Case Report

Understanding the Significance of Mutations in Tumor Suppressor Genes Identified Using Next-Generation Sequencing: A Case Report

Steven Sorscher

Oncology Division, Wake Forest Medical School, Winston-Salem, N.C., USA

Keywords

Tumor suppressor genes · Next-generation sequencing · Mutation allelic frequency

Abstract

Next-generation sequencing (NGS) of tumors has been heralded as a promising tool to identify 'actionable' abnormalities susceptible to therapies targeting these mutated genes. Inhibiting the oncoprotein expressed from a single dominant mutated gene (oncogene) forms the basis for the success of most of the targeted gene therapies approved in the last several years. The well over 20 FDA-approved kinase inhibitors for cancer treatment are examples [Janne et al.: Nat Rev Drug Discov 2009;8:709–723]. These and other similar agents in development might prove effective therapies for tumors originating from tissues other than those for which these drugs are currently approved. Finding such mutations in tumors of patients through NGS is being aggressively pursued by patients and their oncologists. For identified mutated tumor suppressor genes (TSG) the challenge is really the opposite. Rather than inhibiting the action of an oncoprotein, targeting would involve restoring the activity of the wild-type (WT) TSG function [Knudson: Proc Natl Acad Sci USA 1971;249:912–915]. Here, a case is reported that illustrates the implications of a mutated TSG (BRIP1) identified by NGS as potentially actionable. In such cases, measuring allelic mutation frequency potentially allows for the identification of tumors where the loss of heterozygosity of a TSG exists. Without

substantial loss of expression of the WT TSG product, it would seem very unlikely that ‘replacing’ a WT TSG product that is not a lost product would be a useful therapy.

© 2016 The Author(s)
Published by S. Karger AG, Basel

Case Report

A 55-year-old woman was diagnosed with stage III colon cancer in 2014. She had a personal and family history of colonic polyps, and received 12 doses of adjuvant mFOLFOX (5-fluorouracil, oxaliplatin, leucovorin). She has had no recurrence of her malignancy to date, but requested next-generation sequencing (NGS) testing of her cancer.

NGS testing (Foundation Medicine, Inc., Cambridge, Mass., USA) demonstrated an ‘actionable’ abnormality, i.e. mutated BRIP1 (R581). NGS for a germline mutation (MYRIAD, myRisk, Salt Lake City, Utah, USA) identified the same BRIP1 mutation as a heterozygous germline mutation in the BRIP1 (c.1741C>T p.Arg581*) tumor suppressor gene (TSG). Mutation allelic frequency (MAF) (Foundation Medicine, Inc.) demonstrated the following results: BRIP1 (MAF = 20%).

Discussion

This case illustrates a number of challenges when NGS is used to identify actionable abnormalities in TSGs.

First, the deleterious mutation in this TSG (BRIP1) raised the question of whether this is a germline mutation that is simply present in the tumor since the tumor originated from a normal colonic cell harboring the mutated BRIP1. Since this patient has a known germline mutation and since loss of heterozygosity (LOH) of BRIP1 has not been associated with colorectal cancer [1], the reported MAF = 20% confirms the suggestion that the BRIP1 mutation seen in the tumor is not representative of LOH of BRIP1, but rather a carryover of the mutated BRIP1 from a germline mutation.

If there had been LOH for BRIP1, BRIP1 might be an ‘actionable’ abnormality, assuming that the LOH is a driver event. The suggestion of Foundation Medicine to consider olaparib seems reasonable. (Olaparib is a PARP inhibitor, FDA-approved for patients with tumors that are derived from LOH of the BRCA1/2 [2]. In a sense, olaparib presumably ‘replaces’ lost TSG functions by blocking PARP activity which the cancer cell relies on in the setting of lack of BRCA1/2 wild-type gene product function.)

In this case, even though BRIP1’s normal role in DNA damage repair implies a potential role for the PARP inhibitor, without loss of heterozygosity of BRIP1 (MAF = 20%) one would not expect the PARP inhibitor to be effective since the wild-type BRIP1 expressed would mitigate the effectiveness of olaparib.

The presented principles involved in predicting the success of targeting oncoproteins or replacing TSG function are general. Linked genetic polymorphisms in the tumor genome or host genome could be critical in allowing a benefit, as well as many other factors. Also, targeting a so-called ‘passenger mutation’ would be of no benefit. The described case is presented to emphasize that a first step in understanding whether something is truly ‘actionable’ is whether the mutated or lost gene is an oncogene or TSG. If it is a TSG, MAF may clarify whether the mutation or loss is actionable.

Conclusions

In summary, mutated genes with oncogenic function are an attractive target for therapy, as has been the case with many recently approved kinase inhibitors. Because of the understood mechanism of tumorigenesis resulting from loss of TSG function (i.e. loss of heterozygosity) targeting TSG molecular abnormalities will likely be effective only if there is no significant wild-type TSG gene product function. Otherwise, replacing TSG function when it is not lost would seem very unlikely to be of benefit. When the ‘actionable’ mutation is in a TSG, verifying high MAF could prove to be a key and useful test as drugs aimed at replacing lost TSG function become available.

Statement of Ethics

The author has no ethical conflicts to disclose.

Disclosure Statement

The author has no conflicts of interest to declare.

References

- 1 Rafnar T, Gudbjartsson DF, Sulem P, et al: Mutations in BRIP1 confers high risk of ovarian cancer. *Nat Genet* 2011;43:1104–1107.
- 2 Kaufman B, Shapira-Frommer R, Schmutzler RK, et al: Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. *J Clin Oncol* 2015;33:244–250.