Introduction: fibrinogen as a determinant of the metastatic potential of tumor cells

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An association between the hemostatic system and cancer has been well known for many years. Hemostatic complications are a common cause of death in patients with cancer, and abnormalities such as disseminated intravascular coagulation and migratory thromboembolitis have been well described. Many tumor cells possess procoagulant activities that promote local activation of the coagulation system, and tumor-mediated activation of the coagulation cascade has been implicated in both tumor stroma formation and the promotion of hematogenous metastasis. Most solid human and experimental animal tumors contain considerable amounts of fibrinogen-related products, suggesting that fibrin (ogen) is important in stroma formation. Fibrin clots promote migration of several types of cells, including endothelial cells, macrophages, and fibroblasts. Fibrin also promotes neovascularization, supporting the notion that fibrin facilitates tumor stroma formation by mechanisms that are analogous to those in wound repair. Fibrin degradation products display powerful chemotactic, immunomodulatory, and angiogenic properties. Thus, substantial evidence points to a significant role for fibrin(ogen) in tumor progression. The coagulation system has also been implicated in hematogenous tumor cell spread. Following their entry into the circulation, tumor cells must adhere to the microvasculature of a target organ prior to growth. Deposition of fibrin within adherent circulation, tumor cells must adhere to the microvasculature of a hematogenous tumor cell spread. Following their entry into the circulation, tumor cells must adhere to the microvasculature of a target organ prior to growth. Deposition of fibrin within adherent tumor cell aggregates can be detected shortly after tumor cell inoculation and persists for several hours.

The generation of viable mouse lines with selected deficits in key hemostatic factors has provided an opportunity to directly examine the role of fibrinogen in tumor progression and spread. In this Focus on Hematology, Palumbo and colleagues used fibrinogen-deficient and plasminogen-deficient transgenic mice and two transplantable murine tumor cell lines, Lewis lung carcinoma and B16-BL6 melanoma, to determine the effects of these deficiencies on hematogenous pulmonary metastases. Fibrinogen deficiency did not reduce the growth rate of transplanted Lewis lung carcinoma, and Lewis lung carcinoma and B16 melanoma cells were also capable of establishing pulmonary metastatic foci in fibrinogen-deficient mice comparable to those observed in nondeficient mice. Thus, fibrinogen was not strictly required for hematogenous metastases, but fibrinogen deficiency strongly diminished the metastatic capacity of either type of tumor, because fibrinogen-deficient mice showed a consistent and significant reduction in the number of surface pulmonary metastases. This indicates that initial establishment of metastatic foci, but not tumor growth itself, was impaired in fibrinogen-deficient mice. In contrast, plasminogen deficiency had no effect on the number of surface pulmonary metastases for either type of tumor, indicating that plasmin-mediated fibrinolysis was not an important factor. Microscopic analysis of lung tissue from tumor-bearing fibrinogen-deficient mice failed to reveal any differences from control mice in terms of tumor stroma and angiogenesis, thus suggesting that fibrinogen is not required in this system for these processes. In addition, the presence of fibrinogen deficiency did not affect the initial arrest of 125I-deoxyuridine–labeled tumor cells in the lungs, but sustained tumor cell adherence was markedly impaired.

Hirudin, the thrombin inhibitor, has previously been shown to inhibit the metastases of circulating tumor cells, but it is not known whether this activity is solely related to its substrate, fibrinogen. As expected, hirudin administration to normal mice diminished the number of pulmonary metastatic foci by more than 20-fold compared to saline-treated controls. Hirudin administration to fibrinogen-deficient mice also resulted in a significant reduction compared to saline controls, and the level was reduced to nearly zero. Thus, there is at least one fibrinogen-independent mechanism by which hirudin exerts its effect on tumor cell spread, and the effect is not related to direct inhibition of cultured tumor cells.

These studies nicely demonstrate that fibrinogen plays an important role in the pathophysiology of cancer and that it is at the least a major determinant of the metastatic potential of tumors. It appears to facilitate the establishment of metastases by enhancing the sustained adherence of tumor cell emboli in the vasculature of target organs. Tumor cell–associated thrombin generation and local conversion of fibrinogen to fibrin may also be related to metastatic potential, but there is at least one fibrinogen-independent mechanism for thrombin-mediated promotion of tumor metastases. These studies have answered important questions concerning the role of fibrinogen in tumor spread, but other important questions remain unresolved:

1. How does fibrinogen sustain tumor cell adhesion and survival?
2. What is the fibrinogen-independent mechanism by which thrombin promotes tumor metastases?
3. What is the relative importance of soluble fibrinogen, insoluble fibrin, and fibrin(ogen) degradation products in tumor progression?
4. What is the effect of the absence of a fibrin matrix in tumor-bearing fibrinogen-deficient mice on spontaneous tumor metastases?

It seems likely that further experimentation using this transgenic system will provide useful answers to these questions.

References

2. Cavanaugh PG, Sloane BF, Honn KV. Arrest and extravasation of tumor cells prior to growth. Deposition of fibrinogen within adherent circulation, tumor cells must adhere to the microvasculature of a hematogenous tumor cell spread. Following their entry into the circulation, tumor cells must adhere to the microvasculature of a target organ prior to growth. Deposition of fibrin within adherent tumor cell aggregates can be detected shortly after tumor cell inoculation and persists for several hours.
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