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Inflammation May Play Role in Metastasis of Prostate Cancer

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Many would assume that "mounting an immune response" or "having your body fight the cancer" is a good thing. Now, research at the University of California, San Diego (UCSD) School of Medicine strongly suggests that inflammation associated with the progression of tumors actually plays a key role in the metastasis of prostate cancer.

The research, appearing online March 19 in advance of publication in the journal *Nature*, identifies a mechanism which triggers metastasis, which is the spread of cancer in late stages of prostate cancer development. The findings by Michael Karin, Ph.D., professor of pharmacology in UCSD's Laboratory of Gene Regulation and Signal Transduction, and colleagues may help solve the puzzle of why it takes so long for cancer to metastasize, as well as what causes it to do so. Furthermore, this new work may lead to development of anti-metastatic therapies.

A major hypothesis in cancer research has been that whether the cancer metastisizes or not is determined by genetic changes within the cancer cell itself. But this hypothesis didn't explain why metastases appear many years after the initial tumor.

"Our findings suggest that promoting inflammation of the cancerous tissue - for instance, by performing prostate biopsies - may, ironically, hasten progression of metastasis," said Karin. "We have shown that proteins produced by inflammatory cells are the 'smoking gun' behind prostate cancer metastasis. The next step is to completely indict one of them."

More than 200,000 men are diagnosed with prostate cancer in the United States every year. As many as 25,000 men will probably die of prostate cancer in 2007, most as a result of metastatic disease.

Early tumors confined to the prostate can be treated, but no effective treatments are available for metastatic disease, according to Steven L. Gonias, M.D., Ph.D., professor and chair of the UCSD Department of Pathology, a study investigator.

"This study helps explain the paradox that, in certain types of malignancy, inflammation within a cancer may be counterproductive," said Gonias.

In research using mouse models and confirmed in human tissue, the scientists observed that a protein kinase called IkB kinase # (IKK#) turns down the expression of a single gene called Maspin, which has well-established anti-metastatic activity in breast and prostate cancers. They found that the production of Maspin is repressed by a series of events triggered by tumor inflammatory cells, with the result that prostate cancer cells spread.

"An excellent inverse correlation between IKK# activation and Maspin production was detected, such that advanced prostate cancer cells contain high amounts of activated IKK# in their nuclei and express little or no Maspin," said Karin. He noted that a perfect correlation between nuclear accumulation of activated IKK# and

reduced maspin expression was also seen in human prostate cancer, and both correlated with the clinical stage of the disease.

Karin and his colleagues discovered a signaling pathway that increased metastases in a mouse model of prostate cancer. The pathway is activated by a ligand that binds to a Receptor that Activates Nuclear factor Kappa-B (RANK). RANK ligand has been shown in previous studies to be an important inflammatory protein (cytokine) that can lead to bone loss through activation of bone resorbing cells.

RANK ligand, produced by inflammatory cells that invade advanced prostate tumors, triggers a chain reaction in which IKK# is activated, allowing it to enter the nucleus of the cancer cell, repressing Maspin. IKK# is a key linchpin in the pathway that turns off the Maspin gene and activates the metastatic program. The new results also support the view that RANK ligand is a general promoter of prostate, and possibly breast, cancer metastasis.

"Maspin is a very potent inhibitor of metastasis; in a patient with metastasis, cells have found a way to turn off Maspin, which may depend on invasion of the tumor with RANK ligand-producing cells that activate IKK#," said Karin.

Malignancies progress through stages. In early, non-metastatic tumors, a high level of Maspin is present, but it is turned off in late stages. Early tumors contain low amounts of active nuclear IKK#, whereas late-stage tumors contain the highest levels of active nuclear IKK#. The researchers also found a striking elevation in expression of RANK ligand in late tumors, but it was not expressed by the cancer cells. Instead, it is expressed by invading inflammatory cells. Interference with RANK ligand production or activation, as well as interference with IKK# activation, may offer new therapeutic strategies for prevention of metastatic disease.

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