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If Nature Failed Creating the Perfect Prostate Could Inhibitors of Proteolysis Help?

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Is the Prostate a Flawed Organ?

In young man it is working flawlessly and begins deteriorating in the forties, fifties or sixties when some men start to have problems with urinating, a benign prostate hyperplasia (BPH), hematuria and worries about prostate cancer. Rates of diagnosis of prostate cancers is different across the world, with lowest in developing countries, especially in Africa, followed by South and East Asia where it is detected much less frequently than in Europe and in the United States. However, mortality rates are the highest in the developing countries [1-3]. Clearly, advanced prostate cancer treatment available in the medically advanced communities prolongs overall survival in men. For example, decline in prostate cancer mortality in the USA compared with the UK in 1994-2004 coincided with more frequent PSA screening in the USA and more aggressive treatment of the disease [4]. Nevertheless, National cancer Institute (NCI) on its home page estimates that in 2013 it will be approximately 240,000 new cases of prostate cancer and 30,000 deaths related to this disease [5]. Considering that over 30% of men over the age of fifty have histological evidence of prostate cancer on biopsy and that this percentage increases with age, it seems that mortality rate of prostate cancer is not very high in the USA. So it might be that prostate is not such bad organ after all. However, this disease is unpredictable resulting in the mortality as the consequence of the distant metastases [6] most notably, but not exclusively to the bones. Thus it is not a surprise that NCI lists over 460 clinical studies in prostate cancer. They include predominantly androgen deprivation therapy, radiation and others concentrating mainly on reducing cancer cell growth or cancer cell killing. It raises the question if it is any room for different and novel approach for treatment of prostate cancer and its advanced forms.

How to Define Cancer

There are many definition of cancer, mine most favored would be that cancer is a tumor that can form dense network of neovascularization, can invade and can metastasize. These three processes are the most fundamental for all form of cancers. A common motif for these processes is the high and not opposed proteolytic activity [7,8]. Matrix metalloproteinases (MMPs) and urokinase activated plasmin are proteases that hydrolyze connective tissue providing space for growth of vasculature, invasion and movement of metastatic cells. Moreover plasmin activates latent MMPs and potentiates proteolytic activity in proximity of cancer body [9,10]. Angiogenesis is required for tumors to grow, invade and metastasize and angiogenic vessels are less likely to accumulate mutations that permit them to develop drug resistance. Thus, not killing cancer cells but stopping them from dividing or targeting vasculatures that support tumor growth, are considered to be promising tactics to the cancer therapy [11,12].

Angiogenesis

Prostate cancer cells express vascular endothelial growth factor (VEGF) as well as tumor-associated stromal cells. VEGF when bound to receptor stimulates angiogenesis. The humanized monoclonal antibody (bevacizumab) that recognizes all VEGF for prevents binding VEGF to the receptor and can reduce micro vessel density. Also in the phase II clinical studies, it was demonstrated that the combination of bevacizumab and chemotherapy has anti-cancer activity. Similar approach was investigated in clinical trials withtyrosine kinase inhibitors, platelet-derived growth factor (PDGF)-targeted therapy and thalidomide. Yet, there is no solid and meaningful clinical evidence of use of angiogenesis inhibitors for the treatment of prostate cancer patients. Nevertheless, enthusiasm for therapies targeting angiogenesis in prostate cancer stimulated further research and provided encouraging data from the phase II clinical trials, especially these combining bevacizumab and thalidomide with docetaxel (anti-mitotic chemotherapy medication) [13].

However there are no clinical studies on proteases inhibitors, despite of strong evidence of inhibition of angiogenesis and resulted from that reduction of tumor size. The urokinase is commonly overexpressed by prostate cancer cells. The human carcinoma cells expressing uPA are invading the chorioallantoic membrane and metastasize from it to the embryo, but while treated with the antibody against the active site of uPA, invasion and metastasis was drastically reduced [14]. Cells transfected with a plasmid to over-express uPA in prostate cancer cells showed a marked increase in metastasis in comparison with the parental cell phenotype in the rat model and the cells under-expressing uPA displayed drastically decreased metastasis [15]. The tip of neovascular advancing capillary vessels surrounding tumors has been reported to have high amounts of uPA and its receptor [8]. It has been shown that proteolytically inactive uPA bound to receptor prevents cell surface plasminogen activation, and consequently successfully blocks angiogenesis in the mouse model [16]. Also, inactivation of uPA by small molecular inhibitors as well as by its protein inactivator (PAI-1) reduces angiogenesis and drastically shrinks tumor size in animals (Figure 1) [17-20]. In some cases complete remission of tumor was observed in animals bearing human prostate cancer cells [17]. PAI-1 is converting itself quickly to latent, inactive form (t½=2 h). Thus considerable effort has been made to extend it. Numerous human PAI-1 mutants where produced in search to extend their half-life. The most stable with $t_{1/2}$ prolong to more than 700 h opens possibility of its therapeutic use as an anti-angiogenic agents [21-23].

Also, strong experimental evidence and some clinical observations

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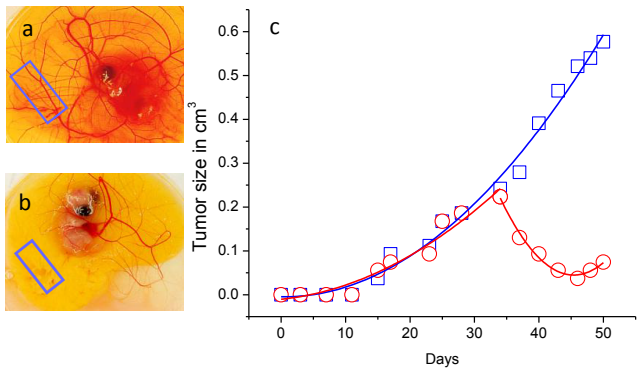

Figure 1: Photographs of 9-day old embryo **a**: control, saline only; **b**: treated by 14-1b PAI-1, 100 μM/embryo, blue rectangle indicates approximate position of dialyzing bag on embryo; **c**: tumor size of the prostate LNCaP xenografts in SCID mouse as a function of time: blue open squares - control group, red open circles – animals treated with 10 nM of PAI-1. PAI-1 was delivered by osmotic pump from day 32 till 46. Tumors sizes are presented as an average of 7 animals in each group (20).

show that elevated levels of MMPs are associated with prostate cancer progression, metastasis angiogenesis and shortened survival in patients [24-26]. It is interesting that inhibition either of urokinase activated plasmin formation or MMPs results in suppression of angiogenesis, invasion, cancer growth and metastasis. Therefore one may conclude that reduction of net proteolytic activity below threshold is sufficient to achieve anti-cancer activity. As it has become clearer that angiogenesis inhibition can be a clinically valuable tool, targeting the uPA/plasmin and MMPs could provide synergy or additive effects in therapy of prostate cancer.

Summary

Reducing angiogenesis by uPA/plasmin and MMPs inhibitors has additional benefits targeting multiple functions of cancer such invasiveness and metastasis even in advanced stages of this disease. There is enough evidence to bring this to the attention of clinicians and encourage them to utilize inhibition of proteolysis in the prostate cancer as useful approach in clinical practice.

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