Cancer and Metastasis Reviews **11**: 283–290, 1992.

The role of fibrin in tumor metastasis

Vincenzo Costantini[1] and Leo R. Zacharski[2]
[1] *Institute of Internal and Vascular Medicine, Università of Perugia, Perugia, Italy and*
[2] *The Department of Medicine, Dartmouth Medical School and the Department of Veterans Affairs Medical Center, White River Junction, Vermont 05009, USA*

Key words: fibrinogen, fibrin, neoplasia, tumor metastasis

Summary

A volume of data that has accumulated for over a century has suggested that fibrin may facilitate the persistence and progression of malignancy. Techniques that have been developed recently have shown that fibrin is indeed a component of the connective tissue stroma in human malignancy but in only a few tumor types. However, therapeutic intervention studies with drugs that limit thrombin activity or enhance fibrinolysis have shown favorable clinical effects in at least one such tumor type. These favorable findings affirm the concept that cause-and-effect relationships do, in fact, exist between thrombin generation with fibrin formation and tumor progression, and suggest that a rational basis exists for the design of future drug intervention trials that target reactions relevant to specific tumor types. These findings also provide a basis for the design of experiments capable of defining further the role of fibrin in the integrity of these tumor types. Because fibrinogen is found much more commonly than fibrin in the connective tissue of a variety of human malignancies, attention might reassumably be directed to determining the possible contribution of this molecule as well as of fibrin to tumor progression.

Introduction

Fibrin has been linked to cancer biology for well over a century [reviewed in reference 1]. The focus of interest in the fibrin-tumor association has been the possibility that fibrin may form around circulating tumor cells that facilitates microvascular entrapment required for metastasis, and also that fibrin may be a biologically important constituent of the tumor connective tissue stroma. Painstaking studies conducted in the late Nineteenth and early Twentieth Centuries [1] of human tissues obtained at autopsy from cancer patients documented the occurrence of thrombi around embolic tumor cells within blood vessels. Such findings were subsequently documented in tumor-bearing experimental animals [2–5]. In certain of these animal models of malignancy, tumor dissemination could be blocked by administering drugs that either limited fibrin formation because of their anticoagulant properties or lysed the fibrin because of their ability to convert plasminogen to plasmin [reviewed in references 2–4].

More recently it has been emphasized that fibrin may be a constituent of the connective tissue stroma of both animal [6–10] and human [11, 12] tumors. Such extravascular fibrin is conceived of a possibly enhancing tumor integrity by providing a scaffolding for tumor cell growth, enhancing angiogenesis, or protecting the tumor from attack by host inflammatory cells that would presumably destroy the tumor [6, 7, 10, 13, 14]. The latter has been generalized into the concept that fibrin may serve as a protective 'cocoon' that surrounds the tumor, and that the tumor resembles a 'wound', from the point of view of its fibrin content, but a

No Body Text -- translate me!
Page 2

wound that cannot heal because it paradoxically serves to perpetuate the 'injury', that is, the tumor itself [6].

If true for human malignancy, such a formulation would be fortuitous indeed because such fibrin could presumably be either removed by fibrinolytic enzymes or prevented from being formed by anticoagulants to the advantage of the patient. Unfortunately, however, the true state of affairs seems not to be so simple and straightforward. For example, the composition of the thrombi found long ago to surround intravascular tumor emboli [1] has not been studied in detail and may consist of either platelets [15, 16] or fibrin (or both). The fact that such thrombi have formed does not necessarily mean that entrapment presumed to be necessary for metastasis formation has occurred, but may rather be merely an associated but not causally related phenomenon.

To assign primary importance to such thrombi in human metastasis would require studies of effects of intervention with antithrombotic drugs. Such studies have indeed been performed but these have shown beneficial effects in only one tumor type so far [17–22] while the natural history of certain other tumor types is unaffected by this form of therapy [18]. Although such an approach is indeed effective in certain experimental animal models of malignancy [2, 15, 23], these lack resemblance to clinical situations, for example, because treatment of humans has invariably been initiated well after diagnosis whereas treatment usually precedes inoculation of tumor cells in animal models. This means that metastasis has almost certainly already occurred in humans so treated and clinical measures of outcome have correspondingly been improved survival and delayed time to tumor progression rather than inhibition of metastasis per se [17–22]. To complicate matters further, fibrinolytic therapy has been shown to be effective in certain clinical settings [20, 21, 24] while success has been claimed for antifibrinolytic therapy in others [25].

Similar difficulties arise upon closer examination of the literature describing the importance of extravascular fibrin deposition at tumor sites [6–10]. Fibrin undoubtedly is formed in certain experimental animal models but the degree to which human malignancy corresponds to such models (if at all) has only recently begun to be clarified. There is, therefore, little basis for generalizations concerning the existence of fibrin in human malignancy let alone its possible role in tumor progression.

The purposes of this paper are to review recent progress in our understanding of fibrin formation in human tumors in terms of the cellular sites of procoagulants responsible for thrombin generation capable of converting fibrinogen to fibrin, to define criteria for the existence of fibrin as opposed to fibrinogen *in situ* in tumor tissues, to examine data from clinical trials of anticoagulant fibrinolytic therapy in cancer that are required to establish cause-and-effect relationships between fibrin formation and neoplastic progression, and finally to focus attention on the potential biologic role of either fibrinogen or fibrin in supporting tumor growth to provide a basis for future studies.

Tumor fibrin formation

For tumor fibrin to form, there must be a pathway that results in the formation of thrombin that, in turn, converts fibrinogen to fibrin. For fibrin formation to be verified, criteria must be developed that can be applied to intact tumor tissues as they exist in patients. The assumption that fibrin exists in human tumors cannot be generalized from studies in experimental animals. Furthermore, assumptions based on data obtained from studies on cells in culture or from other *in vitro* or semipurified systems may not be valid because such conditions may not resemble conditions within complex tissues *in vivo*.

Our approach to this problem was to use immunohistochemical procedures applied to intact human tumor tissues. This approach is useful because high quality antibodies exist to virtually every known clotting factor and fibrinolytic pathway component as well as to both fibrinogen and fibrin. These reagents permitted a systematic search for the existence of each of these elements in tumor tissues and permitted their precise microanatomic localization to either tumor cells, host inflammato-