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Progress and Challenges Towards the Personalized Treatment of Prostate Cancer

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INTRODUCTION

Prostate cancer is a highly heterogeneous disease and each treatment regimen is associated with diverse response patterns. Each case of prostate cancer is caused by a different set of genetic mutations. The core principle of precision medicine is to use the mutational profile to guide treatment. Treatment of lung cancer has illustrated the success of precision medicine. Over the past decade, lung cancer has been increasingly divided into multiple molecular subclasses—from the *KRAS* and *EGFR* mutations in 2004 to multiple subtypes that are sensitive to different treatments [1].

Prostate cancer, on the other hand, lags behind in the area of precision medicine. The repertoire of mutations in castrate-resistant prostate cancer (CRPC) is not fully known, and no class-one data exist to help physicians select therapies in patients with CRPC. As the cost of performing whole genome studies continues to decrease, data from large oncogenomics projects are building a growing knowledge and database in both primary and metastatic prostate cancer.

PROSTATE CANCER IS NOT A "HIGHLY MUTATIONAL" CANCER

Two broad types of mutational processes are believed to be operational in cancer. The first comprises single nucleotide changes (e.g., a *KRAS* mutation, a *BRAF* mutation) or small insertions and deletions (e.g., in *EGFR* or *KIT*). The second comprises genomic rearrangements, such as amplifications, deletions, or fusions. The first type of mutation is relatively easy to target because they define the lesion, whereas the second type is difficult, because the amplifications and deletions often involve large areas where the true driver of the mutation is not known.

A recent publication in *Nature* cataloged multiple mutations that are considered to be highly clinically significant, significant, or borderline significant in 21 different tumor types [2]. In contrast, prostate cancer does not appear to be as "mutational" as other cancers–the most highly significantly mutated gene is *SPOP*, which occurs in about 10% of prostate cancers [3]. *SPOP* is a ubiquitin ligase that is known to cause degradation of a large number of proteins; however, the oncogenic protein is not known. Other genes are rarely mutated in prostate cancer. Genomic rearrangement is the predominant mode of mutagenesis in prostate cancer–roughly 50% of both primary and CRPCs show ETS rearrangement [3]. *PTEN* deletion occurs much more commonly in CRPC (in approximately 50% of cases) compared with primary prostate cancer (in 10%–30% of cases). The *AR* mutation amplification is not evident at all in primary prostate cancer but occurs in 50% or more of patients with CRPC.

One of the challenges in developing precision medicine for prostate cancer is that while researchers have identified many mutations for which approved and experimental drugs are available, they occur with low frequency in prostate cancer. To address this problem across multiple cancer types, including prostate cancer, Memorial Sloan Kettering Cancer Center has opened trials for patients with specific mutations irrespective of cancer type. Currently open trials include vemurafinib for *BRAF* mutant cancers and LDK378 for ALK-driven cancers [4].

MUTATIONS AS PREDICTORS OF RESPONSE IN PROSTATE CANCER

The most effective treatments to date in prostate cancer are those directed at the androgen receptor. Therefore, identification of modulators of response and mediators of resistance is of immediate importance. One set of resistance mechanisms involves mutation of *AR* itself to maintain activity despite low levels of testosterone and in the face of antiandrogens. *AR* mutations are never seen in primary prostate cancer but appear to be gained during selection pressure from castrations; they are very common and heterogeneous in patients who have castration resistant prostate cancer. The first enzalutamide-specific *AR* mutation was recently identified. Emerging data from

patients who have *AR* mutations and *AR* amplifications show they are "locked" into an *AR*-dependent state, suggesting they would be sensitive to *AR*-targeted therapy, including abiraterone or enzalutamide.

Two of the most common genetic alterations in prostate cancer are loss of *PTEN* and *ERG* overexpression through translocation. *PTEN* loss activates the PI3K pathway and decreases *AR* signaling and *AR* dependence. Patients with prostate cancer and *PTEN* loss have lower androgen signaling (e.g., PSA and other androgen responsive genes) and higher grade, more aggressive tumors and often make less PSA. While these patients might be expected to respond to *AR*-targeted therapy, murine responses to enzalutamide were minimal, suggesting that once PI3K is inhibited and the PI3 kinase pathways dampened down, *AR* turns back on, becoming a survival signal [5]. Murine studies of dual inhibition using enzalutamide and BEZ234 showed more dramatic responses, leading to the performance of preclinical trials of combined PI3K/*AR* blockade therapies. When *PTEN* loss is combined with ETS overexpression, PI3K is activated and *AR* signaling is reactivated, which causes aggressive prostate cancer. In patients with *PTEN* loss and *ERG* rearrangement, therapy may need to include *AR*, *PTEN*, and *ERG* inhibition.

Because very few cell lines are available for prostate cancer, researchers at Memorial Sloan Kettering Cancer Center are generating novel prostate cell lines that can recapitulate the prostate and that match the histology, the *AR* status, the *PTEN* status, and the molecular lesions.

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Acknowledgements

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