"Matching" the "Mismatch" Repair–Deficient Prostate Cancer with Immunotherapy

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SUMMARY

Mismatch repair gene mutations are uncommon in advanced prostate cancer; however, in those harboring these alterations, immune checkpoint blockade can be effective. As such, assays that can accurately identify these men are critically important. Cell-free circulating tumor DNA–based sequencing approaches appear to be one viable approach for identifying these patients.

See related article by Ritch et al., p. 1114

In this issue of *Clinical Cancer Research*, Ritch and colleagues have shown that next-generation sequencing of cell-free circulating tumor DNA (ctDNA) can be used to accurately identify patients with mismatch repair deficiency (MMRd) or microsatellite instability (MSI; ref. 1). Because the mismatch repair genes are essential to maintaining genomic fidelity during cell replication, mutations in these genes lead to the rapid accumulation of mutations throughout the genome, often reflected as MSI, and are highly associated with somatic hypermutation. Identifying patients with hypermutated tumors is of paramount importance as prior work has shown that mutational load is strongly correlated with positive clinical outcomes to immune checkpoint blockade, an effect likely driven by increased probability for immune recognition in tumors expressing an abundance of mutationally derived tumor neoantigens. Consistent with this observation, prospective studies have shown that pembrolizumab can induce durable responses in tumors with MMRd and/or MSI, and has led to the approval of this agent for any MMRd/MSI-high solid tumor regardless of histology. However, there remains no definitive companion diagnostic for determining MSI or MMRd status, and it is likely that these assays require tumor type–specific optimization. Given that identifying this genomically defined group can dramatically alter treatment approaches, streamlined pipelines for detecting MMRd/MSI are of critical importance.

To that end, Ritch and colleagues sought to evaluate the use of plasma as a specimen for identifying MMRd/MSI-high prostate cancers. Utilizing a large meta-cohort of patients with advanced prostate cancer who consented to undergo liquid biopsy, the investigators first identified those with a mutational burden $\geq$95th percentile as determined using a targeted plasma-based sequencing panel. This group ($N = 24$) consisted of patients with MMRd ($n = 10$), homologous recombination mutations (HR; $n = 4$), as well as those with unidentified causes of hypermutation ($n = 8$). In addition, two cases of localized hypermutation (termed "kataegis") were observed, likely arising as a consequence of targeted sequencing of genes known to be recurrently altered in advanced prostate cancers. Whole-exome sequencing (WES) revealed lower overall mutational load and number of unstable microsatellites in those cases with HR deficiency or kataegis. Subsequent whole-gene sequencing (including introns and exons) identified two additional cases with MMRd ensuing from an intronic rearrangement and a 450 bp deletion event. IHC assessment of MMR proteins identified two more cases lacking expression of MSH2 and/or MSH6, which the authors postulated may have occurred because of cryptic genomic mutations or epigenetic phenomenon affecting these genes. In total, 16 cases were felt to have an underlying MMRd, either as a consequence of underlying genomic or protein level defects in a MMR genes ($N = 14$) or as inferred on the basis of hypermutation ($N = 2$) and no evidence of an HR gene alteration or kataegis.

Within the group identified as having MMRd, the authors found evidence of a highly polyclonal disease, including dynamic changes in the mutational landscape over time in those who underwent serial liquid tumor biopsy. There was also evidence for polyclonality within the primary tissue in the cases where this was available for analysis. Of the 9 patients in the MMRd cohort who had primary tissue sequenced, 7 had mutational counts that were highly correlated between the primary and ctDNA samples. Interestingly, the two cases without hypermutation detected in the primary only had low-grade tumor samples available for sequencing. Because MMRd has been shown to associate with high Gleason grade cancers, this raises the possibility that these foci may not have been representative of the prostate cancer clone that metastasized (2).

Limited data from 11 MMRd patients with treatment outcomes found that progression-free survival and responses to androgen receptor (AR)-signaling inhibitors were poor. The polyclonal, highly dynamic genomic landscape of these cases provides one plausible explanation for why these patients may have exhibited a more aggressive course. The authors hypothesize that the polyclonal nature of these tumors could lead to subpopulations with *de novo* resistance, while *AR* ligand–binding domain and oncogene hotspot mutations could drive secondary resistance (**Fig. 1**). However, as pointed out, the mere presence of detectable ctDNA may bias these results given that this has also been shown to associate with overall poor prognosis. It is also worth noting that other groups have reported longer progression-free survival and higher response rates in MMRd/MSI-high prostate cancers treated with next-generation AR-signaling inhibitors (see Table 1 in Ritch and colleagues; ref. 1). Larger studies are needed to better define the clinical course of this clinically relevant subgroup.

This article provides important insights into the power of liquid biopsies to define clinically actionable molecular prostate cancer subtypes. While, the initial mutational load analyses over-called the number of hypermutated patients, the subsequent whole-exome and

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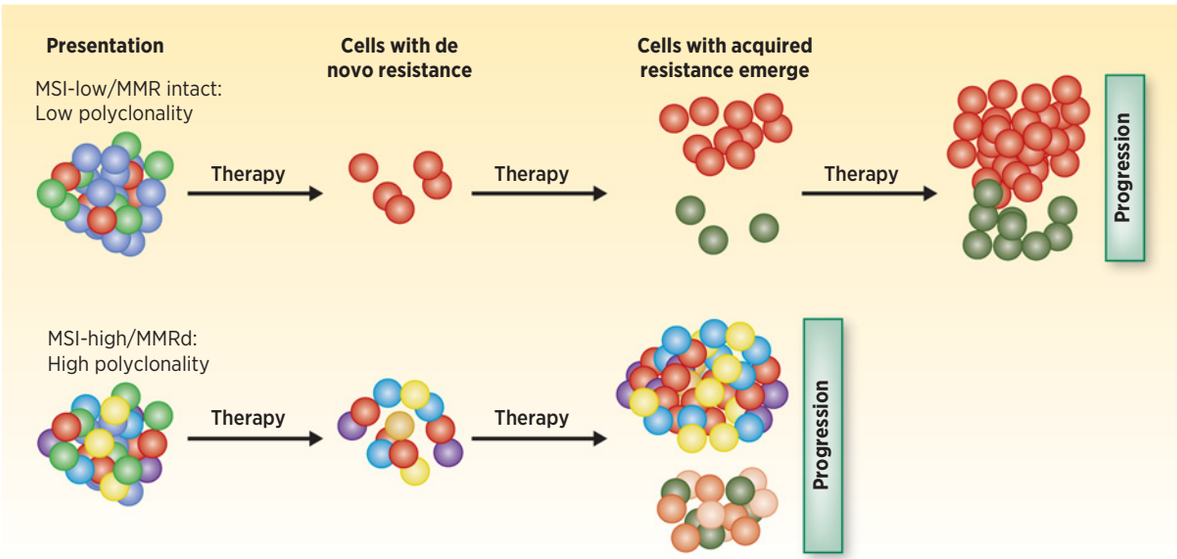

Figure 1.

High baseline polyclonality and genomic instability may drive aggressive clinical course of prostate cancers with MMRd and/or MSI. Cells with *de novo* resistance are more common in MSI-high/MMRd tumors and cells with acquired resistance emerge in greater numbers, leading to early disease progression.

intronic sequencing studies were able to more precisely define those with MMRd, including two cases with inferred MMRd on the basis of excluding other likely causes for the high mutational rate. It also highlights several challenges. For one, it appears that WES may be necessary to accurately define mutational burden, especially in light of the fact that targeted panels can bias mutational count estimates as a consequence of sequencing genes that are known to be recurrently altered. Because WES requires a high fraction of ctDNA, this may not be feasible in many cases. In addition, because MMR mutations in prostate cancers are often the result of complex genomic structural event, targeted exome sequencing can miss important intronic rearrangements and whole-gene sequencing is likely needed (3).

On the basis of this article, it appears that liquid tumor assays specifically designed and optimized to identify patients with prostate cancer with MMRd and/or MSI are needed. Ultimately, the driving motivation should be to develop streamlined approaches for defining those most likely to benefit from immune checkpoint blockade. To that end, additional work is needed to develop strategies that can easily dovetail into clinical workflow and allow for rapid assessment of this important biomarker. One approach would be to focus on the refinement of plasma-based assessment for MSI and whole-gene sequencing of the MMR genes, as these identified most patients that would benefit from immune checkpoint blockade. It is also important to note that the majority of MMRd cases identified in this study also had evidence of hypermutation in the primary tumor as well. This indicates that perhaps the easiest starting point for most patients would be to sequence archival tissue, ideally the highest grade foci available or regions demonstrating variant histologies (e.g., ductal/intraductal foci), with reflexive ctDNA-based sequencing in those cases without clear evidence for an actionable mutation (2, 4). While this study only evaluated for concordance between ctDNA and primary tumors in a small subset, other studies have also shown that many DNA damage repair gene alterations are early (i.e., truncal) events, supporting this approach (5).

This study provides an elegant example of how ctDNA-based sequencing can be used to define actionable prostate cancer subgroups. Moving forward, work is needed to refine these approaches and prospective studies should be pursued to determine whether ctDNA-based biomarkers can accurately predict which patient with prostate cancer might benefit from immunotherapy.

Disclosure of Potential Conflicts of Interest

M.T. Schweizer reports receiving speakers bureau honoraria from Janssen. E.Y. Yu is a paid consultant for Dendreon, Janssen, Bayer, Merck, Seattle Genetics, Clovis, AstraZeneca, Amgen, Pharmacyclics, QED, Incyte, Churchill, EMD Serono, and Tolmar, and reports receiving commercial research grants (to his institution) from Daiichi-Sankyo, Taiho, Dendreon, Bayer, Merck, and Seattle Genetics. No other potential conflicts of interest were disclosed.

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