CORRESPONDENCE

Re: Effect of ADAM28 on Carcinoma Cell Metastasis by Cleavage of von Willebrand Factor

I read with great interest the elegant work by Mochizuki et al. (1) providing novel experimental evidence for the crucial role of von Willebrand factor (VWF), a prominent plasma protein associated with blood coagulation, in resistance to metastasis. The authors found that aggressive human breast and non-small cell lung carcinoma cells expressing high levels of ADAM28 are able to avoid VWF-induced apoptosis at metastatic sites. ADAM28 binds and cleaves VWF, thus enhancing metastasis by favoring cancer cell survival within the blood vessels. I completely agree with the authors in the sense that ADAM28 can be a potential molecular target for cancer therapy, and the development of selective inhibitors of the proteinase is expected. However, another strategy could be to raise the levels of VWF by a pharmacological intervention to stimulate a natural defense against metastasis formation.

Desmopressin (DDAVP), a synthetic peptide analog of vasopressin, has been used during the last decades as a treatment of choice in von Willebrand disease, at least for minor bleedings and for surgical prophylaxis (2). The compound induces a rapid increase in circulating VWF, both in patients and healthy volunteers, by stimulating its release mainly from microvascular endothelial cells (3). In 1999, we communicated for the first time that intravenous infusion of DDAVP can inhibit the development of distant metastasis in a mouse model. At clinically relevant doses, the peptide dramatically reduced the experimental lung colonization of aggressive mammary cancer cells (4). Later, using a transgenic mouse model, we demonstrated that high blood levels of the natural metalloproteinase inhibitor TIMP-1 display a cooperative role in the antimetastatic effect of DDAVP on melanoma cells (5), suggesting a role of tumor proteinases in the degradation of DDAVP-induced effectors.

Considering the antimetastatic properties of DDAVP as well as its well-known hemostatic effect and tolerability, we conducted a pilot veterinary clinical trial in dogs with locally advanced mammary cancer. Perioperative administration of DDAVP at high doses of 1 μg/kg prolonged disease-free and overall survival. An extended trial recently confirmed these results, showing a reduced incidence of local relapses and lung metastasis in treated animals and a particular survival benefit in cases with more aggressive carcinoma (6). It is likely that DDAVP infusion not only inhibits perioperative metastastic events but also combats micrometastases that occurred before surgery.

Perhaps the greatest obstacle for therapy of an advanced cancer is that the outcome of residual metastasis depends on interactions of disseminated cells with homeostatic mechanisms that the tumor cells usurp. The study of Mochizuki et al. (1) had shed light on the implication of ADAM28 in tumor cell aggressiveness and the surprising role of VWF in inducing apoptosis of metastasic cells. The perioperative period is an attractive window of opportunity to take advantage from this knowledge, modulating tumor–host interactions and thus reducing the risk of metastatic disease (7). Because abrupt release of VWF may favor the collapse of early metastic foci, further evaluation of the vasopressin analog DDAVP in clinical trials is warranted.

DANIEL F. ALONSO

References

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Notes

Affiliation of author: Laboratory of Molecular Oncology, Quilmes National University, Buenos Aires, Argentina (DFA).

Correspondence to: Daniel F. Alonso, MD PhD, Laboratory of Molecular Oncology, Quilmes National University, R. Saenz Peña 352, Bernal B1876BXD Buenos Aires, Argentina (e-mail: dfalonso@unq.edu.ar).

Conflicts of interest: D.F. Alonso has served as a consultant for Romikin SA (Argentina), a company which develops novel peptide compounds in oncology, and he currently conducts an R&D program on cancer immunotherapy at the University of Quilmes, sponsored by Elea Laboratories (Argentina).

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