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Review Article

Tumor Fibrin/Fibrinogen Matrix as a Unique Therapeutic Target for Pulmonary Cancer Growth and Metastases

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Abstract

The causes for the death of cancer patients' deaths can be multi-factorials and pathogenesis progresses in clinics. Apart from direct causes from tumor progressions and metastases by genetic inheritance, mutations, deletions, repeating and other types of genetic dysfunction, other clinical complications or factors will more or less speed up the deaths of cancer patients. The cancer assistant therapies have be renewed to be the major forces for improving therapeutic actions for inhibiting cancer complications in clinics. Pulmonary cancer is one of the highest incidence and mortality characteristics cancer categories for complicate disease progression worldwide. This mini-review discusses one of these complicating factors and possible mechanisms of action and therapeutic solutions are given.

INTRODUCTION

The causes for the cancer patients' deaths are multi-factorials in clinics. Apart from direct causes of tumor progressions and disseminations by genetic mutations, deletions, repeating and short sequence copying etc, many clinical complications or histo-pathogenesis factors promote the disease progression and will increase the mortality rates of cancer patients. So many assistant therapies will be offered to the cancer patients who have some serious complicate symptoms and escalation [1-3]. After a long silence, many recent findings have rediscovered that assistant therapies are important options to ameliorate clinical deadly symptoms and exhibit favorable therapeutic efficacies to prolong patients' survivals in many clinical circumstances and aggressive disease progressions.

Venous thromboembolism is an unfavorable clinical complication that causes a lot of cancer patients' deaths in clinics [4]. Many attempts with anticoagulants (AC) and/or fibrinolytic agents (FA) such as warfarin, heparin or oxalysine, etc have been experimentally studied and clinically utilized [1-5]. One of the therapeutic targets of these assistant anticancer agents is fibrin/fibrinogen accumulations and releasing among solid tumor tissues and possibly plasma fibrinogen escalations in animals and humans with solid tumor growths and metastasis [5].

EXPERIMENTAL STUDY

The possible mechanisms of action for promotion of solid tumor growth and disseminations by fibrin/fibrinogen related pathways have been partly given by Prof Dvorak (Harvard University, US) as

- It may form a scaffold to which tumor cells can attach a tumor stroma
- Form a cacoon to shield tumor cells from attack by activated lymphocytes
- It may help angiogenesis in tumor tissues [6,7].

In initial stages of this type of assistant therapeutic applications, many coagulation-related drugs and therapies were designed and observed in experimental studies and clinical evaluations (Figure 1) [5].

Blood coagulation systems and fibrin/fibrinogen matrix surrounding solid tumors are too complicated to be completely elucidated quickly. It is a pathogenic cascade pathway and can be targeted differently. Thence, a lot of human or tumor biological molecules are interrelated with coagulation cascade pathway. As a result, different AC or FA agents might act on different

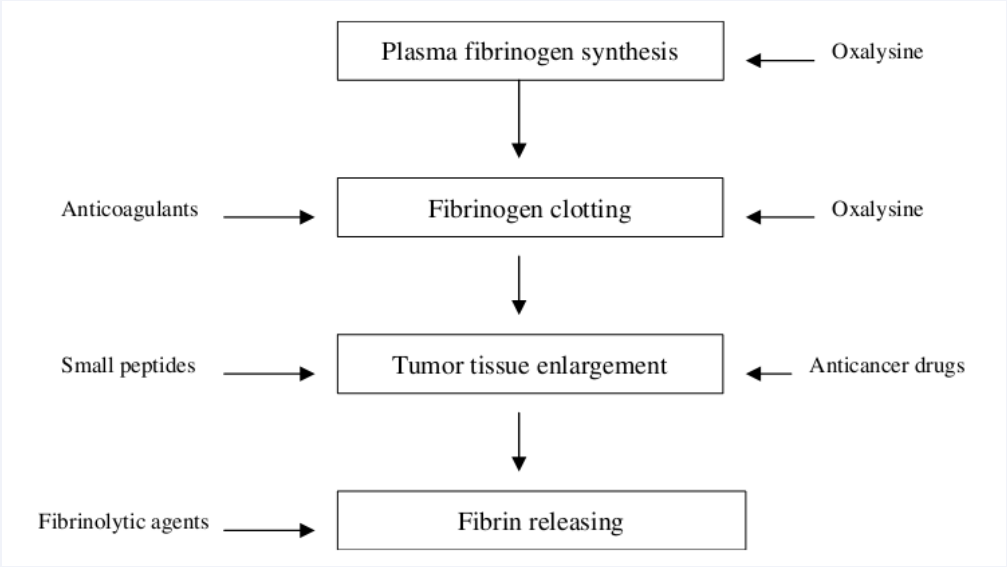

Figure 1 Outlook of different types of assistant therapies against solid tumor growth and metastases via varied fibrinogen-related pathways [5].

cascade steps [5-12]. The relationship between drug therapeutic efficacies and coagulation cascade molecular mechanisms of action and biological molecules are depicted in Table 1. (Table 1) These experimental drug mechanism studies can be translated into effective clinical treatment paradigms presently and in future.

CLINICAL INVESTIGATIONS AND APPLICATIONS

Different from other assistant cancer therapy, AC and FA have already had great therapeutic significance for clinical applications, especially to some solid tumors, like lung cancer. A lot of articles have reported the possibility and capability of AC and FA on solid human cancer treatments [13-20]. Disordered coagulation is encountered in up to 90% of cancer patients bearing solid tumors, and 15% of them develop a localized acute or chronic deep thrombosis that is a driving force for pathological deteriorating categories now. The causes of disordered coagulation can be multi-factorial events, such as neoplasm metastasis, chemotherapy or hormone therapy (impairing the blood vessel walls or promoting coagulate cascade), venous catheters using and immobilization [3,4]. However, disordered coagulation can be caused by multiple blood components, such as platelet [13], plasma and tumor matrix of fibrinogen [14-21] and coagulant components—coagulating factors (1-13) such as thrombin and plasminogen etc [4,5,8-12,14,21]. Most importantly, cancer patients with venous thromboembolism symptoms have been suggested to be given assistant therapy of anticoagulants and/or fibrinolytic agents such as warfarin, heparin, tissue plasminogen activator or oxalysine [1-21] for prolonging the cancer patients' survivals. Originally, AC or FA is assumed for targeting all types of solid tumors clinically. Yet only small proportions of solid tumors (1/3) are sensitive by fibrinogen-related pathway inhibitors in clinical trials. Other 1/3 categories of solid tumors have marginal therapeutic efficacies by AC or FA [5,7]. Most human pulmonary tumors such as non small cell lung cancer (NSCLC) are those being most sensitive by fibrinogen-related pathway inhibitors treatments and interventions [7,17].

Cancer patients who undergo surgery are at high risk of developing a thromboembolic complication. Cancer patients undergoing a surgery have twice the risk of postoperative deep venous thrombosis (DVT) and more than three times the risk of fatal pulmonary embolism than patients who undergo surgery for benign diseases. Now, there is a consensus that prophylaxis low-doses of heparin (5000 IU daily for 8-12 h starting 1-2 h before the operation) should be used in patients undergoing malignant tissue surgery. A subgroup analysis of cancer patients revealed that low-dose unfractioned heparin is able to reduce DVT from 22% (control) to 9% in cancer patients [4]. In non-surgery cancer patients, prophylaxis antithrombosis therapy can be used in cancer patients with a central venous catheter, because central venous catheters will increase the incidence of deep venous thrombosis (DVT) and cancer patients' deaths.

Table 1: Overall mechanisms of action for anticancer drugs against solid tumors via fibrinogen-related pathways.

Drug	Main biological and pharmacological targets and pathways
Heparin and its derivatives	Fibrin/fibrinogen clotting Venous thrombosis
Warfarin	Blood coagulation Venous thrombosis
PG activators	Fibrin fragment releasing Fibrin clotting breakdown
Urokinases	Fibrin clotting breakdown
Proteases	Fibrin/fibrinogen breakdown
Small peptide	Tumor/fibrinogen binding
Oxalysine	Fibrin/fibrinogen clotting Tumor/fibrinogen binding Thrombin activity Tumor-induced plasma fibrinogen level escalations
Anticancer drugs	Tumor/fibrinogen binding Fibrinogen synthesis in tumor tissues

COMBINED ANTI-THROMBOSIS THERAPY WITH ANTICANCER DRUGS

Since anti-thrombosis therapy is an assistant therapy, it is seldom very successful by using anticoagulants alone. Common anticancer drugs are the mainstay of conventional therapies and they are more or less cooperatively active on body's coagulation system [5-10]. Conventional first-line anticancer drugs can affect the binding of fibrinogen with tumor cells and in the same times contribute to blood coagulation changes (up or down) in cancer patients [9,12]. To conclude, anti-thrombosis therapy must be combined with anticancer drugs for improving therapeutic outcomes in cancer patients' treatments.

DISCUSSIONS AND FUTURE DIRECTIONS

The biggest advantageous of conventional FA or AC treatments is very limited toxicity comparing with other types of anticancer drugs in cancer patients' treatment, which is a good quality for successful cancer therapy. Owing to this character, therapeutic efficacies/ toxicity (therapeutic index) should always be high in clinics.

Many AC or FA is biological molecules, which are very specificity to tumor metastatic pathways but less inhibitory efficacies to large volume of tumor tissues. How to solve this drawback of AC or FA is an open question. One of the possibilities might be combined with biological AC or FC with highly cytotoxic chemicals [1-3] and this is the first step to fully perfect assistant cancer therapy. Find ways of optimizing admixtures of different types of drugs should never be overlooked.

The different drug combination systems and rules should be focused because current drug combination strategies are based on empirical rather than science-guided strategies [22,23]. This phenomenon leads to greatly compromise therapeutic efficacies and outcomes in clinics. Invitation of more clinicians into the study of this strategy is the first step to completely overcome all the limitations and hurdles for present cancer therapy in clinics.

To make a real difference, experimental and clinical scientific investigations and studies of pathogenesis and therapeutics is an indispensable avenue to go through. Bur academic and clinical efforts and government funding are necessary. Only increasing funding supports can lead us overthrow all the detrimental factors that a malignant solid tissue promotes.

CONCLUSION

Fibrin/fibrinogen accumulation and releasing in solid tumors is a long discovered clinical event and complicated for clinical interventions and of clinical significance. This type of assistant therapy has been long-term noticed and focused by a lot of attentions from all scientific disciplines. These advancements include new drug development, optimizing chemotherapeutic schedules, drug combinative strategies, pharmacogenetics [24] and individualized antimetastatic therapy [1-3,25,26].

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