

## On the Role of Insoluble Fibrin Clots in Tumor Stroma

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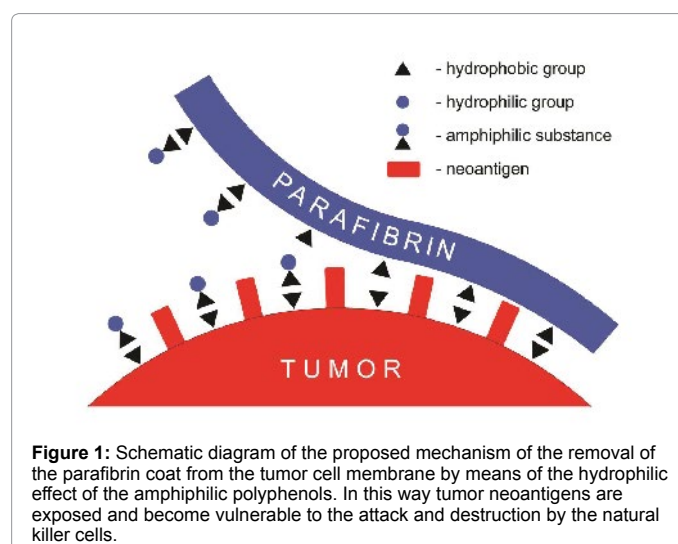
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It was suggested some years ago that solid tumors escape immunological recognition and destruction by coating themselves with a layer of insoluble fibrin [1]. However, very little data was available at that time to support this notion. Only very recently and important paper was published describing insoluble fibrin deposits in the stroma of various tumors that are different from soluble fibrinogen [2]. The authors explain this finding in terms of the malignant cycle of blood coagulation, in which tissue factor is suggested to play an important role in tumor proliferation, invasion and metastasis. They have also indicated that in non-malignant diseases fibrin is gradually removed due to the plasmin fibrinolytic activity, yet in malignant tumors fibrin deposits persist as long as cancer cells survive in the body.

It should however, be noted that here are other pathological instances, in which fibrin is not readily eliminated from the human organs, for example in stroke patients. It is known that cerebral thrombi can be resolved by means a thrombolytic therapy only when installed within 4-5 hours after the onset of thrombosis, but become refractory to fibrinolysis at later times. This was explained in terms of the free radical-induced structural modification of fibrin that makes it resistant to fibrinolysis [3]. Subsequently, it was reported that such a modification can be initiated by the exposure of blood to the redox-active iron ( $Fe^{+3}$ ) that accumulates in the human body as a result of excessive consumption of red meat and/or red cell hemolysis induced by environmental toxins. The proposed mechanism of fibrinogen modification involves a hydroxyl radical-induced reduction of intra-molecular disulfide bridges in the fibrinogen molecule. This results in the exposure of buried hydrophobic epitopes followed by the formation of inter-molecular bonds resistant to the action of proteases [4]. Of note, similar hydrophobic modifications of fibrinogen can be initiated by the exposure of human blood to the action of a specific dithiol reducing agent [5]. This particular reaction is effectively inhibited by redox-active sodium selenite that can also abolish Ebola virus infectivity by virtue of the inhibition of the viral protein disulfide isomerase [6]. In addition, sodium selenite can directly neutralize redox iron by converting it to the inactive divalent ferrous ion ( $Fe^{+2}$ ).

It should also be mentioned that certain cancers were shown to accumulate insoluble fibrinogen without the action of thrombin [7,8]. This important, albeit at that time not fully understood phenomenon, can now be explained in terms the iron-induced pathway of blood coagulation [4] leading to the deposition of insoluble fibrin (*parafibrin*) in the tumor stroma. The most important feature of *parafibrin* is its total resistance to the proteolytic degradation thus making it refractory to the cellular immune destruction. However, the protective coat of *parafibrin* can be removed from the tumor cell surface by means of the action of certain of certain natural hydrophilic substances notably polyphenols (Figure 1). Beneficial health effects of polyphenolic compounds, including their anticancer properties, have been well recognized [9,10]. In conclusion, I argue that the hydrophobic interactions on the surface of cancer cell membranes may become a target for a novel class of anticancer drugs.



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