

PROSTATE CANCER

Thrombospondin-1 in hypoxic vicious cycle

New data reveal a complex role for thrombospondin-1 (TSP1) in prostate cancer, able to both inhibit angiogenesis and stimulate tumor progression. Florence Cabon and colleagues report their findings in *Cancer Research*.

TSP1 is an endogenous antiangiogenic molecule, highly expressed in castration-resistant prostate cancer. Given the importance of neovascularization in cancer progression, it might seem paradoxical for an angiogenesis inhibitor to be associated with advanced disease, but there is more to TSP1 than first meets the eye.

Pharmacological angiogenesis inhibitors (such as sunitinib) have been shown to promote tumor cell migration and metastasis. “We suspected that the association between inhibition of angiogenesis and increased invasion was not molecule-specific but was a more general process resulting from the increased hypoxia,” says Cabon. “This prompted us to re-evaluate the role of TSP1 in tumor progression.”

Investigators performed a number of *in vitro* assays, animal experiments, and clinical analyses to dissect the role of TSP1 in prostate cancer. They found that TSP1 strongly stimulates migration of cultured prostate cancer cells, and that the CD36 receptor—which also mediates the antiangiogenic effects of TSP1—is necessary for migration to occur. This observation led the team to

wonder whether in prostate cancer promigratory TSP1 had lost the ability to block angiogenesis. To address this issue, researchers used small interfering RNA to silence TSP1 in castration-resistant prostate tumors xenografted into nude mice. Inhibiting TSP1 in this context caused an increase in microvessel density, demonstrating that TSP1 still harbored its antiangiogenic properties.

Not only does TSP1 increase hypoxia via the inhibition of blood vessel growth, but a key finding of this study was the demonstration that hypoxic conditions also stimulate TSP1 production and secretion. Thus, a vicious cycle is established in prostate tumors that encourages cell migration.

Finally, researchers evaluated TSP1 mRNA expression in radical prostatectomy specimens from 35 men with clinically localized disease. Comparing expression levels between tumors of different stages revealed an association between TSP1 and invasion; expression was significantly higher in stage pT3b tumors, which invade the seminal vesicles, than in pT3a or pT2 cancers.

Furthermore, TSP1 expression was significantly higher in the tumors of patients who later experienced PSA relapse ($n = 9$), a finding that has clear clinical relevance. “TSP1 is a secreted protein, so we plan to test whether patients’ blood level is predictive of tumor invasion and tumor recurrence after surgery,” says Cabon. “This could be a very useful tool for identifying tumors at risk of relapse.”

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Original article Firlej, V. *et al.* Antiangiogenic thrombospondin-1 triggers cell migration and development of advanced prostate tumors. *Cancer Res.* doi:10.1158/0008-5472.CAN-11-0833