Prostate Cancer Vaccines, Fibrin and Selenium: A Conceptual Review

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Abstract: Cancer immunotherapy is based on a concept that persistent presence of tumors in cancer patients is a result of immunological breakdown and/or downregulation of the tumor immunogenecity. In view of their limited efficacies, it can be argued that the problem lies not in a particular vaccine, but in tumors themselves. It is known that the rapidly dividing cells express free sulfhydryl groups on the membrane surfaces that can undergo disulfide exchange reactions with thiols of other biomolecules. Under physiological conditions sulfhydryl groups of circulating plasma proteins are engaged in the intramolecular disulfide bridges and are not available for the exchange. However, in neoplastic diseases, particularly in the prostate cancer, such an exchange reaction takes place between fibrinogen and human serum albumin resulting in the formation of a fibrin-like aggregate. A characteristic feature of such an insoluble aggregate is its remarkable resistance to proteolytic degradation not only by plasmin but by active lysosomal proteases as well. As a consequence prostate cancer cells accrue a protective coat of 'self ' proteins that is not recognizable by the body's immune system. Moreover, even if some of the unmasked tumor antigens do elicit immune response, the fibrin coat is refractive to degradation by the proteases released by natural killer cells. Consequently, in order to achieve successful immunotherapy the protective barrier of disulfide crosslinked fibrinogen-albumin complex has to be first eliminated. This can be done by the pretreatment with four-valent sodium selenite but not with other chemical forms of selenium. Selenite oxidizes thiols of the tumor cell membranes to disulfides thus making them unavailable for the exchange reaction with partially reduced plasma proteins. Although selenite is known to be toxic to humans when given orally, its body's concentration can be safely increased by the parenteral administration. In conclusion, specific chemical properties of sodium selenite warrant its careful evaluation as a potential improvement of the efficacy of prostate cancer vaccines thus contributing to the reduction of mortality of this deadly form of cancer

Keywords: Prostate cancer, immunotherapy, fibrinogen, albumin, disulfide exchange.

INTRODUCTION

An idea of immune-based therapies of cancer was initiated over 100 years ago by William B. Coley who had first observed tumor regression in inoperable cancer patients after injection with pyogenic bacterial extracts [1]. However, because of lack of understanding of a mechanism of action of this type of therapy, Coley's findings have been ignored for many years. Only more recently new data became available indicating that certain viruses and bacteria can be used as anti-cancer agents [2, 3]. Moreover, it was demonstrated that exotoxins of group A streptococci can function as 'superantigens' capable of activating T cells followed by their massive infiltration of the tumor [4]. Despite positive results obtained in some cases [5], the limited effectiveness of cancer vaccines is still a puzzle and thus brings to our attention Paul Ehrlich's idea of the importance of immune surveillance rather than the activity of natural killer (NK) cells. More recently, an alternative explanation was offered by which immunogenic tumors avoid destruction by inducing T-cell tolerance [6].

ROLE OF FIBRIN(OGEN) IN CANCER IMMUNOTHERAPY

Yet there is another, albeit not generally recognized reason why tumors may avoid immune recognition and destruction. This concept is based on the role of fibrin that forms a protective coat on the surface of tumor cells making them "invisible" for the immune surveillance system. Fibrin is normally formed from fibrinogen by the action of enzyme thrombin generated as a result of blood coagulation activation. The function of fibrin in hemostasis is to form a clot at the site of vessel wall injury that has to be gradually removed by the fibrinolytic enzymes to ensure proper wound healing. Intravascular fibrinolysis is achieved by the release of plasminogen activators, specifically tissue type (tPA) that generate plasmin on a solid phase of fibrin clots [7]. However, under certain pathologic conditions fibrin is not effectively removed leading to atherosclerosis that was argued to be a result of free radical modification of fibrin(ogen) [8]. Certain neurological diseases are also known to be associated with increased production of oxygen centered free radicals [9, 10] and the concurrent deposition of fibrin(ogen)-reactive antigen in the patient's brains [11]. The presence of insoluble fibrin(ogen)-albumin complex in Alzheimer's brain tissue is another example of the resistance of such a complexes to immune and/or fibrinolytic elimination [12].

It is well known that the persistent presence of fibrin matrix in prostate cancer tissue is associated with a continuous release of tPA [13]. Yet despite such a high fibrinolytic activity in the stroma of prostate cancer, fibrin lysis is not achieved thus creating a state of permanent thrombosis [14]. Association of thrombosis with cancer was already observed over one hundred years ago by Trousseau [15] and later on confirmed by numerous investigators [16-20]. The most

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plausible explanation for the occurrence of fibrin in cancer tissues is inhibition of fibrinolysis reported by several researchers [21-23]. Importance of fibrinolytic inhibition in cancer is further supported by the finding that the treatment of mice with two potent inhibitors (Aprotinin and EACA) have significantly increased lung B16F10 melanoma metastasis [24].

There is, however, no readily available explanation why fibrin in cancer tissues is resistant to fibrinolytic degradation. One of the causes could be that the properties of such fibrins are different that those of normal hemostatic clots. Thus, it has been reported that fibrin deposits continue to be formed in patients anticoagulated with warfarin [25] suggesting an alternative mechanism of their formation. This notion was confirmed by the observation that the fibrin-like material is formed in cancer tissue without thrombin generation [26]. It has been suggested that the enzyme-induced coagulation does not contribute to progression of adenocarcinoma of the prostate [27]. Therefore the question arises about a possible mechanism of fibrin formation in neoplastic tissues other than the classical activation of blood coagulation. The most likely explanation is the formation of fibrin-like insoluble aggregate ("neofibe") by the action of hydroxyl radicals on fibrinogen [28]. A characteristic feature of free radical-modified human fibrinogen is its remarkable resistance to fibrinolytic degradation [29]. Very recently evidence has accumulated showing that chronic inflammation plays an important role in several degenerative diseases such as cancer, diabetes and cardiovascular disorders [30, 31]. Chronic inflammation is, in turn, associated with the excessive production of free radicals [32] that facilitates cellular malignancy and proliferation [33]. According to Ames [34] chronic infection and inflammation contribute to approximately one-quarter of all cancer cases worldwide. Another important factor in cancer pathogenesis is iron overload known to contribute to the generation of the most biologically active hydroxyl radicals [35-37]. Iron is contained in red meat and thus its excessive consumption may explain the positive association with advanced prostate cancer [38], as well as other forms of cancer [39-45].

A very important fact should be noted namely that cancer tissue, in addition to fibrin-like material, contains insoluble forms of human serum albumin (HSA) [46] shown to be associated with fibrinolytic inhibition [47]. In connection with this the following fact is of extreme importance for the concept presented in this paper. Under certain conditions fibrinogen can form a complex with HSA by virtue of a disulfide exchange reaction [48]. Normally, practically all cysteine residues in fibrinogen are engaged in the intramolecular disulfide bridges that hold together alpha, beta and gamma polypetide chains of this protein. However, in cases of congenital fibrinogen abnormalities single nucleotide base changes result in Ser-->Cys or Arg-->Cys substitutions that endows fibrinogen with an extra cysteine residue [49, 50]. Such a modification of fibrinogen makes it vulnerable to the disulfide exchange reaction and the formation of a complex with human serum albumin. These type of complexes can be formed *in vitro* by exposure of human plasma to hydroxyl radicals generated in the presence of iron and/or copper ions as well as by the limited reduction with a dithiol reagent [51]. In both cases the insoluble fibrinogen-albumin complex is resistant to degradation not only by plasmin, but by active proteases such as trypsin or chymotrypsin. This phenomenon may explain the protection of fetus as a "foreign" antigen in pregnancy by forming fibrinolytically resistant feto-maternal barrier as demonstrated by Wasiutynski *et al*. [52].

On the basis of these findings, a concept was put forward according to which the reducing condition of the cancer environment causes the expression of extracellular cysteine residues [53] and/or generation of hydroxyl radicals that, in turn, catalyze the formation of insoluble fibrinogen- HSA complexes. Such complexes when deposited on the surfaces of cancer cells form a protease-resistant coat that is presented as "self " to the innate and/or extrinsic cellular immune systems. Therefore, rather an unsettling conclusion can be drawn that no matter how potent is a given vaccine under the *in vitro* conditions, its *in vivo* efficacy will always depend on their ability to overcome the intricate cancer camouflage.

POTENTIAL SIGNIFICANCE OF SELENIUM

In view of the above-mentioned mechanisms, the resistance of prostate and other forms of cancer to immunotherapy was suggested to be linked to selenium [54], a ubiquitous metalloid essential in human nutrition. There is a number of important publications on the preventive and therapeutic role selenium in cancer [55-62]. Because of a wide range concentration of selenium in soil, its daily intake may greatly vary depending on a geographical location and diet. Yet despite a plethora of publications on this subject there is still a considerable confusion as to which form and dose of selenium are clinically effective [63-65]. This problem was also very recently addressed in a comprehensive review by Schrauzer [66]. Apparently not all forms of selenium are equally effective, very likely due to their different chemical reactivity [67-70]. Thus, only four-valent sodium selenite but not six-valent selenate is redox active and can react with polythiols to oxidize them to their corresponding disulfides. On the other hand, organically bound selenium, as in selenomethionine, was shown to be ineffective in the rat model of prostate cancer [71]. Selenite is also known to directly activate NK cells [72], to trigger apoptosis in prostate cancer cells [73], and to contribute to the to eradication of the multidrug resistant acute myeloid leukemia [74]. Moreover, supplementation of selenium was shown to enhance chemotherapeutic effect of Taxol and Doxorubicin in these cells beyond that seen with the chemotherapeutic drugs alone [75]. The recent findings indicating that the anticancer action of selenium involves transactivation of p53 [76] suggest that selenite may be useful not only for the prevention but also for treatment of human prostate cancer [77, 78]. It has recently been argued that, in light of a sufficient scientific evidence [79-82], selenium should be introduced into clinical trials of cancer therapy [83].

The proposed mechanism of anticancer action of sodium selenite (Na_2SeO_3) is based on its affinity to sulhydryl (-SH) groups of proteins (P) on the surface of tumor cells converting them to *intra*-molecular disulfides according to the following reaction:

$$P\text{-}[SH]_2 + Na_2SeO_3 \text{ ----> } P\text{-}S\text{-}S\text{-}P + NaOH + SeO$$

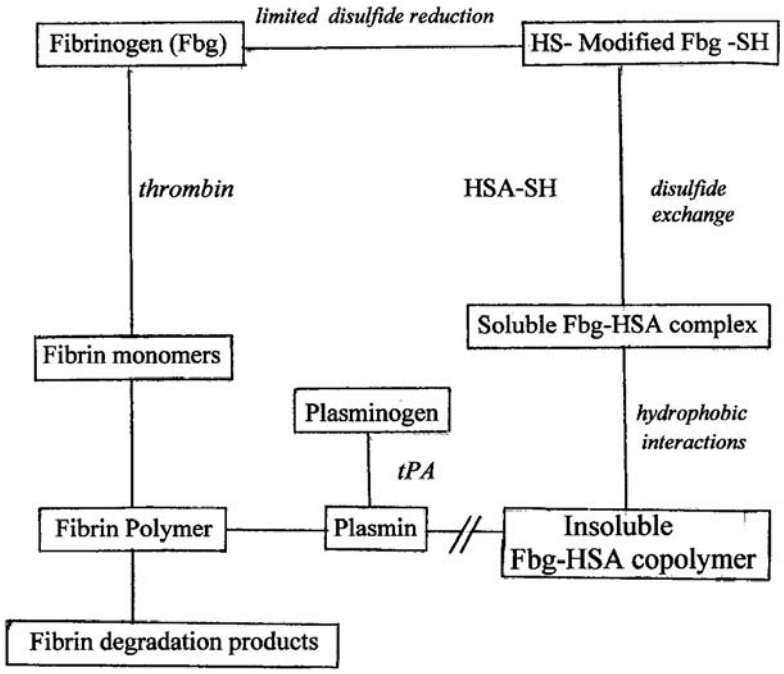

Fig. (1). Schematic representation of the physiologic conversion of fibrinogen to fibrin with thrombin, and its proteolytic degradation with plasmin. Under reducing conditions of prostate cancer stroma some of the intramolecular disulfides become converted to free sulfhydryls (-SH), which subsequently undergo disulfide exchange with those of human serum albumin (HSA). The resulting soluble complex interacts with hydrophobic regions on cancer cell membranes and thus renders the complex insoluble and resistant to proteolytic degradation.

In this way protein polysulfhydryls on cell walls become unavailable for the formation of *inter*-molecular disulfide bridges between fibrinogen and albumin molecules thus preventing their deposition on the cell surfaces [84]. Since both these proteins belong to the 'self ' family of molecules, the cellular immune system does not recognize them and consequently saves them from destruction. But even if the tertiary structure of a modified fibrinogen-albumin complex differs somewhat from their native states and elicits immune response, proteolytic enzymes released from NK cells cannot degrade it because of its highly hydrophobic nature similar to that of amyloid polypetide [85]. In the case of prostate cancer the first line of attack is the release of massive amounts of tPA that is not consumed in the process of plasminogen activation because of altered surface properties of the modified fibrin(ogen) similar to the thrombolytic resistance [86]. This phenomenon explains why prostate cancer is generally believed to be associated with activated fibrinolysis, which in fact represents only an increased *potential* for fibrinolysis.

CONCLUSION

In conclusion, the most important issue in the immune therapy of prostate cancer seems to be resistance of tumor cells to a complete eradication by various types of vaccines. It is suggested in this review that the problem is not with vaccine themselves, but with their inability to recognize prostate tumor as a foreign body. This is due to the formation of a protective coat composed of 'self ' fibrinogen-albumin complex that is not recognizable by the cellular immune system and is also refractory to proteolytic degradation. A putative mechanism of the protective coat formation versus normal fibrin clot generation is presented in Fig. (**1**).

Therefore, in order to achieve successful prostate tumor elimination a protective coat should be prevented from the deposition around the cancer cells. This can be achieved by the administration of sodium selenite that blocks sulfhydryl groups, and thus prevent disulfide exchange to occur between fibrinogen and albumin, and their deposition on the surface of cancer cells. To obtain desirable results with the use of emerging vaccine cancer therapies optimal concentrations of selenite have to be determined in human subjects. In view of a potential toxicity of oral sodium selenite at higher concentrations (over 600 mcg/day), alternative parenteral routes of administration, such as intravenous, transdermal and/or transcutaneous should be investigated as demonstrated in patients with septic shock [87]. Finally, it should be noted that there are several studies in animal models, which support the concept of vaccine immunotherapy against prostate cancer [88, 89].

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