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RESEARCH HIGHLIGHT

SPDEF: a molecular switch for E-cadherin expression that promotes prostate cancer metastasis

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In order to design effective therapies for prostate cancer, a clear understanding of mechanisms that contribute to various components of prostate cancer progression is necessary. Study of metastasis suppressor genes, i.e., genes that can inhibit metastasis, is an important field of study that can lead to identification of therapeutic targets to diminish metastasis. E-cadherin has been implicated as an important inhibitor of metastasis. Thus, understanding how it is regulated may lead towards defining mechanism of metastasis suppressor activity. Through a series of studies using genetically-modified cells, Pal *et al.* determined that SAM Pointed Domain ETS transcription Factor (SPDEF) serves as a molecular switch to turn on E-cadherin expression and thus regulate tumor aggressiveness. They determined SPDEF achieved regulation of expression through binding to and regulating the SPDEF promoter. These findings provide a strong rationale to explore targeting SPDEF for inhibition of prostate cancer metastasis.

Prostate cancer is one of the most common cancers among men within western cultures. While most cases of prostate cancer are indolent, some cases will become aggressive leading to metastatic disease and eventual death. The progression of tumors to aggressive metastatic disease is due, in part, to tumor cells gaining mobility and invasiveness through changing cell adhesion properties and altering cytoskeletal arrangements.[1] The molecular mechanisms that are responsible for converting benign tumors into aggressive tumors are not fully understood. This gap of knowledge complicates treatment since it is difficult to determine which tumors require conservative versus aggressive treatment. In many instances, patients are overtreated resulting in serious therapeutic complications.[2] There is a need to find biomarkers to differentiate between indolent and aggressive tumors to improve treatment options and patient outcome.

Biomarkers identification is often based on correlations derived from clinical tissues and *in vitro* functional studies. In the case of prostate cancer, it has been reported that that reduced or loss of E-cadherin expression a common occurrence in tumor cells as that they transition into becoming invasive.[3] The loss of E-cadherin is considered a component of epithelial to mesenchymal transition (EMT), in which cancer cells gain a mesenchymal phenotype that is considered to have increased invasive properties compared to the epithelial phenotype. Loss of E-cadherin facilitates the loss of cell adhesion and quiescence promoting both cell proliferation and invasion.[4] Since its reduced expression is seen as a significant event in tumor progression and invasion, it has been suggested that loss E-cadherin expression could be used as a marker for tumor progression [5] However, the molecular events that lead to the loss of E-cadherin during tumor progression are unknown.

In a recent publication, Pal *et al.*[6] identified SAM Pointed Domain ETS transcription Factor (SPDEF) serves as a molecular switch for E-cadherin expression and thus tumor aggressiveness. SPDEF is highly expressed in prostate epithelial cells; however, its role in prostate cancer is controversial. It was previously demonstrated that SPDED expression increased in prostate adenocarcinoma compared to benign prostate tissue and also increased with prostate cancer grade.[7] In contrast, loss of SPDEF was associated with increased prostate cancer aggressiveness and had functional characteristics of a metastasis suppressor gene.[8] This study was supported by two additional studies suggesting that SPDEF had metastasis suppressor function[8,9] and *in vivo* demonstration of metastasis suppressor function in murine models of prostate cancer.[10] The observation that SPDEF expression is inversely correlated with tumor aggressiveness, and patient prognosis, suggests that SPDEF may be used as a prognostic marker for aggressive prostate cancer;[9] however, the molecular controls that regulate SPDEF itself are still unknown.

Several prostate cancer cell lines were examined for SPDEF and E-cadherin expression, and it was observed that the expression of SPDEF and E-cadherin inversely correlated with aggressiveness, with the most aggressive cells showing the lowest expression of SPDEF and E-cadherin. It was also observed that overexpression of SPDEF lead to an increase in the expression of E-cadherin and decreased expression of SPDEF led to a decrease in the expression of E-cadherin, suggesting that SPDEF may control the expression of E-cadherin. This was supported by showing that a decrease or increase in E-cadherin expression did not significantly change the expression of SPDEF, suggesting that SPDEF is both upstream of and regulates E-cadherin expression.

Upon further investigation, it was also shown that SPDEF binds to the promoter region of E-cadherin, promoting the expression of E-cadherin. Reintroducing the expression of SPEDF to aggressive prostate cancer cell lines led to an increase in E-cadherin expression, and decrease in cell motility and invasiveness; showing that SPDEF controls the expression of E-cadherin and can inhibit tumor progression from indolent to metastatic disease.

These findings identify a novel mechanism through which SPDEF could inhibit metastasis. Additionally, they are consistent with the possibility that SPDEF is a metastasis suppressor gene. In addition to regulating E-cadherin, SPDEF has also been reported to negatively regulate MMP9, which aids in invasion by breaking down surrounding matrix;[10] suggesting that SPDEF could be

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used as a target for preventing prostate cancer progression into aggressive metastatic disease, by increasing E-cadherin expression and decreasing MMP9 expression to prevent metastasis. However, in order to use SPDEF as a target for prostate cancer treatments, it is imperative to find the molecular control for SPDEF expression and activity. It should also be noted that overexpression of SPDEF in conjunction with forced E-cadherin knock down had no effect on cell motility and invasiveness;[6] suggesting that in cases where E-cadherin loss is due to mechanisms that do not involve SPDEF, SPDEF will not be useful as a marker or molecular target. The use of SPDEF as a target for prostate cancer treatment may only be useful in early non-metastatic prostate cancers. E-cadherin has been reported to have a dual function in tumor progression as re-expression of E-cadherin in tumor cells after metastasis can promote tumor growth and survival in metastatic sites by activating cell survival signaling pathways.[11,12] More research is needed to determine a role for SPDEF and E-cadherin expression as prognostic markers and therapeutic targets for treating prostate cancer.

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