EDITORIAL

Mismatch Repair Deficiency in Lung Tumors: Adding a New Layer of Complexity on Pie Slices

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Lung cancer represents the first cause of cancer-related death worldwide and ranks second in terms of incidence in both sexes.[1] The revolution of personalized medicine, started at the beginning of this century on the basis of seminal research works,[2,3] has laid the foundations for the modern management of these diseases that no more rely on the non–small cell and small cell dichotomy only but take into account multiple layers of complexity. Despite a "pie-based" approach is increasingly used in NSCLC to define specific clinical entities on the basis of molecular data and treat patients accordingly, the biggest slice is still that where weak immunotherapy-related biomarkers act as probabilistic tools for patient selection. Moreover, when dealing with SCLC, the goal of a reliable tailored approach seems to be still a far to reach.

Maintaining the integrity of the cell genome is a fundamental cornerstone of life, safeguarded by complex and interrelated mechanisms collectively identified as the DNA damage response. These mechanisms include mismatch repair (MMR), nucleotide excision repair, base excision repair, nonhomologous end joining, homologous recombination, and the Fanconi anemia pathway. Because of their prominent role in genetic preservation, DNA damage response mutational events have been implicated in tumorigenesis of multiple tumors,[4] and some of them have been found to predict the efficacy of specific treatments, such as, for example, immune checkpoint inhibitors (ICIs) in MMR-deficient (MMR-D) or microsatellite instable (MSI) tumors.[5] Such evidence led to the Food and Drug Administration agnostic approval of the anti–programmed cell death protein-1 (anti–PD-1) ICI pembrolizumab in MMR-D or MSI-high (MSI-H) solid tumors after prior treatment, followed by first-line approval in patients with MMR-D or MSI-H metastatic colorectal cancer. Moreover, another ICI directed against PD-1, dostarlimab, was found to be active in MMR-D solid tumors in a phase 1 trial.[6]

MMR-D and MSI-H tumors display higher levels of tumor-infiltrating lymphocytes and heightened expression of the PD-1 receptor and its ligand, programmed death-ligand 1. In addition, the MSI-driven oncogenic pathway results in a high tumor mutational burden, generating immunogenic neoantigens through frameshift mutations that may be recognizable by the immune system.[7] Figure 1 reveals the MMR pathway and the main features of MMR-D tumors.

Despite findings in other tumors, the role of MMR mutations remains more elusive in lung cancer. Available studies have reported a prevalence of such mutations in NSCLC ranging from 0.2% to 0.8%. Specifically, in 2015, Warth et al.[8] used a sensitive mononucleotide marker panel to explore the prevalence of MSI in 480 lung adenocarcinomas (LUADs). MSI-H LUADs were identified in four cases (0.8%), all at stage I, and none of them were treated with ICIs.[8] In 2017, Takamochi et al.[9] obtained less remarkable results: by including 341 patients with NSCLC who underwent radical surgery, using the PROMEGA panel to detect MSI status, only one patient tested positive for MSI. In a recent work, Tian et al.,[10] in a large cohort of 12,484 patients with lung cancer tested by next-generation sequencing, only 66 (0.5%) were identified as MSI-H. Similarly, in a retrospective analysis of 4996 patients with NSCLC, 58 cases (1.16%) resulted

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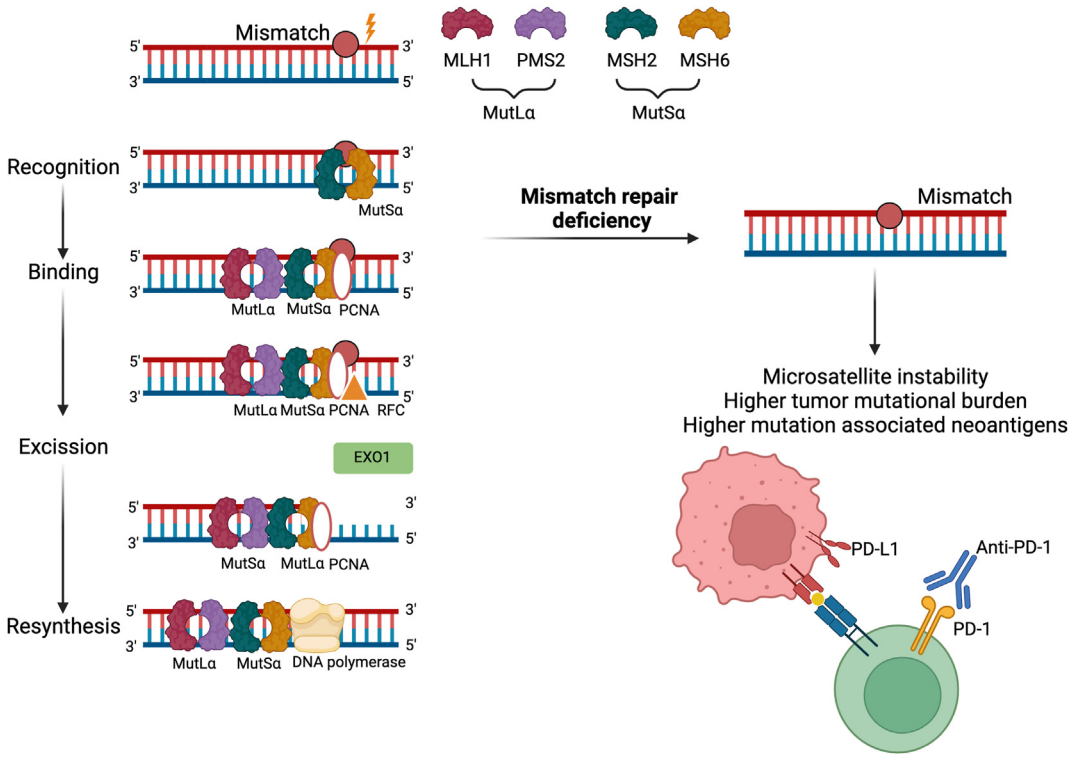

Figure 1. MMR pathway and its clinical implications. PD-1, programmed cell death protein-1; PD-L1, programmed death-ligand 1.

MMR-D or MSI-H when tested by next-generation sequencing and bioinformatics algorithms for MSI.[11]

In the present issue of the *Journal of Thoracic Oncology*, Yang et al.[12] investigated the clinicopathologic features of MSI-H and MMR-D patients with lung cancers identified in a cohort of patients diagnosed with NSCLC (n = 5171) and with SCLC (n = 315). Patients were genotyped through MSK-IMPACT and MSK-ACCESS, two hybrid next-generation sequencing platforms for tumor tissue and plasma samples, respectively.[12]

The MSI status was assessed using MSI Sensor and MiMSI for tissue samples, two independent methods that classified tumors into MS stable, MSI indeterminate, and MSI-H. In cases of indeterminate status, the Idylla system (a real-time polymerase chain reaction–based system) or MMR immunohistochemistry and polymerase chain reaction was used. Plasma evaluation was carried out using ADMIE MSI call, an allelic distance-based MSI estimator. For patients who had previously consented to germline evaluation, germline MSK-IMPACT next-generation sequencing was used. All next-generation sequencing MSI-H or MMR-D cases were subsequently tested using MMR immunohistochemistry and the Idylla system (only in cases of residual tissue or DNA). MLH1 promoter methylation was then assessed in a subset of MSI-H tumors using the Infinium MethylationEPIC (850K) platform. The authors identified 21 patients with NSCLC and six patients with SCLC as MSI-H or MMR-D, leading to a prevalence of 0.41% and 1.9%, respectively.

Nevertheless, despite the low numbers, thanks to the deep clinicopathologic analysis, some interesting hypotheses raise from this work. Looking at clinical characteristics, it is noteworthy that most patients with NSCLC were ever smokers, even among patients with LUAD. To validate these findings, the authors compared them with a consecutive MSS LUAD patient series (n = 840). In this context, MSI-H and MMR-deficient LUADs were significantly more prevalent among patients with a smoking history compared with MSS LUADs (100% versus 68%, $p = 0.02$). A similar trend was observed when comparing MSI-H and MMR-deficient NSCLC with a group of MSS NSCLC current or former smokers: there was a variation in terms of histologic subtype distribution on the basis of MSI and MMR status ($p = 0.006$), with MSI-H and MMR-D cases having fewer LUADs (52% versus 79%) and more lung squamous cell carcinomas (LUSCs) (38% versus 12%), consistent with the tendency for MSI-H or MMR-D to be more closely linked to smoking. Nevertheless, most MMR gene mutations were not caused by smoking-associated transversions. This latter information seems to rule out a causative role of smoking for these specific genomic alterations. To what extent, on the other side, these two factors may act synergically thus warranting further studies. Indeed,

retrospective data from patients with Lynch syndrome suggest an increased incidence of both colorectal cancer and adenomas in smokers, especially current ones.[13] Median tumor mutational burden was significantly higher in MSI-H and MMR-D cases, even when controlling for smoking habits. This mirrors what has been already observed in other solid tumors and, taken together with the absence of a significant association for PD-L1 expression levels and percentage of tumor-infiltrating lymphocytes, confirms the specificity of this rare subset of NSCLC.

When looking at the SCLC cohort, the prevalence of MSI-H and MRR-D is even more interesting, especially as research is struggling to find biomarkers to inform treatment choices in this population. Indeed, although different subtype classifications have been proposed to date,[14] clinical decision making is still based on staging, patient performance status, and comorbidities, leading to a "one size fits all" approach. At the same time, the high rate of combined small cell histological features in MSI-H and MRR-D cases suggests a possible intriguing tool to guide MMR testing, if confirmed by larger case series.

The fact that both patients with SCLC treated with ICI had durable benefit is noteworthy, as long-term efficacy of such agents (especially when used alone) is an exception. This is in line with data from KEYNOTE-158 trial where two of six patients with SCLC treated with pembrolizumab had confirmed response and only one patient had an increase of tumor diameters as best response, neither reaching 20% cutoff.[15]

In conclusion, this work sheds light on clinicopathologic characteristics of MSI-H and MMR-D lung cancer, a rare entity, with a deep and consistent analytical pipeline.

Although strong clinical conclusion cannot be made owing to the small number of patients included in this study, mirroring the rarity of such alterations, these data add further insights in understanding lung cancer. Indeed, although we are approaching the clinical arena by looking at different slices of the pie, we should never forget to explore the many different layers that actually make each piece.

CRediT Authorship Contribution Statement

Massimiliano Cani: Conceptualization, Writing—original draft preparation, Visualization, Software.

Paolo Bironzo: Conceptualization, Writing—original draft preparation, Supervision, Editing.

Silvia Novello: Conceptualization, Supervision, Validation.

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