Although prostate-specific antigen (PSA) has been shown by Fortier et al. (1) to inhibit endothelial cell proliferation, migration, and invasion as well as metastatic spread, the value of these findings has to be questioned. This skepticism is due to the fact that, in all the experiments carried out, very high concentrations of PSA—equivalent to many thousands of ng/mL—were used. These high concentrations are very uncommon in humans, since the vast majority of men with prostate cancer have PSA levels well below 1000 ng/mL (2–4). More importantly, patients will experience symptomatic metastatic disease at PSA levels that are a fraction of those used in the experiments carried out by the authors (5–7). Hence, it is difficult to state whether, in the vast majority of patients with prostate cancer, PSA has any antiangiogenic or antimetastatic properties. It would have been far more informative if the authors had used concentrations of PSA that more closely reflect the levels detected in patients with prostate cancer. Without this information, it is too speculative to consider that elevations of PSA may be a defense against cancer progression and that the administration of PSA may be a rational therapeutic approach in the treatment of prostate cancer.

**CORRESPONDENCE**

**Re: Antiangiogenic Activity of Prostate-Specific Antigen**

Masood A. Khan

**REFERENCES**


**NOTE**

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**RESPONSE**

We thank Dr. Khan for the letter regarding our early evidence for a role of prostate-specific antigen (PSA) as an endogenous antiangiogenic protein (1). Dr. Khan questions the validity of our conclusions by mentioning that the concentrations of PSA used in our experiments are not physiologic and very uncommon in humans. We agree that one should exercise caution when extrapolating in vitro bioactivity to predict potential effects in an in vivo setting. Nonetheless, we believe that our data do demonstrate the potential physiologic relevance of PSA in the regulation of tumor growth.

It is critical to note that the concentrations of PSA in prostatic and breast exudates would be expected to be far higher than the diluted levels found in the general circulation and typically measured in patients. Indeed, levels of PSA leading to endothelial cell responses in our in vitro assays (8–120 μg/mL) approximate PSA levels found by Diamandis et al. in breast duct fluids (3 μg/mL), and are up to 200 times lower than PSA levels found in seminal fluid (2000 μg/mL) (2–4). Thus, elevated plasma concentrations of PSA represent only a minute amount of the total PSA that escapes from glands and is diluted into the bloodstream.

In addition, the concentrations of biologically active molecules in in vitro angiogenesis assays are typically an order of magnitude higher than effective in vivo concentrations, as we demonstrated for Endostatin™ protein (5). These differences in activity between in vitro and in vivo concentrations may be due to myriad factors, including cell line sensitivity (see Fig. 1, A and C, in our study) and variable responses to angiogenic stimulators (fibroblast growth factor-2 versus vascular endothelial growth factor; Fig. 2 in our study) (1). Our preliminary in vivo findings required the daily administration of 9 μM (about 300 μg) to demonstrate antitumor effects in the mouse B16BL6 metastatic melanoma model; blood levels of PSA administration were not measured in this study (1).

We recently obtained further data that reinforces our earlier observations. We expressed a recombinant human PSA in the yeast *Pichia pastoris* and compared its activity with that of PSA purified from seminal plasma in a modified Boyden chamber migration assay (6). This assay is more sensitive to the inhibitory effects of PSA than those assays used in our preliminary report and demonstrated that concentrations in the 100 nM (3 μg/mL) range for both forms of PSA resulted in 50% inhibition of endothelial cell migration.

As we suggested in our report (1), the local antiangiogenic effects of PSA may account for the slow progression of prostate cancer relative to other malignancies. Indeed, as estimated by Montic et al. (7), approximately 40% of men more than 60 years old showed evidence of subclinical prostate malignancies. Most important, we do not in any way recommend against the important use of PSA as a marker of prostate cancer or its progression, nor do we recommend that patients or clinicians modify present therapeutic strategies based on our preliminary findings. Instead, our findings indicate that PSA is an endogenous antiangiogenic molecule, it may have therapeutic relevance, and it is not prostate specific.

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**REFERENCES**


NOTES

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