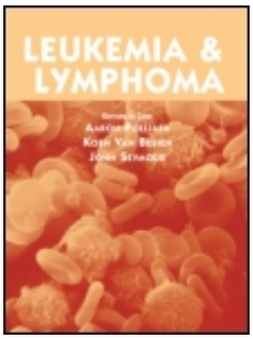

Leukemia & Lymphoma

ISSN: 1042-8194 (Print) 1029-2403 (Online) Journal homepage: informahealthcare.com/journals/ilal20

The BRAF-V600E mutation in hematological malignancies: a new player in hairy cell leukemia and Langerhans cell histiocytosis

Tamar Tadmor, Enrico Tiacci, Brunangelo Falini & Aaron Polliack

To cite this article: Tamar Tadmor, Enrico Tiacci, Brunangelo Falini & Aaron Polliack (2012) The BRAF-V600E mutation in hematological malignancies: a new player in hairy cell leukemia and Langerhans cell histiocytosis, Leukemia & Lymphoma, 53:12, 2339-2340, DOI: 10.3109/10428194.2012.706289

To link to this article: https://doi.org/10.3109/10428194.2012.706289

Leukemia & Lymphoma, December 2012; 53(12): 2339–2340

ISSN: 1042-8194 print / 1029-2403 online
DOI: 10.3109/10428194.2012.706289

informa
healthcare

COMMENTARY

The BRAF-V600E mutation in hematological malignancies: a new player in hairy cell leukemia and Langerhans cell histiocytosis

Tamar Tadmor[1], Enrico Tiacci[2], Brunangelo Falini[2] & Aaron Polliack[3]

[1]*Hematology Unit, Bnai-Zion Medical Center, Haifa, Israel,* [2]*Institute of Hematology, University of Perugia, Perugia, Italy and* [3]*Department of Hematology, Hadassah University Hospital and Hebrew University Medical School, Jerusalem, Israel*

BRAF, a serine–threonine protein kinase, is an essential component of the RAS–RAF–MEK–ERK signaling pathway. This pathway is central in the regulation of cell proliferation and survival, and is typically triggered by extracellular growth factors binding to receptor tyrosine kinases.

BRAF is a frequently mutated oncogene in a variety of cancers [1]. The most common (>90%) BRAF mutation is a single nucleotide substitution resulting in a Val-to-Glu replacement in the kinase domain at position 600 (V600E) of the BRAF protein, which then becomes constitutively active independently from extracellular signals [1]. This mutation occurs in more than half of malignant melanoma [2] and up to 60% of papillary carcinoma of the thyroid [3]. It is also detectable in 8–10% of colorectal cancers and in a smaller proportion of non-small cell carcinoma of the lung and ovarian carcinoma [4]. Highly recurrent mutations of the BRAF gene are rarely observed in hematological malignancies. Among myeloid neoplasms, BRAF-V600E is frequently detected in Langerhans cell histiocytosis (LCH) [5]. Regarding B-cell lymphomas and leukemias, it has recently been shown to be the disease-defining genetic lesion of hairy cell leukemia (HCL) [6]. Essentially almost all cases of HCL examined until now show the BRAF-V600E mutation. In contrast, this mutation is not expressed in the overwhelming majority of related B-cell lymphoproliferative disorders, including splenic marginal zone lymphoma, HCL-variant, unclassifiable splenic leukemia/lymphoma, Waldenstrom macroglobulinemia, chronic lymphocytic leukemia and mantle cell lymphoma [6–8]. Because of its specificity, the BRAF-V600E mutation provides a simple and very reliable genetic test on whole-blood samples [9] for confirmation of HCL diagnosis, particularly in borderline or controversial cases which are sometimes difficult to distinguish from HCL-like disorders [10].

Gene expression profiles [11] and, more recently, the identification of BRAF-V600E [6] have greatly contributed to our understanding of the pathogenesis and biology of HCL. Indeed, several unique features of leukemic hairy cells such as their morphology, adhesive properties and homing patterns are at least in part explained by the up- or down-regulation of specific genes (reviewed in [12]). The constant presence of BRAF-V600E in HCL highlights activation of the RAF–MEK–ERK pathway as a critical event in the pathogenesis of HCL. Moreover, the observation that the constitutive phosphorylation of MEK and ERK in HCL cells is decreased by a specific inhibitor of active BRAF confirms the BRAF-V600E mutation as the key trigger of MEK–ERK pathway activation in HCL [6]. More recently, modulation of the mitogen activated protein kinase (MAPK) pathway by a specific microRNA signature has also been reported in HCL [13].

In this issue of ***Leukemia and Lymphoma***, there are two articles relating to the absence of BRAF-V600E mutation in a variety of hematological malignancies excluding HCL [14,15]. Trifa and colleagues [14] report the absence of BRAF-V600E in a cohort of 402 patients with various chronic and acute myeloid neoplasms, while Ping *et al.* [15] show the same findings in a total of 780 patients, including 578 cases with different myeloid leukemias and myeloproliferative neoplasms, 176 lymphoid malignancies other than HCL, and 26 patients with multiple myeloma. These two reports are not of course the first publications to record the lack of the BRAF-V600E mutation in myeloid disorders, but confirm other observations, for example that of Pardanani and Tefferi [16] who reported absence of this mutation in 285 patients with a wide spectrum of myeloid neoplasms – including essential thrombocytosis, polycythemia vera, primary idiopathic myelofibrosis, hypereosinophilic syndrome, systemic mastocytosis, myelodysplastic syndromes and acute myeloblastic leukemia. The findings described by Ping and colleagues, as well as those by Trifa and colleagues, further support the view that the BRAF-V600E mutation is mainly restricted to patients with HCL and LCH [17].

Altogether, these data suggest that hematological tumors harboring the BRAF-V600E mutation are dependent on the MAPK signaling pathway for their proliferation. In contrast, the vast spectrum of myeloid and lymphoid neoplasms, excluding LCH and HCL, which lack BRAF-V600E are either more dependent on other intracellular pathways for their proliferation and survival or activate the MEK–ERK pathway through other means (e.g. RAS mutations).

Correspondence: Dr. Tamar Tadmor, Bnai-Zion Medical Center, Hematology, 47 Golomb Street, Haifa, 31048 Israel. E-mail: tamar.tadmor@b-zion.org.il

This commentary accompanies an article to be published in *Leukemia & Lymphoma*. Please refer to the table of contents of the print issue in which this commentary appears.

Targeting the BRAF oncogene provides a new therapeutic opportunity for BRAF-mutated tumors, and the clinical efficacy of BRAF kinase inhibitors has already been reported in melanoma [18,19]. HCL, and possibly LCH, may therefore represent another potential field of clinical application of these inhibitors in the future.

Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article at www.informahealthcare.com/lal.

References

[1] Davies H, Bignell GR, Cox C, et al. Mutations of the BRAF gene in human cancer. Nature 2002;417:949–954.
[2] Brose MS, Volpe P, Feldman M, et al. BRAF and RAS mutations in human lung cancer and melanoma. Cancer Res 2002;62:6997–7000.
[3] Cohen Y, Xing M, Mambo E, et al. BRAF mutation in papillary thyroid carcinoma. J Natl Cancer Inst 2003;95:625–627.
[4] Kobayashi M, Sonobe M, Takahashi T, et al. Clinical significance of BRAF gene mutations in patients with non-small cell lung cancer. Anticancer Res 2011;31:4619–4623.
[5] Badalian-Very G, Vergilio J-A, Degar BA, et al. Recurrent BRAF mutations in Langerhans cell histiocytosis. Blood 2010;116:1919–1923.
[6] Tiacci E, Trifonov V, Schiavoni G, et al. BRAF Mutations in hairy-cell leukemia. N Engl J Med 2011;364:2305–2315.
[7] Arcaini L, Zibellini S, Boveri E, et al. The BRAF V600E mutation in hairy cell leukemia and other mature B-cell neoplasms. Blood 2012;119:188–191.
[8] Boyd EM, Bench AJ, van't Veer MB, et al.High resolution melting analysis for detection of BRAF exon mutations in hairy cell leukemia and other lymphoid leukemias. Br J Haematol 2011;155:609–612.
[9] Tiacci E, Schiavoni G, Forconi F, et al. Simple genetic diagnosis of hairy cell leukemia by sensitive detection of the BRAF-V600E mutation. Blood 2012;119:192–195.
[10] Foucar K, Falini B, Catovsky D, et al. Hairy cell leukemia. In Swerdlow S, Campo E, Harris NL, et al., editors. WHO classification of tumors of haematopoietic and lymphoid tissues. 4th ed. Lyon, France: IARC; 2008. pp 188–190.
[11] Basso K, Liso A, Tiacci E, et al. Gene expression profiling of hairy cell leukemia reveals a phenotype related to memory B cells with altered expression of chemokine and adhesion receptors. J Exp Med 2004;199:59–68.
[12] Tiacci E, Liso A, Piris M, et al. Evolving concepts in the pathogenesis of hairy-cell leukaemia. Nat Rev Cancer 2006;6:437–448.
[13] Kitagawa Y, Brahmachary M, Tiacci E, et al. A microRNA signature specific for hairy cell leukemia and associated with modulation of the MAPK-JNK pathways. Leukemia 2012 Jun 4. [Epub ahead of print]
[14] Trifa AP, Popp RA, Cucuianu A, et al. Absence of BRAF V600E mutation in a cohort of 402 patients with various chronic and acute myeloid neoplasms. Leuk Lymphoma 2012;53:2496–2497.
[15] Ping N, Wang Q, Wang Q, et al. Absence of BRAF V600E mutation in hematologic malignancies excluding hairy-cell leukemia. Leuk Lymphoma 2012;53:2498–2499.
[16] Pardanani A, Tefferi A. BRAF mutations in hairy-cell leukemia. N Engl J Med 2011;365:961; author reply 961–962.
[17] Tiacci E, Trifnov V, Schiavoni G, et al. BRAF mutations in hairy-cell leukemia. N Engl J Med 2011;364:2305–2315.
[18] Sosman JA, Kim KB, Schuchter L, et al. Survival in BRAF V600-mutant advanced melanoma treated with vemurafenib. N Engl J Med 2012:366:707–714.
[19] Dienstmann R, Tabernero J. BRAF as a target for cancer therapy. Anticancer Agents Med Chem 2011;11:285–295.