4) complex, whose function is to drive cell cycle progression by phosphorylating RB protein (Figure 3). Several studies have estimated the risk of developing cutaneous melanoma among *CDKN2A* mutation carriers. In familial cases, the overall penetrance is 30% by age 50 and 67% by age 80. Among sporadic *CDKN2A* carriers, the risk is 14% by age 50 and 28% by age 80.⁴¹

RB1

Carriers of the *RB1* germline mutation have a fourfold to 80-fold elevated risk to develop melanoma. Unlike in sarcomas, the incidence of melanomas does not correlate with radiotherapy use, which is likely due to loss of heterozygosity (LOH) for the *RB1* allele. This demonstrates that there is an intricate linkage between the *CDKN2A*/CDK/RB pathways of tumor suppression in humans.⁴²

MC1R

MC1R variants are considered to be low to moderate risk melanoma loci. A meta-analysis found that presence of *MC1R* variants is associated with 1.5–2.5 fold odds ratio of developing melanoma; however, the risk appears to be pigmentation-independent, suggesting that *MC1R* has some cancer effects independent of pigmentation (Figure 3).⁴²

Receptor tyrosine kinase (RTK). The *c-KIT* gene encodes the RTK for stem cell factor (*SCF*), which transmits activation signals via the RAS-GTPase and in turn leads to sequential activation of *RAF*, *MEK*, and *ERK*, which leads ultimately to phosphorylation of key transcription factors and proteins involved in cell proliferation and cell cycle regulation (Figure 3). Pharmacologic targeting of *KIT*-mutated melanomas took place in two phase II trials of imatinib. In one trial, 28 patients with metastatic *KIT*-altered melanomas were treated with two complete responses and two partial responses.⁴³ In the second trial, 43 patients with metastatic melanomas were treated with imatinib revealing only partial responses in 23.3% and disease stabilization in 30.2% and disease progression in 46.5%.⁴⁴ Thus, only modest effects were seen with imatinib; however, other RTK inhibitors (sunitinib, nilotinib, and dasatinib) are currently being tested for efficacy (Figure 3).⁴²

Epidermal growth factor receptor (EGFR)

Unlike squamous cell carcinoma, neither activating *EGFR* mutations nor focal *EGFR* amplifications have been observed in melanoma. Most studies linking *EGFR* activation to melanoma biology have relied on protein expression or activation studies. Based on in vitro studies, it was thought that pharmacological blockade of *EGFR* with gefitinib could suppress growth in melanoma cell lines (Figure 3).⁴⁵ Phase II trials of *EGFR* inhibitor gefitinib in 46 metastatic melanoma patients revealed disappointing results. The median progression-free survival was only 1.4 months and median overall survival was 9.7 months.⁴⁶

BRAF

BRAF activation is thought to be at the heart of melanomagenesis. This gene encodes a protein belonging to a family of protein kinases which plays a role in regulating the MAP kinase/ERKs signaling pathway (Figure 3). The MAP kinase pathway affects cell division, differentiation and secretion. Other than oncologic conditions, *BRAF* mutations have been

associated with cardiofaciocutaneous syndrome. *BRAF* mutations have been observed in approximately 50% of melanomas and to a lesser extent in other cancers.⁴⁷ These mutations also occur at high frequencies in melanocytic nevi (>80%).⁴⁸ The exact relationship between *BRAF* mutations and sun exposure is still unclear. Yet, *BRAF* mutations are much more common in melanomas arising on sun-exposed lesions than in acral melanomas.⁴⁹ Strikingly, *BRAF* mutations are absent in uveal melanoma.⁴⁹ The data suggests that *BRAF* mutations are important in induction of proliferation and senescence of melanocytic nevi and in melanoma progression, but are not the sole drivers of oncogenic melanocytic transformation.⁵⁰ Selective *BRAF* inhibitors have been approved by the FDA. For example, vemurafenib, a selective inhibitor of mutated *BRAF* has shown clinical efficacy in the metastatic setting (Figure 3).⁵¹ The rates of overall survival in a phase III study with vemurafenib were 84% (N=336).⁵¹ This medication was eventually approved by the FDA in 2011.

MEK

Recent research has revealed that *MEK* mutations are present in melanoma. *MEK* inhibition was investigated prior to the advent of selective *RAF* inhibitors and was found to have exquisite potency against *BRAF* melanomas. AZD6244, a *MEK* inhibitor, has shown clinical promise both as single agents and in combination with *RAF* inhibitors (Figure 3).⁵²

Merkel Cell Carcinoma

Merkel Cell Carcinoma (MCC) is a highly aggressive neuroendocrine tumor that is very rare, yet twice as lethal as melanoma with a greater than 33% mortality rate.⁵³ It was once thought that light skin pigmentation and sun exposure were risk factors for the development of MCC; however, the recent identification of Merkel cell polyomavirus (MCV) has dramatically changed our understanding of the pathophysiology of this malignancy.⁵⁴ Immunodeficiency and immunosuppression also may play a role in the pathogenesis of MCC with increased rates in solid organ transplant recipients and in individuals with HIV and AIDS.⁵⁵

Merkel cell polyomavirus (MCV). The MCV encodes two major families of genes: 1) Large T antigen (LT) an Small T antigen (ST) and 2) late genes (viral proteins). The MCV LT antigen sequences harbor mutations, which prematurely truncate the protein thereby eliminating the helicase function of the LT. The hsc70 and RB binding motif are left intact. The truncation does not appear to affect the RB binding domain.⁵⁶ The high degree of association of MCV with MCC is beginning to be exploited in diagnostics as well as prognostication. One study has shown that patients with MCV-positive tumors had 5-year survival rates of 45% as compared to 13% 5-year survival rates in cases with MCV-negative MCC.⁵⁷ Finally, viral proteins in tumor cells are also promising targets for future therapies. For example, immunization with the DNA MCV vaccine was recently shown to be successful in reducing the tumor volume and in prolonging survival in a murine MCC model.⁵⁸

Recent advances and improvement in our comprehension of the pathogenesis of these periocular cutaneous malignancies have translated into great strides in diagnosis and

management of patients. Molecular genetics have opened doors to targeted therapy for many of these neoplasms where resection and radiation were the only options in the past. Now, there are ongoing clinical trials of treatments that may bring promise to patients in whom resection is not an option or would cause significant morbidity. This may eventually lead to primary medical rather than surgical management of many cutaneous malignancies.

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Figure 1.

Sonic hedgehog pathway. In the absence of ligand, the Sonic hedgehog (Shh) receptor, patched (PTCH) inhibits signaling through inhibition of the transmembrane protein Smoothened (SMO). Ligand occupation of PTCH inactivates the receptor and allows activation of SMO that, in turn, results in the induction of GLI transcription factors. Vismodegib, cyclopamine, and itraconazole are inhibitors of SMO whereas arsenic trioxide acts by inhibiting GLI.

Figure 2.

Epidermal growth factor receptor (EGFR) pathway. EGFR is a receptor tyrosine kinase that, when bound to growth factor, causes downstream activation and phosphorylation of the protein kinase cascade and eventual transcription of EGFR target genes. Cetuximab, erlotinib, and gefitinib are examples of EGFR inhibitors that act specifically by inhibiting the receptor tyrosine kinase.

Figure 3.

Pathways in melanomagenesis. The receptor tyrosine kinase, when bound to a growth factor activates the ERK/MAP kinase pathway. The G-protein coupled receptor MC1R (melanocortin 1 receptor), when occupied by ligand melanocortin (MC) activates BRAF through cAMP. Oncogenic BRAF constitutively activates MEK and this results in a strong and sustained activation of ERK. The gene *CDKN2A* encodes p16, which inhibits cyclin-dependent kinase 4 (CDK4). CDK4, when activated, leads to phosphorylation of the Retinoblastoma protein (Rb) and subsequent cell-cycle progression. Loss of *CDKN2A*, therefore, leads to tumorigenesis through this pathway. So far, medications have been developed to inhibit the receptor tyrosine kinase itself as well as BRAF and MEK, directly.