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The search for new treatment strategies for malignant pleural mesothelioma

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Chapter 5

Targeting BAP1: a New Paradigm for Mesothelioma

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Abstract

New treatment strategies for malignant pleural mesothelioma (MPM) are important. BAP1 mutations are present in 47-67% of the MPM tumors, making this a good target for treatment. Multiple functions of BAP1 are investigated in the preclinical situation. Due to many functions of BAP1, the phenotypic effect of BAP1 is diverse. Preclinical data on inhibitors reversing these phenotypic effects are promising. However, the mechanism of BAP1 is not fully elucidated yet and further research about the mechanism and possible inhibitors is necessary.

Keywords

malignant mesothelioma, BAP1, mutation, loss, targeting, inhibitor.

Malignant mesothelioma (MM) is a rare but aggressive tumor arising in mesothelial cells lining the pleural and peritoneal cavity. MM has a poor prognosis and most patients die within the first 2 years after diagnosis [1-4]. A variety of new treatment strategies are currently being tested to improve the outcome of this disease. Besides immune-oncology (IO) therapies and anti-vascular agents which are under investigation, new avenues in the field of molecular genetics are also examined.

BRCA-associated protein 1 (BAP1) is one of the molecular targets that has been identified as a potential novel target in the treatment of MM. BAP1 has a number of regulatory functions in the cell, including its function as deubiquitinating enzyme (DUB) with predominantly nuclear localization. Through its deubiquitinase activity and the effects thereof on transcription, BAP1 functions as a tumor suppressor regulating target genes in transcription, cell cycle control, DNA damage repair and cellular differentiation [5-8]. BAP1 germline mutation in patients with mesothelioma was first reported in 2011 [9]. These patients are often diagnosed at an early age with a number of skin disorders including skin tumors and uveal melanomas. Furthermore, BAP1 mutation carriers are more likely to develop a peritoneal or pleural mesothelioma [10, 11]. For mesothelioma patients with a germline BAP1 mutation, prognosis seems to be better with a 5-year survival rate of 47%, when compared with 6.7% for patients who did not have the mutation [11].

Although germline mutations are rare in sporadic mesothelioma [12], somatic BAP1 aberrations are more common in mesothelioma tumors. About 47–67% of the mesothelioma tumors contain a BAP1 genetic aberration. BAP1 somatic mutations are more frequent in the epithelioid subtype than in the sarcomatoid subtype. Besides single point mutations in the BAP1 gene, copy number loss, rearrangements and multiple alterations are found as well [13-20]. The somatic BAP1 mutation can easily be identified with immunohistochemistry (IHC) and these observations are consistent with sequencing results [16, 17, 19].

BAP1 as a drug target in mesothelioma

Based on the apparent causal role of BAP1 mutations in mesothelioma development, it would be interesting to identify therapeutic agents that reverse the phenotypic effects of BAP1 protein loss. BAP1 has many interaction partners that may function as attractive drug targets, along with downstream substrates of BAP1.

BAP1 together with ASXL1 forms a polycomb repressive deubiquitinase (PR-DUB) complex that deubiquitinates histone 2A (H2A) [5, 6, 8, 21]. Together with the polycomb repressor complex (PRC) that ubiquitinates histones, the PR-DUB takes care of the transcriptional balance and control. Loss of BAP1 causes significantly altered expression of several

polycomb target genes. For instance, alterations in the BAP1/ASXL1 interaction cause an increased ubiquitination of H2A leading to deregulation of cell cycle progression and hindered senescence [5]. The regulation of histones by BAP1 suggests that an interaction with histone deacetylase (HDAC) inhibitors could be beneficial. In MM, the effect of HDAC inhibitors on H2A is not known, but in uveal melanoma, HDAC inhibitors reduced levels of H2A ubiquitination in BAP1-depleted cells. One potential explanation for this reduction is the transcriptional repression of the PRC1 component BMI1 by HDAC inhibitors [22, 23]. Recently, it was found that BAP1 loss also reduces HDAC2 expression [24], and BAP1 knockdown in MM cell lines increases the sensitivity for HDAC inhibitors leading to cell death, a process known as synthetic lethality. The exact mechanism behind this sensitizing effect is not known, but these results indicate that HDAC inhibitors could be effective in patients with a BAP1 loss. However, in the VANTAGE 014 study, a phase III trial including 661 patients, the HDAC inhibitor vorinostat did not improve overall survival in an unselected group of patients compared with placebo [25]. From half of these patients material is still available and it would be important to correlate the BAP1 status with response to HDAC inhibition for these patients.

Enhancer of zeste homolog 2 (EZH2), an enzymatic subunit of the PRC2, is upregulated in MM [13, 26-28]. LaFave et al. [27] described that BAP1 loss leads to increased EZH2 levels in cell lines and BAP1-knockout mice. Although others could not observe a clear association between BAP1 loss and EZH2 upregulation in MM biopsies using immunohistochemistry, the development of EZH2 specific inhibitors is gaining interest of pharmaceutical companies [13, 28]. In MM cell lines, treatment with an EZH2 inhibitor decreased cell proliferation, reduced invasion and inhibited clonogenicity in soft agar. In line with these results, treatment with EZH2 inhibitors in MM-tumor bearing mice significantly reduced tumor size with no toxicity [26, 27]. Importantly, BAP1 mutant mice were more responsive to the EZH2 treatment compared with wild-type mice [26]. Also in other tumor types, phase I studies with EZH2 inhibitors showed promising results [28]. This approach is being tested in a phase 2, 2-part, single-arm study of tazemetostat 800 mg administered two times a day (BID) orally (NCT02860286). In the first part, unselected patients with MM will be entered, followed by patients with a BAP1 mutation. This can elucidate whether EZH2 inhibitors could be used as therapeutic agents that reverse the phenotypic effects of BAP1 protein loss in MM.

Another interaction partner of BAP1 is host cell factor 1 (HCF1), which plays a role in cell cycle progression by activating transcription of promoters bound by the E2F family. BAP1 deubiquitinates HCF1 and recently multiple groups showed that BAP1 mutation results in increased HCF1 ubiquitination, impairing E2F activation. Decreased activation of E2F causes problems in cell cycle progression and inhibition of cell growth [5, 7, 21, 29, 30]. Lower levels of HCF1 result in decreased interaction of BAP1 with transcription factor Yin Yang 1 (YY1),

which controls cellular proliferation. The latter interaction, however, is not yet described in MM [31]. These interaction partners may provide options for new therapeutic intervention strategies.

Conclusions

Based on the prevalence of BAP1 mutations that cause BAP1 protein loss, it is important to identify therapeutic agents that reverse the phenotypic effects. Multiple interaction partners and proteins under the influence of BAP1 are described and preclinical data of inhibitors targeting these partners are promising. Since the exact molecular mechanism of BAP1 function is yet to be fully clarified, further research on BAP1 action may reveal even more therapeutic possibilities. Due to the many interaction partners and functions of BAP1, it could be wise to test combinations of therapeutic agents that can possibly reverse the phenotypic effect of BAP1 protein loss. BAP1 can be considered as one of the new, promising targets in MM and ongoing (clinical) research is in progress.

References

1. Martini, N., et al., *Pleural mesothelioma*. Ann Thorac Surg, 1987. **43**(1): p. 113-20.
2. Suzuki, Y., *Pathology of human malignant mesothelioma--preliminary analysis of 1,517 mesothelioma cases*. Ind Health, 2001. **39**(2): p. 183-5.
3. van Zandwijk, N., et al., *Guidelines for the diagnosis and treatment of malignant pleural mesothelioma*. J Thorac Dis, 2013. **5**(6): p. E254-307.
4. Remon, J., et al., *Malignant mesothelioma: new insights into a rare disease*. Cancer Treat Rev, 2013. **39**(6): p. 584-91.
5. Wang, A., et al., *Gene of the month: BAP1*. J Clin Pathol, 2016. **69**(9): p. 750-3.
6. Bononi, A., et al., *Latest developments in our understanding of the pathogenesis of mesothelioma and the design of targeted therapies*. Expert Rev Respir Med, 2015. **9**(5): p. 633-54.
7. Misaghi, S., et al., *Association of C-terminal ubiquitin hydrolase BRCA1-associated protein 1 with cell cycle regulator host cell factor 1*. Mol Cell Biol, 2009. **29**(8): p. 2181-92.
8. Scheuermann, J.C., et al., *Histone H2A deubiquitinase activity of the Polycomb repressive complex PR-DUB*. Nature, 2010. **465**(7295): p. 243-7.
9. Testa, J.R., et al., *Germline BAP1 mutations predispose to malignant mesothelioma*. Nat Genet, 2011. **43**(10): p. 1022-5.
10. Ohar, J.A., et al., *Germline BAP1 Mutational Landscape of Asbestos-Exposed Malignant Mesothelioma Patients with Family History of Cancer*. Cancer Res, 2016. **76**(2): p. 206-15.
11. Baumann, F., et al., *Mesothelioma patients with germline BAP1 mutations have 7-fold improved long-term survival*. Carcinogenesis, 2015. **36**(1): p. 76-81.
12. Sneddon, S., et al., *Absence of germline mutations in BAP1 in sporadic cases of malignant mesothelioma*. Gene, 2015. **563**(1): p. 103-5.
13. Shinozaki-Ushiku, A., et al., *Diagnostic utility of BAP1 and EZH2 expression in malignant mesothelioma*. Histopathology, 2016.
14. Hida, T., et al., *BAP1 immunohistochemistry and p16 FISH results in combination provide higher confidence in malignant pleural mesothelioma diagnosis: ROC analysis of the two tests*. Pathol Int, 2016. **66**(10): p. 563-570.
15. Kato, S., et al., *Genomic Landscape of Malignant Mesotheliomas*. Mol Cancer Ther, 2016. **15**(10): p. 2498-2507.
16. Nasu, M., et al., *High Incidence of Somatic BAP1 alterations in sporadic malignant mesothelioma*. J Thorac Oncol, 2015. **10**(4): p. 565-76.
17. Yoshikawa, Y., et al., *Frequent inactivation of the BAP1 gene in epithelioid-type malignant mesothelioma*. Cancer Sci, 2012. **103**(5): p. 868-74.
18. Guo, G., et al., *Whole-exome sequencing reveals frequent genetic alterations in BAP1, NF2, CDKN2A, and CUL1 in malignant pleural mesothelioma*. Cancer Res, 2015. **75**(2): p. 264-9.
19. Lo Iacono, M., et al., *Targeted next-generation sequencing of cancer genes in advanced stage malignant pleural mesothelioma: a retrospective study*. J Thorac Oncol, 2015. **10**(3): p. 492-9.
20. Righi, L., et al., *BRCA1-Associated Protein 1 (BAP1) Immunohistochemical Expression as a Diagnostic Tool in Malignant Pleural Mesothelioma Classification: A Large Retrospective Study*. J Thorac Oncol, 2016. **11**(11): p. 2006-2017.
21. Eletr, Z.M. and K.D. Wilkinson, *An emerging model for BAP1's role in regulating cell cycle progression*. Cell Biochem Biophys, 2011. **60**(1-2): p. 3-11.
22. Landreville, S., et al., *Histone deacetylase inhibitors induce growth arrest and differentiation in uveal melanoma*. Clin Cancer Res, 2012. **18**(2): p. 408-16.
23. Bommi, P.V., et al., *The polycomb group protein BMI1 is a transcriptional target of HDAC inhibitors*. Cell Cycle, 2010. **9**(13): p. 2663-73.
24. Sacco, J.J., et al., *Loss of the deubiquitylase BAP1 alters class I histone deacetylase expression and sensitivity of mesothelioma cells to HDAC inhibitors*. Oncotarget, 2015. **6**(15): p. 13757-71.
25. Krug, L.M., et al., *Vorinostat in patients with advanced malignant pleural mesothelioma who have progressed on previous chemotherapy (VANTAGE-014): a phase 3, double-blind, randomised, placebo-controlled trial*. Lancet Oncol, 2015. **16**(4): p. 447-56.
26. Kemp, C.D., et al., *Polycomb repressor complex-2 is a novel target for mesothelioma therapy*. Clin Cancer Res, 2012. **18**(1): p. 77-90.
27. LaFave, L.M., et al., *Loss of BAP1 function leads to EZH2-dependent transformation*. 2015. **21**(11): p. 1344-9.

28. Kim, K.H. and C.W. Roberts, *Targeting EZH2 in cancer*. Nat Med, 2016. **22**(2): p. 128-34.
29. Bott, M., et al., *The nuclear deubiquitinase BAP1 is commonly inactivated by somatic mutations and 3p21.1 losses in malignant pleural mesothelioma*. Nat Genet, 2011. **43**(7): p. 668-72.
30. Machida, Y.J., et al., *The deubiquitinating enzyme BAP1 regulates cell growth via interaction with HCF-1*. J Biol Chem, 2009. **284**(49): p. 34179-88.
31. Yu, H., et al., *The ubiquitin carboxyl hydrolase BAP1 forms a ternary complex with YY1 and HCF-1 and is a critical regulator of gene expression*. Mol Cell Biol, 2010. **30**(21): p. 5071-85.

