Molecular Diagnostics of Melanoma in Clinical Practice
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Melanoma is an increasingly common diagnosis, with more than 75,000 new cases each year. Unlike many other cancers, melanoma does not respond to traditional chemotherapy or radiation. Because treatment options are limited, there is a significant need for pharmaceutical research and development. Recent advances in molecular diagnostics have led to the development of targeted therapies for certain types of melanomas.

Approximately 65% of melanomas harbor somatic mutations of \textit{BRAF}, a gene that is part of the mitogen-activated protein kinase (MAPK) pathway.\textsuperscript{2,3} Commonly, \textit{BRAF} mutations are associated with thinner primary lesions and tend to develop in skin without chronic sun damage.\textsuperscript{4} \textit{BRAF} mutations lead to increased tyrosine kinase activity and cell proliferation.\textsuperscript{3,5} In 80% of patients harboring a mutation, the mutation is a single-point substitution where a glutamic acid is replaced by a valine at residue 600 (V600E). Patients with a proven V600E \textit{BRAF} mutation are eligible for treatment with selective \textit{BRAF} inhibitors, such as vemurafenib and dabrafenib. These patients have an overall response rate of greater than 50% and show improvement in both progression-free survival as well as overall survival.\textsuperscript{3}

When melanoma develops in chronically sun-exposed skin or exhibits a nodular growth pattern, it is more likely to have a mutation in \textit{NRAS}.\textsuperscript{3,5,6} \textit{NRAS} is also part of the MAP Kinase pathway and is located upstream from \textit{BRAF}. Mutations in \textit{NRAS} result in constitutive activation of \textit{BRAF}, which then causes uncontrolled cell proliferation. In general, \textit{BRAF} and \textit{NRAS} mutations are mutually exclusive. Although there are no targeted therapies for tumors with \textit{NRAS} mutations, it is important to document \textit{NRAS} mutations since these tumors can respond negatively when treated with selective \textit{BRAF} inhibitors.\textsuperscript{7} It has been hypothesized that this phenomenon is due to enhanced activation of downstream proteins in the MAPK pathway when subjected to \textit{BRAF} inhibition.\textsuperscript{9}

Another type of mutation found in melanomas involves the \textit{KIT} gene. Typically, \textit{KIT} mutations are found in acral and mucosal melanomas, as well as melanomas of chronically sun-exposed skin.\textsuperscript{8,10} This mutation is mutually exclusive with the \textit{BRAF}/\textit{NRAS} mutations and involves activation of a tyrosine kinase. The \textit{KIT} mutation is an ideal target for molecular testing because targeted therapeutic agents, tyrosine kinase inhibitors (TKIs), have already been developed. Moreover, treatment with TKIs has led to greatly improved short-term survival for patients with other \textit{KIT}-mutated tumors, such as gastrointestinal stromal tumors.\textsuperscript{11} To date, early studies in \textit{KIT}-mutated melanoma show promising results.\textsuperscript{8,10}

In conclusion, several molecular aberrations have been identified within melanoma. Before ordering molecular testing, clinicians should consider the type of melanoma (eg, cutaneous versus acral) and whether there are any metastases. Patients with cutaneous melanoma should first be tested for \textit{BRAF} (+/- \textit{NRAS}), and then tested for \textit{KIT} if the first results are negative. On the
other hand, patients with acral or mucosal melanomas should be tested for BRAF (+/- NRAS) and KIT mutations simultaneously. If the patient has metastatic disease, the preferred specimen is the most recent metastasis since this tissue is felt to provide the most accurate representation of current tumor biology. Overall, it is important for clinicians to understand the basics principles of molecular diagnostics in melanoma in order to facilitate the most current and efficacious treatment for their patients.

References:


