Taking the Guesswork Out of Uveal Melanoma
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Therapy for melanoma is making remarkable progress. Only 8 years after the initial discovery of mutations in the BRAF oncogene, a new small-molecule inhibitor specific for mutant BRAF, PLX4032 (also known as RG7204), induced tumor shrinkage in more than 80% of patients with cutaneous melanoma containing BRAF mutations and extended progression-free survival by an average of 7 months.1,2 Although BRAF-targeted therapy is not curative, it is possible that its combination with immunotherapy to potentiate anti-tumor T-cell responses may lead to durable responses.3 The mutant BRAF amino acid that is targeted by PLX4032 is present in 50% of cutaneous melanomas but is absent from certain other subtypes of the disease, such as uveal melanoma, which represents 5% of all melanomas.

Uveal melanoma, the most common intraocular cancer, arises from melanocytes within the choroidal plexus of the eye and metastasizes almost exclusively to the liver. Building on their earlier work,4 Van Raamsdonk et al.5 report in this issue of the Journal that more than 80% of uveal melanomas carry mutations in either GNA11 or GNAQ. These genes encode members of the q class of G-protein alpha subunits, which are involved in mediating signals between G-protein–coupled receptors and downstream effectors, such as protein kinases A and C. The proteins encoded by GNAQ and GNA11 — Go_q and Ga_11, respectively — have 90% sequence homology with each other but appear to have differing functional roles. Both proteins have oncogenic activities and can transform melanocytes, albeit only those that have been immortalized, suggesting that mutation of either gene is necessary but not sufficient for malignant transformation.

Mutations affecting G-protein–coupled receptors and their downstream effectors — in particular, alpha subunits of the heterotrimeric proteins binding to guanosine triphosphate (GTP) — are emerging as an important source of susceptibility to cancer in humans. Heterotrimeric GTP-binding proteins are made up of three subunits: alpha, beta, and gamma. When inactive, the alpha subunit binds guanosine diphosphate (GDP). When the alpha subunit is stimulated by an activated G-protein–coupled receptor, it too becomes activated, binding to GTP (thereby forcing its dissociation from the beta and gamma subunits, which remain attached to one another) and setting off a chain of signaling events. Within the binding site of the alpha subunit, GTP binds to a specific glutamine or arginine at amino acid position 209 — which in its mutated form results in constitutive G-protein activation. Mutations have been reported in genes encoding other heterotrimeric G-protein alpha subunits in a variety of cancers, and these mutations also affect arginine or glutamine residues that bind to GTP or GDP. GNAS (a homologue of GNAQ and GNA11) is amplified in 12% of ovarian carcinomas, in 20% of breast cancers that are negative for human epidermal growth factor receptor 2 (HER2), and in 13% of hormone-receptor–positive breast carcinomas.6 Furthermore, the expression of the G-protein–coupled receptor encoded by Grm1 induces melanomas in transgenic mice with 100% penetrance.7

In both studies, Van Raamsdonk et al.4,5 report the presence of GNAQ and GNA11 mutations in blue nevi (benign intradermal melanocytic proliferations affecting the conjunctiva and periorbital skin) in addition to uveal melanoma. Patients with blue nevi are at risk for uveal melanoma. GNAQ or GNA11 mutations have not been identi-
fied in cutaneous melanomas, but GNAQ mutations have been detected in melanocytic tumors of the central nervous system, suggesting that a stem cell capable of giving rise to both neuronal cells and melanocytes is the target for transformation. Indeed, such a stem cell has been identified in the human dermis.8

Epidemiologic studies point to a causative role for ultraviolet irradiation in uveal and cutaneous melanoma, but the types of mutations in GNAQ, GNA11, and BRAF are not typically induced by medium-wave ultraviolet B light (315 to 280 nm). It is less clear what effect ultraviolet A light (320 to 400 nm) has on DNA, since such long-wave light can induce reactive oxygen species, which are greatly enhanced by melanin. Potentially, oxidative stress and oxidative damage induced by ultraviolet A light are the two major contributors to the genesis of melanoma, since melanocytes are highly sensitive to oxidative damage, with a repair capacity lower than that of skin fibroblasts.9 The downstream effectors of Gαq and Gα11 remain to be elucidated and are potential targets for therapy. In their previous study, Van Raamsdonk et al.4 observed activation of the mitogen-activated protein kinase pathway consequent to increased production of Gαq and Gα11 through mutation, leading them to propose clinical trials with MEK inhibitors to treat uveal melanoma. A phase 2 clinical trial is under way.

Because mutation of GNA11 or GNAQ is not sufficient on its own to induce malignant transformation, aberrations in other pathways are probably critical to the genesis of uveal melanoma. The identification of these pathways would be a useful next step.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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