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Review Article

BRAF Mutations: Prognostic and Therapeutic Markers in Human Cancers

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The *BRAF* gene encodes the B-Raf protein, a proto-oncogenic kinase which transmits extracellular signals to the nucleic transcription machinery. As part of the Ras-Raf-MEK-ERK pathway, the B-Raf protein has important functions in cell division, differentiation, migration, apoptosis and protein secretion.

Davies *et al.* published the first report regarding *BRAF* mutations in human cancers in 2002 [1]. Several Studies have identified *BRAF* mutations in a variety of human cancers, including melanoma, thyroid cancer, colon and colorectal cancer, glioma, lung cancer, sarcoma, breast and ovarian cancer, etc. [2-7]. The V600E mutation accounted for 80% of all *BRAF* mutations identified in these cancers and for 66% in malignant melanoma [1]. Other *BRAF* mutations were found in different types of cancers at low frequencies [1]. The V600E mutation attributes to enhanced kinase activity for B-Raf and results in constitutive activation of the downstream signaling pathway, leading to increased cell proliferation and survival [8]. Findings from these and subsequent studies led to the development of new therapeutic drugs targeting to *BRAF* mutations. In this review, the current knowledge of *BRAF* mutations in human cancers and the impact of these mutations on clinical diagnosis, prognosis and therapy will be discussed.

BRAF and Melanoma

According to the WHO histological classification, cutaneous melanoma is one of the malignant melanocytic tumors affecting predominantly fair-skinned Caucasians [9]. *BRAF* mutations were found in approximately 66% of cutaneous melanomas and the V600E mutation accounted for 92% of these mutations [1]. A meta-analysis based on four clinical studies with 674 melanoma revealed that the V600E mutation increases the risk of mortality in melanoma patients by 1.7 times [3]. In line with these exciting findings, developing drugstargeting to *BRAF* mutations has made significant progress lately. FDA approved using vemurafenib to treat late-stage melanoma patients in 2011 and usingtrametinib and dabrafenib to treat V600E or V600K positive patients with unresectable or metastatic melanoma in 2013. A phase II trial (BRIM-2) involving 132 previously treated melanoma patients with positive BRAF V600E mutation produced a confirmed response rate of 53%, with a median duration of response of 6.8 months [10-12]. A phase III randomized clinical trial showed that vemurfenib was associated with a relative reduction of 63% in the risk of death and of 74% in the risk of tumor progression in previously untreated melanoma patients with positive BRAF V600E mutation, suggesting an improved overall survival of these patients [13]. Therefore, testing whether the V600E or V600K mutation exists in melanoma is of critical therapeutic importance.

BRAF and Histocytosis

BRAF mutations were also detected in more than 50% cases of two rare histiocytic disorders, Langerhans Cell Histiocytosis (LCH) and Erdheim-Chester disease (ECD). LCH, characterized by neoplastic proliferation of langerhans cells, indeed affects multiple organ systems and results in a high fatal rate (20% in disseminated cases). It can be diagnosed based on CD1a and CD207 positivity in affected langerhans cells. The finding of the *BRAF* V600E mutation in 35 of 61 (57%) archived LCH lesions not only supported LCH as a neoplastic disease but also suggested LCH might be treatable by RAF pathway inhibitors [14]. However, the presence or absence of the BRAF V600E mutation in langerhans cells does not confirm or rule out a diagnosis of LCH; the results should be correlated with clinical findings and histopathologic features. Two other mutations were found in LCH patients including the in-frame insertion of 12 nucleotides, leading to insertion of 4 amino acids (*BRAF* 600DLAT), and a missense mutation, *BRAF* T599A [15]. The 600DLAT mutation might activate the MEK-ERK signaling pathway. In contrast, the T599A mutation did not induce MEK-ERK signaling.

ECD is a rare form of non-Langerhans cell histiocytosis, andis characterized by the infiltration of single or multiple tissues and organs. It can be diagnosed by foamy $CD68^{+}CD1a^{-}S100^{-}$ histiocytes. Several studies showed that the *BRAF* V600E mutation is present in 47-54% of ECD cases, which impelled to assess the therapeutic effects of B-Raf inhibitors on V600E positive ECD patients [16-18]. A recent paper from Haroche *et al.* showed that three ECD patients with *BRAF* V600E mutationhad excellent responses to vemurfenib treatment [19]. Moreover, the LCH skin lesions in one of these patients disappeared, indicating the possible therapeutic effect of this drug on LCH.

BRAF and Thyroid Cancer

Papillary thyroid cancer (PTC) is the most common endocrine malignancy among all thyroid cancers. Activating BRAF V600E mutation is present in 18-87% of various thyroid cancers, primarily in papillary thyroid cancer. Kebebew et al. reported that the prevalence of the *BRAF* V600E mutation was higher in conventional PTC (51.0%) than in follicular variant PTC (24.1%) and follicular thyroid cancer (1.4%) [6]. A retrospective multicenter study with 1849 PTC patients revealed that the V600E mutation significantly increased the cancer-related mortality in PTC patients [4]. Guerra et al. demonstrated that *BRAF* V600E mutation defines a PTC molecular subtype and predicts a poor disease outcome [20]. Overall, the*BRAF* V600E mutation is associated with an aggressive tumor phenotype and predicts a poorer

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disease outcome for PTC. Testing for this mutation may be useful for selecting initial therapy and for follow-up monitoring.

BRAF and Colorectal Cancer

There are about 9-14% of patients with colorectal cancer having the *BRAF* V600E mutation. A meta-analysis involving 11773 patients with colorectal cancer concluded that the BRAF mutation increased the risk of mortality in these patients for more than two times [3]. Combined testing results from microsatellite instability assays and BRAF mutation tests in 1253 colorectal patients showed that microsatellite stable and the *BRAF* mutation are independent adverse factors for patient survival [7]. Di Nicolantonio *et al.* reported that the *BRAF* mutation in colorectal cancer rendered the tumor resistance to anti-EGFR therapy and wild-type *BRAF* is required for response to panitumumab or cetuximab [21]. Thus, *BRAF* genotype could be used to select eligible patients for the treatment with these drugs.

BRAF and Other Cancers

BRAF mutations have been found in many other cancer types, including lung cancer, sarcoma, glioma, ependymoma, liver cancer, stomach cancer, breast and ovarian cancer, esophageal cancer, lymphoproliferative and myeloproliferative disorders, multiple myeloma, and hairy cell leukemia, although at frequencies (<10%) [22]. The clinical implication and utility of *BRAF* gene mutation testing in these types of cancers remain to be determined.

Conclusion and Perspective

BRAF was primarily used as a prognostic factor and therapeutic target in melanoma, colorectal cancer, and papillary thyroid cancer. While it is exciting to see that several drugs targeting to the *BRAF* V600E mutation were approved for clinical therapy, more effort is needed to develop a secondary generation of effective B-Raf inhibitors because drug resistance has been noticed. With continuously accumulated clinical data and available genotype information for *BRAF*, the prognostic and therapeutic value of *BRAF* mutations in other cancers will be revealed, which will eventually help to develop effective target-specific cancer therapy.

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