Letter to the Editor

Cancer Research

Urokinase Exerts Antimetastatic Effects by Dissociating Clusters of Circulating Tumor Cells—Letter

Juan Garona[1] and Daniel F. Alonso[1,2]

Blood-borne spread is responsible for the vast majority of cancer-related deaths, and it is recognized that clusters of circulating tumor cells (CTC) are much more likely to cause metastasis than single CTCs. In the November issue of *Cancer Research*, Choi and colleagues utilized an elegant *in vivo* confocal system in the 4T1 mouse model of breast cancer metastasis to analyze the dynamics of CTC clustering in blood vessels and demonstrated that the thrombolytic agent urokinase prevented the assembly of CTC clusters (1). Urokinase is a plasminogen activator that starts fibrinolysis by converting plasminogen to active plasmin and also participates in extracellular matrix remodeling during tumor invasion (2).

It is important to note that the study of Choi and colleagues (1) is in line with our previous research in the F3II mouse mammary carcinoma model, which demonstrated that although pharmacologic inhibition of urokinase blocks primary tumor invasion, it is unable to control progression of the metastatic disease (3). Moreover, we have shown that the highly potent, selective urokinase inhibitor B623, a 4-substituted benzo[b]thiophene-2-carboxamidine, induces clustering of F3II cells *ex vivo* in the presence of plasma and, thus, enhances metastatic lung colonization *in vivo* (4).

[1]Laboratory of Molecular Oncology, National University of Quilmes, Buenos Aires, Argentina. [2]National Council of Scientific and Technical Research (CONICET), Buenos Aires, Argentina.

Corresponding Author: Daniel F. Alonso, Quilmes National University, R. Saenz Peña 352, Buenos Aires B1876BXD, Argentina. Phone: 5411-4365-7100, ext. 4257; Fax: 5411-4365-7132; E-mail: dfalonso@unq.edu.ar

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Choi and colleagues have shed light on the process of CTC cluster formation, leading to new concepts for early pharmacologic interventions to prevent metastatic spread into secondary organs (1). In this regard, the perioperative period is an attractive "window of opportunity" to modulate tumor–host interactions and reduce the risk of metastatic disease. A recent phase II dose-escalation trial in breast cancer patients explored the potential utility of perioperative administration of desmopressin, a profibrinolytic and hemostatic agent that stimulates the release from endothelial cells of urokinase and tissue-type plasminogen activator, as well as the von Willebrand factor, a multimeric plasma protein implicated in metastasis resistance (5). Interestingly, intravenous infusion of desmopressin was associated with a rapid postoperative drop in CTC counts, as measured by quantitative PCR of cytokeratin-19 transcripts (5). We consider that further evaluation of treatment strategies interfering the formation and/or stability of CTC clusters in the blood of cancer patients is warranted.

Disclosure of Potential Conflicts of Interest

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References

1. Choi JW, Kim JK, Yang YJ, Kim P, Yoon KH, Yun SH. Urokinase exerts antimetastatic effects by dissociating clusters of circulating tumor cells. Cancer Res 2015;75:4474–82.
2. Aguirre-Ghiso JA, Alonso DF, Farias EF. Functional expression of the uPA/uPAR system in cancer metastasis. In: Lyden D, Welch DR, Psaila B, editors. Cancer metastasis: biologic basis and therapeutics. New York, NY: Cambridge University Press; 2011. p. 223–36.
3. Alonso DF, Farias EF, Ladeda V, Davel L, Puricelli L, Bal de Kier Joffe E. Effects of synthetic urokinase inhibitors on local invasion and metastasis in a murine mammary tumor model. Breast Cancer Res Treat 1996; 40:209–23.
4. Alonso DF, Bertolesi GE, Farias EF, Gomez DF, Bal de Kier Joffe ED. Inhibition of fibrinolysis by a synthetic urokinase inhibitor enhances lung colonization of metastatic murine mammary tumor cells. Oncol Rep 1996;3:1055–8.
5. Weinberg RS, Grecco MO, Ferro GS, Seigelshifer DJ, Perroni NV, Terrier FJ, et al. A phase II dose-escalation trial of perioperative desmopressin (1-desamino-8-D-arginine vasopressin) in breast cancer patients. Springerplus 2015;4:428.

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