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RESEARCH HIGHLIGHT

Reciprocal interactions between tumor and endothelial cells: effects of selective vasopressin V2 receptor peptide agonists

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Recent experimental evidence suggested that the synthetic peptide desmopressin (DDAVP) interferes tumor angiogenesis by inducing the formation of angiostatin. It is also known that DDAVP stimulates the endothelial release of von Willebrand factor, a key element in resistance to metastasis. Vasopressin V2 receptor agonists such as DDAVP seem to evoke dual angiostatic and antimetastatic effects, breaking cooperative interactions of tumor and endothelial cells during tumor progression.

Keywords: tumor vascularization; desmopressin; von Willebrand factor; angiostatin; peptide analog

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Introduction

Understanding cancer progression is only feasible in the context of detailed insights into the interactions of cancer cells with the tumor milieu. Such interactions are determined by structural and biochemical properties of the extracelullar matrix as well as by communication with non-neoplastic cells present in the tumor microenvironment such as cancer-associated fibroblasts, mesenchymal stem cells, lymphocytes, tumor-associated macrophages and endothelial cells[1]. During angiogenesis, endothelial cell proliferation and migration are induced which ultimately leads to formation of new blood vessels from the pre-existing vasculature [2]. Physiologically, this process takes place during embryogenesis, the female reproductive cycle, and wound healing.

In tumor angiogenesis, the ‘‘angiogenic switch’’ is turned on, causing the normally quiescent vasculature to constantly sprout new vessels, thus promoting tumor growth [3]. A large number of endogenous molecules are involved in the regulation of the angiogenic process several of these have been studied for potential therapeutic applications [4]. Therefore, the angiogenic switch can be represented as a balance, which tips toward neovascularization when angiogenesis-stimulating factors exceed angiogenesis-inhibiting factors. Angiogenesis stimulators include vascular endothelial growth factors (VEGF), epidermal growth factors, fibroblast growth factors, platelet-derived growth factors, and their associated tyrosine kinase receptors, and matrix metalloproteinases. Anti-angiogenic regulators include angiostatin, endostatin, tumstatin and thrombospondin-1. Angiostatin is an internal fragment of plasminogen containing at least three of its kringles and it is produced in the tumor stroma [5]. Components of the plasminogen-activator system, including the serine proteases urokinase -type (uPA) and tissue-type (tPA), are involved in the proteolytic conversion of plasminogen to angiostatin in vitro, although the in vivo processes are not fully understood [6,7]. Complete inhibition of angiostatin formation by cell lines secreting uPA and/or tPA was

observed with specific serine protease inhibitors [6]. Angiostatin inhibited endothelial cell migration and tube formation in vitro and was shown to be inversely correlated with VEGF [8]. Using in vivo preclinical models of lung cancer it was also shown that exogenous administration of angiostatin potently blocked neovascularization and growth of metastases [9]. Despite showing clinical potential, one major disadvantage of angiostatin is its short half-life (15 minutes), leading to a need for continuous administration [10, 11].

As previously mentioned, subtle changes in the relative balance of pro- and anti-angiogenic factors can activate the angiogenic switch. The switch begins with perivascular detachment and vessel dilation, followed by angiogenic sprouting, new vessel formation and maturation, and the recruitment of perivascular cells. Angiogenesis will continue as long as the tumor grows, and the blood vessels specifically feed hypoxic and necrotic areas of the tumor to provide it with essential nutrients and oxygen [12]. Tumor vasculature is structurally and functionally abnormal characterized by increased vessel permeability, dilatation and tortuosity, reduced pericyte coverage, and abnormal basement membranes [13, 14]. Leakiness of tumor blood vessels has been indicted as contributing directly to tumor growth and metastasis by increasing tumor interstitial pressure that facilitates efflux of cancer cells and by creating foci of hypoxia and acidosis [15,16]. In addition, hypoxia upregulates the production of angiogenic factors by cancer and stromal cells, which further aggravate vessel disorganization and thereby fuel non-productive angiogenesis in an endless self-reinforcing loop. Abnormal tumor vessels can also impede the function of immune cells in tumors, as well as the transport and/or distribution of chemotherapeutics [17].

The concept of reciprocal interactions between tumor and endothelial cells can be found in the earliest work on tumor-induced angiogenesis [18]. It has been postulated that the complex interplay between tumors and their vasculature depends on more than perfusion alone and that tumor-endothelial cell crosstalk and paracrine modes of regulation must be considered [19]. It seems that a deeper comprehension of these interactions will promote the design and development of novel mechanistically-acting drugs.

Recently, we reported for the first time that the synthetic peptide desmopressin (1-deamino-8-D-arginine vasopressin, DDAVP) is able to reduce tumor angiogenesis by inducing the formation of angiostatin. The compound stimulates the secretion of uPA by cancer cells, thus excising angiostatin from plasminogen by controlled proteolysis [20]. DDAVP is an analog of the antidiuretic hormone vasopressin, firstly described in 1967 [21]. In contrast to vasopressin, which binds to the different vasopressin receptors, DDAVP is a selective agonist for the V2 cell membrane receptor [22]. This vasopressin receptor subtype is expressed in the kidney collecting duct, mediating the antidiuretic action, and is also present in endothelial cells, mediating most of the non-renal effects of DDAVP, including a potent hemostatic effect [23]. The presence of vasopressin receptors was documented in various human cancer cell lines [24], including breast, colorectal and small cell lung cancer, among others. DDAVP exhibited modest cytostatic effects on receptor-expressing cancer cells [25]. Such action was clearly mediated through agonist V2 receptor signaling, and thus involved activation of adenylate cyclase followed by intracellular cAMP elevation and protein kinase A (PKA) activation.

DDAVP has been used as a treatment of choice in von Willebrand disease, at least for minor bleedings and for surgical prophylaxis [26]. The compound induces a rapid increase in circulating von Willebrand factor (VWF) by stimulating its release from Weibel-Palade bodies mainly from microvascular endothelial cells, through a specific agonistic action on V2 vasopressin receptors. Interestingly, recent studies have implicated VWF as a regulator of metastasis, playing a protective role against tumor cell dissemination in vivo [27]. It appears that VWF can induce the death of metastatic cells early after their arrest in the microvasculature of the target organ. More recently, it was found that aggressive human breast and lung cancer cells with high levels of ADAM28 (a disintegrin and metalloproteinase 28) are able to avoid VWF-induced apoptosis at micrometastatic sites. ADAM28 binds and degrades VWF, thus favoring the survival of metastatic cells in the tissue microenvironment [28]. This novel experimental evidence accounts for the crucial role of VWF in resistance to metastasis.

Previously, we reported that administration of DDAVP can inhibit the formation of blood-borne metastasis in an experimental animal model. At clinically relevant doses, DDAVP inhibited lymph node and lung metastasis from aggressive mammary tumors [29, 30]. Considering the hemostatic and antimetastatic properties of DDAVP, we designed a pilot veterinary clinical trial in dogs with locally-advanced mammary cancer, administering the peptide at high doses by intravenous infusion, before and after excision of the primary tumor. Perioperative DDAVP was well tolerated using this short-term treatment approach, and significantly prolonged disease-free and overall survival [31]. An extended veterinary trial recently confirmed these observations, showing a reduced incidence of local relapses and lung metastasis in treated

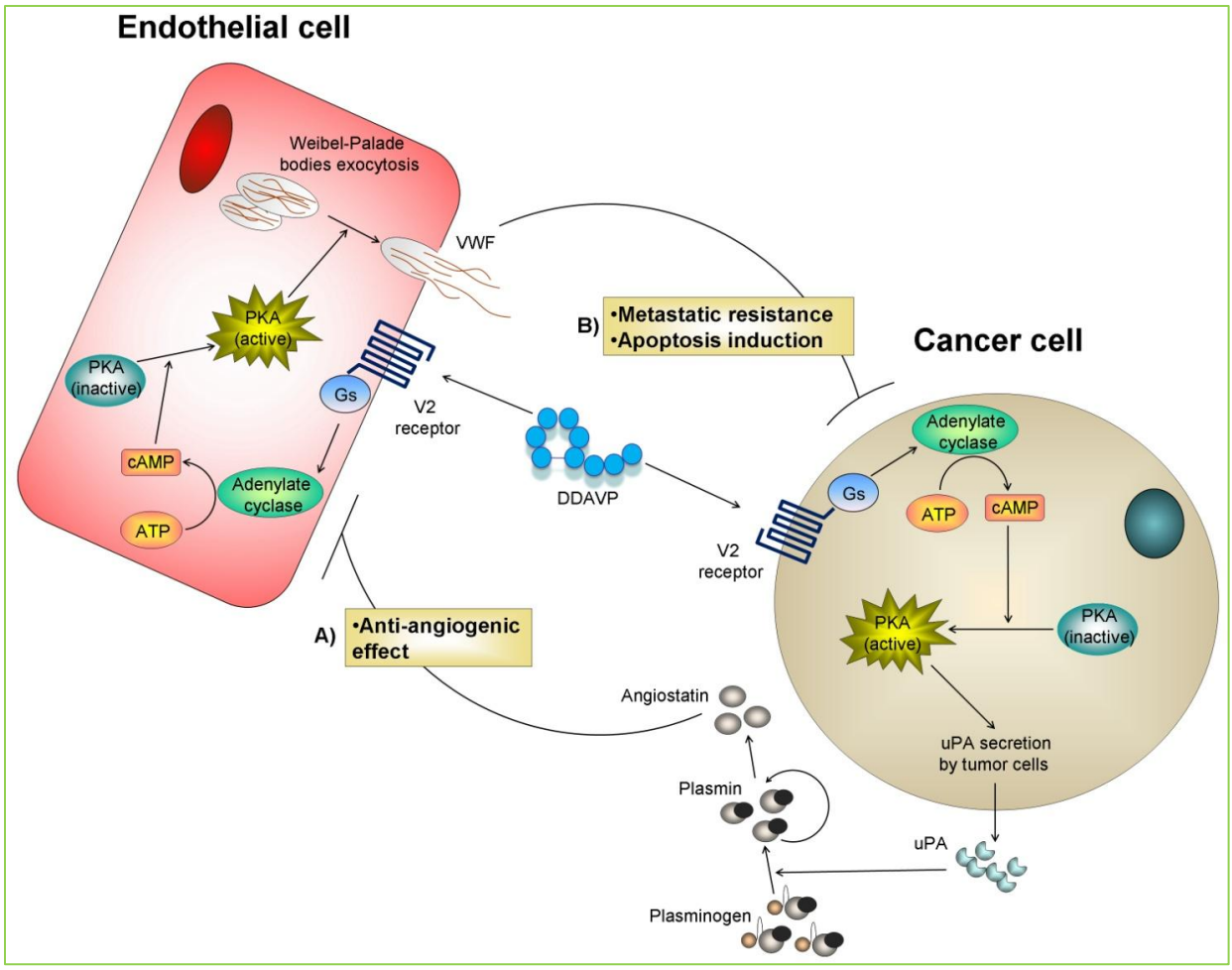

Figure 1. Hypothetical model for the effects of DDAVP on reciprocal interactions between tumor and endothelial cells. DDAVP triggers V2 receptor agonist signaling in both tumor and endothelial cells, causing adenylate cyclase activation followed by cAMP-dependent PKA activation. A) DDAVP stimulates tumor-mediated production of angiostatin, a strong angiogenesis inhibitor. The compound induces secretion of soluble uPA, favoring angiostatin generation by the proteolityc cleavage of plasminogen. B) Simultaneously, DDAVP activates endothelial release of VWF by exocytosis of Weibel-Palade bodies. VWF plays a protective role against tumor cell dissemination and may cause apoptosis of micrometastatic foci.

animals having high-grade carcinoma [32]. The perioperative period is therefore an attractive window of opportunity to modulate tumor-host interactions in order to reduce the risk of metastatic disease [33].

The biological effects of perioperative administration of DDAVP on both endothelial and V2 receptor-expressing cancer cells are complex, and required further investigations. Nonetheless, the peptide seems to induce a dual, reciprocal angiostatic and antimetastatic effect, breaking the cooperative function of cancer cells and endothelial cells during tumor progression. As schematized in Figure 1, DDAVP induces a tumor-mediated production of angiostatin, a potent anti-angiogenic effector [20]. At the same time, the compound also activates endothelial release of VWF [23], which in turn obstructs biological mechanisms of cancer spread and may cause apoptosis of micrometastatic cells arrested in the target organ [27].

Peptides such as DDAVP have a great potential as therapeutic agents due to their ease of rational design and target specificity. We have developed a panel of novel vasopressin V2 receptor agonists, derivatized from DDAVP. The synthetic peptide 1-deamino-4-valine-5-glutamine-8-D-arginine vasopressin (designnated [V4Q5] DDAVP) exhibited a significantly higher antitumor activity than the parental compound [34]. Further studies with DDAVP and its analog are warranted to determine their potential in cancer therapy through modulation of tumor-endothelial cell interactions.

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