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Researchers discover new pathways that drive metastatic prostate cancer

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Elevated levels of Cyclin D1b could function as a novel biomarker of lethal metastatic disease in prostate cancer patients, according to a pre-clinical study published ahead of print on December 21 in the *Journal of Clinical Investigation* by researchers at the Kimmel Cancer Center at Jefferson.

The group, headed by Karen E. Knudsen, Ph.D., Professor and Hilary Koprowski Chair, Departments of Cancer Biology, Urology, and Radiation Oncology at Thomas Jefferson University and Deputy Director for Basic Science at the KCC, found that Cyclin D1b, a variant of the cell cycle regulator Cyclin D1a, functions independently of the cell cycle to promote metastasis in both early and late stage prostate cancer.

Rather, Cyclin D1b, but not Cyclin D1a, regulates a large gene network, the researchers found, which was shown to cooperate with androgen receptor (AR) signaling to fuel metastatic progression in multiple models of prostate cancer.

Studies have shown that Cyclin D1b expression is elevated in early stages of prostate cancer (in up to 30% of primary disease), and researchers have now demonstrated that this occurs more frequently in late stage castration-resistant prostate cancer: up to 80%.

Cyclin D1b expression is also highly correlated with that of the pro-metastatic gene SNAI2 (Slug), which the group identified as regulated

by cooperative signaling between Cyclin D1b and AR.

"Numerous clinical and pre-clinical studies have effectively demonstrated that AR signaling is critical for progression to metastatic disease, but our knowledge of AR targets which can induce metastatic phenotypes is limited," said Dr. Knudsen. "Our data describe how cross talk between the cell cycle and AR can rewire the AR signaling axis to enhance the expression of genes which elicit metastasis in both early and castration resistant prostate cancer models."

"We found that Cyclin D1b can directly promote AR dependent expression of the gene SNAI2 (Slug), which dramatically increased metastatic events to soft tissues in animal models," she added.

Metastatic castration resistant prostate cancer represents the most lethal form of the disease, which arises when AR is reactivated despite continued hormone therapy.

Soft tissue metastasis to the liver and lung represents a particularly aggressive form of prostate cancer, whose presence predicts for decreased survival time in prostate cancer patients.

Currently, there is little knowledge as to how these metastatic events occur, and identification of pathways and biomarkers of this lethal event could greatly benefit prostate cancer patients.

Using various in vitro and in vivo models, researchers found that Slug enhances the ability of cells to colonize soft tissues, which resulted in a higher incidence of metastasis in the liver and lung.

Given the inability to manage AR signaling in metastatic castration resistant prostate cancer, Slug driven pathways could be leveraged to dramatically limit the incidence of soft tissue metastasis and improve

patient morbidity and mortality, researchers believe.

"Identification of AR driven pathways which mediate metastatic progression represents a significant leap forward in our attempts to effectively manage prostate cancer progression," said Dr. Knudsen. "Cyclin D1b and Slug can likely be used as biomarkers to identify patients with an increased risk of metastasis, and will eventually provide us with novel "druggable" targets downstream of AR and Slug which can be exploited to dramatically reduce the incidence of these lethal metastatic tumors."

Provided by Thomas Jefferson University