Some proteogenomic signatures linked to prostate cancer progression in patients with African and European ancestries

April 9 2024

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Certain proteogenomic signatures in the prostate cancers of men of African and European ancestries were associated with higher risk of metastasis and/or recurrence of the disease, according to a study presented at the American Association for Cancer Research (AACR) Annual Meeting 2024, held April 5–10.

A study that combines proteomics and genomics is a field of research known as proteogenomics. Shyh-Han Tan, Ph.D., associate professor at the Uniformed Services University of the Health Sciences (USUHS) Department of Surgery and scientist at the Henry M. Jackson Foundation (HJF), who presented the study, explained it as similar to detecting errors in a person's instruction manual.

"The DNA in every cell is like an instruction manual where genes are the specific sections that carry instructions for making proteins—the building blocks needed for the cell to work properly," Tan said. "But errors in the instructions, or DNA mutations, can lead to the generation of faulty proteins. The advantage of a proteogenomic study is that it can examine both the DNA and proteins to help understand where the errors are occurring. Since every one of us has slight differences in our DNA, this can hopefully lead to a more precise understanding of prostate cancer."

Tan and his colleagues conducted a proteogenomic analysis using early-stage prostate cancer tissue specimens of 57 patients of African ancestry and 55 patients of European ancestry obtained from the Center for Prostate Disease Research (CPDR), a research program of the USUHS Department of Surgery and the John P. Murtha Cancer Center at the Walter Reed National Military Medical Center.

"The availability of equal access to care in this military cohort was

advantageous because it allowed us to limit the socioeconomic factors that might influence patient outcomes and to focus on the genomic and proteomic alterations as a molecular factor in health disparity," said Cara Schafer, Ph.D., assistant professor at USUHS Department of Surgery and HJF scientist, who is the study's lead author. "These proteogenomic comparisons can help us bridge the gap in our understanding of why prostate cancer remains more deadly in men of African ancestry."

Among their findings were mutation signatures and recurrent copy number alterations, which are changes in DNA, along with increases in protein expression in both cohorts that correlated with a higher risk for disease progression, as defined by biochemical recurrence (BCR) and/or metastasis following surgery. For example, they found:

- Expression levels of some proteins associated with risk for BCR and metastasis were differentially altered between the tumors of patients with African and European ancestries. For example, several NADH:ubiquinone reductase subunit proteins (e.g., NDUFS8 and NDUFV3) in the oxidative phosphorylation pathway were expressed at higher levels on tumors from patients of African ancestry, which Tan suggested could be inhibited with drugs such as metformin. In contrast, tumors from patients of European ancestry had an increased expression of several apolipoproteins (e.g., APOB and APOC1) in the cholesterol metabolism pathway.
- Mutation signatures related to aging were higher in prostate cancer from men of European ancestry, which Tan said is consistent with the older age at diagnosis of this patient cohort.
- Signatures associated with DNA repair deficiency were higher in prostate cancer from men of African ancestry, which Tan said might contribute to the efficacy in response to radiation therapy or drugs that target the DNA damage repair pathways, such as PARP inhibitors.

- In tumors from the European ancestry cohort, more frequent gene alterations were found at chromosomes 3p, 17p, and 18q. In tumors from the African ancestry cohort, more frequent alterations were found at chromosomes 1p, 1q, 3q, 13q, and 19p.
- The 17p13 locus had a higher rate of deletion in the European ancestry cohort. This locus spans a relatively large region on the chromosome with about 70 genes, including TP53—a known tumor suppressor gene.
- The 1p36 locus, which has previously been associated with prostate cancer susceptibility, was more frequently amplified in patients in the African ancestry cohort.

"Differences in our genetic ancestry and the variations in gene mutation signatures can partly explain why some cancers are more aggressive than others and can reveal weaknesses in the cancer cells that can be used as a target for therapy," Tan said. "Additionally, it is important to understand that although we may find a mutation more frequently in one group or the other, as long as the patient has an identifiable mutation, their cancer can be susceptible to targeted treatment. That's the benefit of doing studies like these—it doesn't focus on one group or the other, but everyone most affected by prostate cancer."

Tan said the next step is to compare their proteogenomic results against publicly available data sets to confirm if the associations they found hold true in a larger set of patients, and to verify using preclinical models whether prostate tumors with specific gene alterations are sensitive to certain available treatment compounds.

Limitations of the study include its comparatively small sample size and an imbalance between the average age at diagnosis of the patients in each cohort, since men of African ancestry in the CPDR clinic tend to be diagnosed at a younger age. Also, the tumor samples were from patients in the early stage of disease, so the findings do not reflect the more

varied mutation profiles seen in late-stage or metastatic prostate cancer.

Provided by American Association for Cancer Research