INNOVATION PARTNERSHIPS
UNIVERSITY OF MICHIGAN

Detection of CDK12 Alterations to Predict Prostate Cancer Therapeutic Sensitivity

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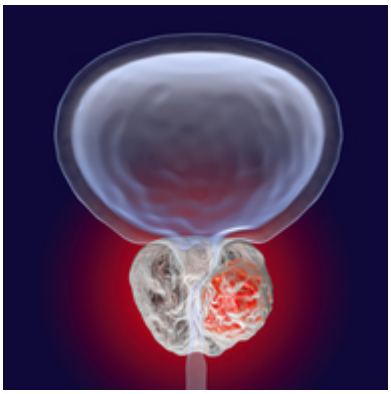

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OVERVIEW

Discovery of a new molecular subtype of metastatic castrate resistant prostate cancer

- Predicts sensitivity of tumor cells to cell cycle inhibitors and immunotherapy
- May eventually be detected in non-invasive samples like urine or circulating tumor cells

BACKGROUND

Prostate cancer (PCa) is the second most common cancer in men worldwide, with an incidence that increases greatly with age and that affects 15% of men at some point during their life. The majority of newly diagnosed PCa cases are localized and thankfully have an excellent short term rate of survival. For the approximately 20% of patients who present with advanced or metastatic disease, 5-year survival is less than one-third. The approach to treatment for patients with metastatic or recurrent cancer after primary treatment has been androgen deprivation therapy (ADT), an intervention that reduces circulating testosterone levels to deprive prostate cancer cells their primary stimulus for growth. Still, prostate cancer cells eventually develop resistant mechanisms which allow them to grow in spite of lowered testosterone levels. Patients with metastatic castration resistant prostate cancer (mCRPC) have historically been treated with salvage cytotoxic chemotherapy or, more recently, newer agents with varying mechanisms of action that only increase survival by a limited number of months. In short, mCRPC remains an incurable disease, and a need exists for molecular predictors of response to existing and future interventions.

INNOVATION

Researchers have discovered a new molecular subtype of metastatic castrate resistant prostate cancer which may predict sensitivity of tumor cells to cell cycle inhibitors and immunotherapy. The investigators have discovered that biallelic loss of cyclin-dependent kinase 12 (CDK12) is enriched in patients with mCRPC when compared to primary prostate cancer. They further demonstrated that CDK12-mutant prostate cancer defines a new molecular subtype of mCRPC, distinct from other established genetic drivers of prostate cancer, which is characterized by focal tandem duplications (FTDs) that lead to increased gene fusions and marked differential gene expression.The focal tandem duplications associated with the loss of CDK12 lead to recurrent gains in several genes with key functions in the cell cycle and DNA replication. Furthermore, CDK12-mutant cancers are highly immunogenic, exhibiting elevated neoantigen burden from gene fusions as well as increased immune infiltrating cells, but display chemokine-mediated mechanisms of immune evasion. Together, these latter two findings are those which suggest that CDK12 status can be used to predict sensitivity of mCRPC patients to cell cycle inhibitors and/or immunotherapy. Future modifications to this discovery could include the detection of CDK12 alterations in non-invasive samples, such as urine or circulating tumor cells, or single-cell sequencing methods.