Invited Commentary

Luminal and Basal Subtypes of Metastatic Prostate Cancer

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Despite the considerable treatment advances over the past 15 years, metastatic castration-resistant prostate cancer (mCRPC) continues to contribute to significant mortality and morbidity, with an estimated 34 130 deaths projected in the US in 2021.[1]

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Because the molecular background of castration-resistant progression is incompletely understood, the selection of treatment for mCRPC is based on clinicopathologic risk stratification. However, individuals within clinically defined risk categories of mCRPC display widely different outcomes, with a subset of patients developing refractory disease associated with poor survival despite the many therapeutic options available.[2] As such, the development and validation of prognostic and predictive biomarkers to improve the selection of therapy for mCRPC represent an important need.

In this issue of *JAMA Oncology*, Aggarwal et al[3] describe the results of a retrospective analysis of 634 men with mCRPC from 4 recent clinical trial cohorts. The primary objective was to define molecular subtypes of mCRPC and correlate these with the clinically established luminal and basal classification[4] and investigate the association between these molecular subtypes and clinical outcomes. By integrating tumor transcriptomic and genomic profiles, the investigators showed that 45% (288 tumors) were classifiable as luminal and 55% (346) as basal. In agreement with a report on primary prostate tumors,[5] the luminal subtype was enriched for androgen response pathway genes and had better overall survival compared with basal tumors (33.1 vs 18.7 months; hazard ratio [HR], 0.39; 95% CI, 0.20-0.74; $P = .004$ in one cohort and 32.0 vs 21.7 months; HR, 0.57; 95% CI, 0.33-0.97; $P = .04$ in a second cohort) when patients were treated with androgen-signaling inhibitors (ASIs). In contrast, this association was not apparent among patients treated with chemotherapy. Consistent with dependence on oncogenic androgen receptor signaling in luminal tumors, treatment of patients in this subgroup with ASIs was associated with significantly better survival (median overall survival, 32.0 vs 8.7 months; HR, 0.27; 95% CI, 95% CI, 0.14-0.53; $P < .001$) compared with chemotherapy. These data suggest that luminal subtype is both prognostic and predictive for response to ASI therapy. The authors appropriately concluded that use of ASI would be recommended in this population. Although the number of cases was small and prospective studies are needed to confirm this, the worst survival outcome was seen among patients with luminal tumors treated with chemotherapy, suggesting a potential negative effect of chemotherapy in this subgroup. If confirmed, these results would be practice changing for choice of treatment in luminal subtype of mCRPC.

In basal tumors, the authors identified alterations in the oncogenes *FOXA1* ($P = .03$) and *MYC* ($P < .001$), and loss of tumor suppressor *RB1* ($P < .001$).[3]Accordingly, these tumors showed enrichment in pathways involved in cell cycle regulation, DNA damage repair, and *MYC* target genes. Of note, neuroendocrine (small cell) differentiated tumors were predominantly (53 of 59 [90%]; $P < .001$) clustered as basal tumors. In fact, their data suggest that neuroendocrine tumors may represent the most basal tumors along the luminal-basal spectrum. There was nonsignificantly improved survival with ASI treatment compared with chemotherapy in the basal subgroup, suggesting that there may be heterogeneity within basal tumors. The identification of *RB1*, *FOXA1*, and *MYC* alterations in basal tumors is of particular interest because each of these pathways has been implicated in androgen-independent mCRPC progression and resistance to ASIs. In particular, *RB1* and *TP53* loss was associated with resistance to androgen receptor antagonists and increased dependence on DNA damage repair pathways, opening the prospect that *PARP* inhibitors may be effective in this subgroup of patients.[6] Thus, there are likely subgroups within the basal tumors that may benefit from chemotherapy or molecularly targeted treatments while a subset remains dependent on androgen pathway signaling.

Collectively, the findings suggest the applicability of the luminal-basal subtypes to mCRPC and provide a framework for unraveling the molecular complexity of mCRPC.[3] Analogous to breast cancer, in which the concept of luminal- and basal-like cells and oncogenesis is clinically established,[4] these subtypes are associated with differences in prognosis and response to treatment, suggesting that they likely represent fundamental molecular subtypes of oncogenesis. The finding that these subtypes are largely stable in individuals aligns with preclinical and clinical studies showing that there are likely both basal and luminal prostate cancer cell precursors that give rise to the different biologic characteristics.[7] This study's findings also provide a rationale to expect that these subtypes represent a potentially powerful tool for personalized therapeutic decision-making that may improve outcomes in mCRPC.

ARTICLE INFORMATION

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