EBioMedicine 39 (2019) 7–8

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

EBioMedicine
Published by THE LANCET

Splicing molecular biology and novel therapies in diffuse malignant peritoneal mesothelioma

Andrea Napolitano

Medical Oncology, Università Campus Bio-Medico, Rome, Italy

Diffuse malignant peritoneal mesothelioma (DMPM) is a rare and aggressive disease arising from the peritoneum with very limited therapeutic options [1]. In about 60% of the cases, DMPM is associated to professional exposure to asbestos. Less commonly, DMPM can also arise as part of the hereditary *BAP1* tumor predisposition syndrome. Cases associated to germline mutations in *BAP1* and other genes generally have a longer survival [2]. Selected patients with favorable clinical and pathological characteristics are usually candidate to cytoreductive surgery (CRS) followed in the operating room by hyperthermic perioperative chemotherapy (HIPEC). Systemic chemotherapy is used for patients when surgical resection is not feasible, as a palliative treatment [1].

The search for novel and more effective therapies, specific for DMPM has been hindered by the rarity of the disease. From a clinical perspective, DMPM is under-represented in early phase clinical trials investigating the efficacy of novel drugs; for example, only two patients with DMPM (representing 5% of the total population) were enrolled in the phase II NIBIT-MESO-1 trial testing the combination of tremelimumab and durvalumab in patients with mesothelioma [3].

One additional limitation is represented by the fact that most of the research on targetable molecular pathways has been carried out in the context of malignant pleural mesothelioma (MPM), which is more prevalent compared to DMPM, although equally rare. A comprehensive genomic analysis of MPM by Bueno et al. recently identified recurrent gene mutations (particularly in *BAP1*, *NF2*, *TP53*, and *SETD2*), gene fusions, and, interestingly, splicing alterations associated to mutations in the SF3B1 subunit of the spliceosome [4].

This multi-protein complex processes the pre-mRNA transcripts by removing non-coding introns in a tightly regulated fashion. Increasing evidence points out at splicing alterations and spliceosome mutations as important players in cancer progression and metastasis [5].

Genomic profiling conducted on a cohort of DMPM found recurrently mutated genes similar to those reported previously [6]. However, direct translation of findings from MPM to DMPM might not necessarily be the best approach since they arise from different anatomical loci and they appear to be driven by distinct genetic alterations. For example, actionable ALK rearrangements have been recently identified in about 3% of DMPM patients, but in none of those affected by MPM [7]. Therefore, the need for novel rational therapies specifically developed and validated in DMPM models is high.

Moving from these premises, Sciarrillo et al. for the first time investigated the role of splicing as a novel potential therapeutic target in DMPM. They showed that DMPM expression of splice factor genes is higher compared with normal mesothelium tissues; that overexpression of the splicing factor SF3B1 is associated with significantly worse clinical outcome, and that its modulation *in vivo* might represent a novel therapeutic approach in DMPM [8]. These results are of great interest, as they might represent a significant step toward the development of targeted therapies against DMPM.

H3B-8800, an orally available modulator of the SF3B complex is currently being investigated in a clinical trial for cancers bearing mutations in genes encoding SF3b components (NCT02841540) [9]. However, clinical development specifically for DMPM might be again slowed by the rarity of the disease. It is therefore crucially important to collaborate for a clinical validation of these results.

Finally, open questions remain that have to be explored in the preclinical setting, taking advantage of the murine model developed by Sciarrillo et al. First, as DMPM has proven to be resistant to most conventional treatments, it will be critical to explore potential synergies between SF3B modulators, chemotherapy and –even more interestingly- immunotherapy. Indeed, modulating the cancer cell transcriptome might generate potential neoantigens to prime an activated immune system [10].

Disclosure

The author declared no conflicts of interest.

References

[1] Sugarbaker PH. Update on the management of malignant peritoneal mesothelioma. Transl lung cancer Res 2018 Oct;7(5):599–608 [cited 2018 Nov 29]. Available from http://www.ncbi.nlm.nih.gov/pubmed/30450299.

[2] Pastorino S, Yoshikawa Y, Pass HI, Emi M, Nasu M, Pagano I, et al. A subset of mesotheliomas with improved survival occurring in carriers of BAP1 and other germline mutations. J Clin Oncol 2018 Oct 30. https://doi.org/10.1200/JCO.2018.79.0352 [cited 2018 Nov 29];JCO2018790352. Available from:.

[3] Calabrò L, Morra A, Giannarelli D, Amato G, D'Incecco A, Covre A, et al. Tremelimumab combined with durvalumab in patients with mesothelioma (NIBIT-MESO-1): an open-label, non-randomised, phase 2 study. Lancet Respir Med 2018 Jun 1;6(6):451 [cited 2018 Nov 29]. Available from http://www.ncbi.nlm.nih.gov/pubmed/29773326.

DOI of original article: https://doi.org/10.1016/j.ebiom.2018.12.025.
E-mail address: a.napolitano@unicampus.it.

https://doi.org/10.1016/j.ebiom.2018.12.042

[4] Bueno R, Stawiski EW, Goldstein LD, Durinck S, De Rienzo A, Modrusan Z, et al. Comprehensive genomic analysis of malignant pleural mesothelioma identifies recurrent mutations, gene fusions and splicing alterations. Nat Genet 2016;48(4):407–16 [Internet]. Available from: https://doi.org/10.1038/ng.3520.

[5] Oltean S, Bates DO. Hallmarks of alternative splicing in cancer. Oncogene 2014 Nov 13;33(46):5311-8 [cited 2014 Feb 18]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/24336324.

[6] Joseph NM, Chen Y-Y, Nasr A, Yeh I, Talevich E, Onodera C, et al. Genomic profiling of malignant peritoneal mesothelioma reveals recurrent alterations in epigenetic regulatory genes BAP1, SETD2, and DDX3X. Mod Pathol 2017;30(2):246–54 [Internet]. Available from: https://doi.org/10.1038/modpathol.2016.188.

[7] Hung YP, Dong F, Watkins JC, Nardi V, Bueno R, Dal Cin P, et al. Identification of *ALK* rearrangements in malignant peritoneal mesothelioma. JAMA Oncol 2018 Feb 1;4(2):235 [cited 2018 Nov 29]. Available from: https://doi.org/10.1001/jamaoncol.2017.2918.

[8] Sciarrillo R, Wojtuszkiewicz A, El Hassouni B, et al. Splicing modulation as novel therapeutic strategy against diffuse malignant peritoneal mesothelioma. EBioMedicine 2019;39:215–25.

[9] Seiler M, Yoshimi A, Darman R, Chan B, Keaney G, Thomas M, et al. H3B-8800, an orally available small-molecule splicing modulator, induces lethality in spliceosome-mutant cancers. Nat Med 2018 May;24(4):497–504 [Internet]. March 2017. Available from: http://www.nature.com/doifinder/10.1038/nm.4493.

[10] Kahles A, Lehmann K-V, Toussaint NC, Hüser M, Stark SG, Sachsenberg T, et al. Comprehensive analysis of alternative splicing across tumors from 8,705 patients. Cancer Cell [Internet] 2018;0(0):211–24 Available from: https://www.cell.com/cancer-cell/fulltext/S1535-6108(18)30306-4?rss=yes.