Two missing genes linked to aggressive prostate cancer

New data are suggesting that the loss of two genes, MAP3K7 and CHD1, may be a unique driver of aggressive prostate cancer development. Researchers at the University of Colorado Cancer Center have just published a study in the journal Cancer Research which identifies a new distinct subtype of lethal prostate cancer marked by MAP3K7 and CHD1 deletions. The novel findings may point to a new avenue of treatment of aggressive prostate cancer.

The researchers found that 50% of prostate cancer patients with combination MAP3K7 and CHD1 deletions have recurrent prostate cancer. In addition, they found that approximately 10% of all prostate cancers harbor combined MAP3K7-CHD1 deletions.

"This was a multi-disciplinary study by multiple investigators at multiple institutions showing a particularly aggressive type of prostate cancer that kills people," said senior study author Scott Cramer, PhD, professor in the University of Colorado School of Medicine Department of Pharmacology, and cancer center investigator.

Dr. Cramer and colleagues analyzed tumor samples from publicly available databases. They found that MAP3K7-CHD1 loss was a major genetic marker of cancers that eventually went on to be of the aggressive type. The MAP3K7 and CHD1 protein loss correlated with the Gleason grading system in the clinical samples. The findings suggested that possibly 25% of prostate cancer-related deaths may be related to MAP3K7-CHD1 loss.

The investigator also used a sophisticated stem cell model to grow artificial prostate tumors with these gene deletions. After growing mouse prostate stem cells in culture--without the two genes--they combined the engineered stem cells with prostate cells to make artificial prostates, and then grafted them into mouse models. This allowed the researchers to prospectively watch the growth of prostates to see the effects of these specific genetic changes.

They found that the artificial prostate glands developed aggressive cancer similar to what was seen in the database of human cancers. The loss of the genes MAP3K7 and CHD1 greatly disrupted the ability of prostate stem cells to create healthy prostate tissue. Instead, the loss of the genes led to cancerous cells with characteristics of neuroendocrine and neural cells. Overall, combined MAP3K7–CHD1 suppression appeared to greatly disrupt normal prostatic lineage differentiation. The deletion of these two genes resulted in significant androgen receptor loss, increased neuroendocrine differentiation, and increased neural differentiation.

Dr. Cramer said the stem cell model used in this study may provide a platform for significant future research. His team is now trying to discover ways to target these lethal prostate cancer cells. The researchers are testing thousands of drug candidates against cells with MAP3K7-CDH1 deletions to identify drugs that selectively kill cells with these deletions. They are also planning additional testing to further refine the prognostic ability of testing for these deletions.

The new findings may lead to a new tool for screening so that men can decide between watchful waiting (active surveillance) and opting for more aggressive therapy.

REFERENCES