Letter to the Editor

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Implication of von Willebrand Factor as a Regulator of Tumor Cell Metastasis: Potential Perioperative Use of Desmopressin and Novel Peptide Analogs

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The review article by Luo et al. in *Acta Haematologica* [1] regarding the multifunctional role of the hemostatic glycoprotein von Willebrand factor (vWF) was of great interest to us. Among other functions, recent studies have implicated vWF as a regulator of angiogenesis and tumor cell metastasis. Using a vWF-deficient mouse model, Terraube et al. [2], in 2006, demonstrated that vWF plays a protective role against tumor cell dissemination in vivo. It appears that the glycoprotein can induce the death of metastatic cells early after their arrest in the microvasculature of the target organ. More recently, Mochizuki et al. [3] provided novel experimental evidence for the crucial role of vWF in resistance to metastasis. They found that aggressive human breast and non-small cell lung cancer cells with high levels of ADAM28 (a disintegrin and metalloproteinase 28) are able to avoid VWF-induced apoptosis at micrometastatic sites. ADAM28 binds and degrades vWF, thus favoring the survival of metastatic cells in the tissue microenvironment.

In the review of Luo et al. [1], some interesting remaining questions have been addressed, such as if the vWF involvement in metastasis suggests a therapeutically manageable correlation with tumor progression. In this sense, an attractive strategy could be to raise the levels of vWF by a pharmacological intervention. More than a decade ago, we reported that intravenous administration of the synthetic peptide desmopressin (1-deamino-8-D-arginine vasopressin, DDAVP) can inhibit the formation of blood-borne metastasis in an experimental mouse model [4]. At clinically relevant doses, it was also shown that DDAVP inhibited lymph node and lung metastasis from aggressive mammary tumors [5]. DDAVP has been used as a treatment of choice in von Willebrand disease, at least for minor bleedings and for surgical prophylaxis. The compound induces a rapid increase in circulating vWF by stimulating its release mainly from microvascular endothelial cells, through a specific agonistic action on V2 vasopressin receptors [6].

Taking into account the hemostatic and antimetastatic properties of DDAVP, we designed a pilot veterinary clinical trial in dogs with locally advanced mammary cancer, administering the peptide at high doses (1 μg/kg) by intravenous infusion, before and after excision of the primary tumor. Perioperative DDAVP was well tolerated using this short-term treatment approach, and it prolonged disease-free and overall survival significantly [7]. An extended veterinary trial recently confirmed these observations, showing a reduced incidence of local relapses and lung metastasis in treated animals with high-grade carcinoma [8]. The perioperative period is an attractive window of opportunity to modulate tumor-host interactions in order to reduce the risk of metastatic disease [9]. Abrupt release of vWF induced by DDAVP at the target organ may produce apoptosis in the early metastic foci.

Peptides such as DDAVP have a great potential as therapeutic agents due to their ease of rational design and target specificity, and cancer therapy constitutes an important field for peptide compounds. With the aim of designing novel antitumor compounds, we have recently developed a panel of DDAVP analogs. Notably, the synthetic peptide 1-deamino-4-valine-5-glutamine-8-D-arginine vasopressin exhibited a significantly higher antitumor activity against human breast cancer cells than the parental compound [10]. We consider that further studies with DDAVP and its analog are warranted to determine their potential in cancer therapy.

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