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IIT KANPUR TEAM IDENTIFIES A NOVEL TARGET TO TREAT PROSTATE CANCER

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Vital discovery: Bushra Ateeq's team found that the DLX1 protein, which is expressed at higher levels in the prostate cancer cells, has a huge role in the growth of the tumour, and metastasis.

Researchers at the Indian Institute of Technology (IIT), Kanpur, have discovered that a particular gene (DLX1) which plays an important role in the development of jaws, skeleton, and interneurons in the brain has an important role to play in the growth and development of prostate cancer.

The DLX1 protein is found at elevated levels in prostate cancer patients, the reason why the DLX1 protein has been used as a urine-based biomarker. Now the team of researchers led by Dr. Bushra Ateeq, Professor at the Department of Biological Sciences and Bioengineering, IIT Kanpur has found that the DLX1 protein, which is expressed at higher levels in the prostate cancer cells, has a huge role in the growth and development of the tumour and the spread of the cancer to other organs in the body (metastasis).

Using small molecules as inhibitors, the researchers have shown in mice a new therapeutic strategy to treat people with DLX1-positive prostate cancer.

First, the researchers found around 60% of the prostate cancer tissues have higher levels of DLX1 protein. And when the team genetically ablated the DLX1 gene that produces the protein, the ability of cancer cells to grow, develop and spread to other parts of the body was compromised.

"We used mice models to further ascertain the role of DLX1 protein in prostate cancer growth and metastasis," says Sakshi Goel from IIT Kanpur and first author of a paper published in *Nature Communications*.

To carry out the experiments in mice, the researchers first genetically engineered prostate cancer cells that expressed higher levels of DLX1 protein to generate the cells which cannot produce the DLX1 protein. Both types of cancer cells were then implanted in two groups of mice. While mice that had received cancer cell implants expressing higher levels of the protein developed huge tumour, the mice that were implanted with DLX1-ablated cancer cells developed only small tumours, and had fewer cancer cells migrating to other organs.

The second experiment on mice was to examine the ability of cancer cells to metastasis and grow in bones. "Prostate cancer cells have a tendency to metastasize in bones. So, we checked the role of DLX1 protein in cancer metastasis," says Goel. For this, they used cancer cells that were either DLX1-ablated or those expressing higher levels of the protein, and implanted the cancer cells into the tibia (bone) of the mice. A month after implant, the tumour growing in the tibia was monitored using CT scan. Mice implanted with cancer cells with elevated levels of DLX1 exhibited more bone damage than the cells that were DLX1-ablated. "These findings proved the role of DLX1 in prostate tumour growth and bone metastases," Goel says.

Androgen receptor is responsible for promoting the development of prostate cancer. Also, about 50% of prostate cancer harbour an aberrant gene which is a product of two genes (TMPRSS2

and ERG) being fused together and results in production of higher levels of ERG protein.

“Interestingly, exploring the association between these important factors revealed that about 96% of TMPRSS2-ERG fusion-positive prostate cancer patients show high levels of DLX1 protein as well. In concert with this, about 70% of the patients with high androgen receptor signaling also have elevated DLX1 protein levels,” says Prof. Ateeq.

The researchers have further shown that both androgen receptor and fusion gene product, ERG are responsible for increased level of DLX1 in prostate cancer cells. Having understood the mechanism responsible for prostate cancer growth and development, and it’s spread to distant organs, the researchers turned their attention to finding a way to reduce the expression of DLX1 protein in the cancer cells. They found that a particular protein (Bromodomain and extra terminal or BET) assists the function of both androgen receptor and ERG. “We found that if the BET protein is inhibited using small molecules, the function of both the androgen receptor and the ERG protein to upregulate DLX1 gets inhibited. As a result, the expression of the DLX1 protein and its tumorigenic potential is reduced,” says Goel.

Preclinical mice studies showed that administering BET inhibitors alone or in combination with anti-androgen drugs resulted in about 70% reduction in tumour burden along with diminished distant metastases. “Those prostate cancer patients with higher levels of DLX1 may benefit by this treatment strategy. There are several commercially available diagnostics tests for detecting DLX1 levels, therefore it is relatively easy to categorize the patients who could respond to BET inhibitors,” says Prof. Ateeq.

This decision of U.S. Nuclear Regulatory Commission was awaited by specialists

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