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.

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