Science is much more than a body of knowledge. It is a way of thinking. This is central to its success. Science invites us to let the facts in, even when they don’t conform to our preconceptions.”

Carl Sagan
10. APPENDIX

10. 1 List of Publications


10.2 List of conferences attended

1. Participated in 2\textsuperscript{nd} International Symposium on Translational Research: Natural products and cancer held in Lonavala from 9-12 December 2007.

2. Participated in 78\textsuperscript{th} Annual Conference of Society of Biological chemists-(India) held in Pune from October 30th-November 1, 2009.

3. Participated in 3\textsuperscript{rd} International Symposium on Translational Research: Cell signaling and cancer therapy held in Bhubaneswar from December 18-21, 2009.
Curcumin suppresses breast tumor angiogenesis by abrogating osteopontin-induced VEGF expression

GOUTAM CHAKRABORTY, SHALINI JAIN, SMITA KALE, REMYA RAJA, SANTOSH KUMAR, ROSALIN MISHRA and GOPAL C. KUNDU

National Center for Cell Science, Pune, India

Received April 9, 2008; Accepted June 2, 2008

DOI: 10.3892/mmr_00000005

Abstract. The development and progression of malignant tumors depends on the formation of new blood vessels inside the tumor. This phenomenon is termed tumor angiogenesis. Angiogenesis is one of the fundamental processes that occur during cancer progression, and depends on the expression and activation of various angiogenic molecules, cytokines, growth factors, kinases and transcription factors. We recently demonstrated that the chemokine-like ECM-associated protein osteopontin (OPN) turns on the angiogenic switch by upregulating expression of vascular endothelial growth factor (VEGF) in a human breast cancer model. Furthermore, we proposed that targeting OPN-induced VEGF expression could be a potential therapeutic approach for the treatment of breast cancer. In this study, we demonstrate that curcumin (diferuloylmethane) abrogates OPN-induced VEGF expression and curbs OPN-induced VEGF-dependent breast tumor angiogenesis in vivo. We also explore the fact that curcumin in combination with anti-VEGF or anti-neuropilin (NRP)-1 antibody exhibits enhanced anti-angiogenic activity compared to curcumin alone. Our results indicate that curcumin suppresses OPN-induced VEGF expression and tumor angiogenesis, and suggest that this study may aid in the development of a curcumin-based OPN-targeted therapeutic approach to the control of breast tumor angiogenesis.

Introduction

Breast cancer is considered to be one of the most common cancer threats worldwide. According to the World Health Organization (WHO), it is the most deadly cancer in females, with more than 500,000 deaths attributed to it globally each year. To date, the major cause of breast cancer is not clearly understood. However, experimental evidence has revealed that the expression profiles of certain oncogenic molecules or biomarkers are significantly associated with breast cancer progression, and have shown great promise in breast cancer therapy (1,2). Osteopontin (OPN), a chemokine-like ECM-associated small integrin binding ligand N-linked glycoprotein (SIBLEING), has recently been identified as one of the major markers of breast cancer progression (3,4). Elevated expression of OPN at tumor sites as well as in the serum of breast cancer patients has signalled the prognostic importance of this protein in breast cancer (5,6). Moreover, the targeting of OPN and its downstream signaling pathways has shown great promise in the therapeutics of various cancers, breast cancer included (7). The role of OPN in breast cancer progression is therefore being intensely investigated.

Angiogenesis, or the formation of new blood vessels from existing ones, is a key step in tumor growth, survival, progression and metastasis (8). Tumor angiogenesis is thought to result from the secretion of "angiogenetic factors" by tumor cells. These include growth factors, cytokines and a number of small molecules (9,10). Of these, vascular endothelial growth factor (VEGF) has been recognized as the most important (11). Highly malignant tumors are characterized by enhanced vascularization, which is further correlated with elevated VEGF expression (12). Previous reports suggest that tumor-derived VEGF interacts with tumor or endothelial cell surface receptors via autocrine or paracrine mechanisms and promotes tumor angiogenesis (13-15). We recently demonstrated that OPN augments VEGF expression and promotes VEGF-dependent breast tumor angiogenesis (16). Therefore, we can hypothesize that targeting OPN-induced VEGF might serve as a potential therapeutic approach for the treatment of breast cancer.

Curcumin (diferuloylmethane) is a polyphenol derived from the rhizomes of Curcuma Longa, traditionally used as an anti-inflammatory compound, and appears to be useful in the prevention and treatment of various cancers (17-19). Curcumin has exhibited a significant inhibitory effect on several malignant cancers, including breast cancer (20). It has also been reported that curcumin downregulates the activation of NF-κB and suppresses tumor growth in various cancer models (21-23). We have previously reported that curcumin suppressed OPN-induced MMP-2 activation and tumor growth in a murine melanoma model (24). However, the role of curcumin in the regulation of OPN-induced VEGF-dependent breast tumor angiogenesis is not well defined. In this study, we demonstrate that curcumin abrogates OPN-induced VEGF expression and suppresses VEGF-dependent breast tumor angiogenesis.

Correspondence to: Dr Gopal C. Kundu, National Center for Cell Science, Pune 411 007, India
E-mail: kundu@ncsc.res.in

Key words: osteopontin, vascular endothelial growth factor, curcumin, human breast cancer, tumor angiogenesis
Quercetin and sulforaphane in combination suppress the progression of melanoma through the down-regulation of matrix metalloproteinase-9

SAURABH J. PRADHAN, ROSALIN MISHRA, PRIYANKA SHARMA and GOPAL C. KUNDU

National Center for Cell Science, Pune 411 007, India

Received June 26, 2010; Accepted August 16, 2010

DOI: 10.3892/etm.2010.144

Abstract. Malignant melanoma is one of the most common types of cancer in the US and worldwide. The epidemiological data suggest that dietary modification may reduce the incidence of this disease. Quercetin (3,5,7,3',4'-tetrahydroxyflavone), a flavonoid isolated from onion, exhibits anti-oxidant, anti-inflammatory and anti-cancer effects. D.L-sulforaphane [1-isothiocyanato-4-(methylsulfinyl)-butane], a cruciferous vegetable-derived isomer isolated from broccoli, is highly effective in protection against cancer. Matrix metalloproteinases (MMPs), extracellular matrix degrading enzymes, are involved in embryogenesis, inflammation, angiogenesis and cancer. MMP-9 in particular plays a crucial role in the regulation of invasion, tumor growth and metastasis. Previous studies have reported that both quercetin and sulforaphane independently reduce tumor growth and metastasis in breast, prostate, lung and other types of cancers. However, the combined effects of quercetin and sulforaphane on the regulation of tumor growth and the mechanism(s) of actions underlying this process have not yet been investigated. In the present study, we report for the first time that quercetin and sulforaphane in combination inhibit the proliferation and migration of melanoma (B16F10) cells more effectively than either compound used alone. Moreover, these compounds in combination significantly suppressed melanoma growth as compared to their individual use in a mouse model. This combined effect was predominantly due to a decrease in MMP-9 expression in the mouse tumors. Taken together, our findings revealed that the administration of quercetin and sulforaphane in combination rather than alone may be a more effective approach for the treatment of malignant melanoma.

Introduction

Malignant melanoma is one of the most common types of cancer in the US as well as worldwide. It is an aggressive disease with high metastatic potential and resistance to many cytotoxic agents (1). Melanoma cells have low levels of spontaneous apoptosis, and chemotherapeutic drugs function by inducing apoptosis (1). Many dietary agents, including kinase inhibitors, have been inversely correlated to the spread of malignant melanoma (2-4). The alkylating agent dacarbazine is currently being used in clinical trials in combination with novel therapeutic agents (4). Quercetin (3,5,7,3',4'-tetrahydroxyflavone) is a flavonoid isolated from onion, whereas sulforaphane [1-isothiocyanato-4-(methylsulfinyl)-butane] is a member of an isothiocyanate family of chemopreventive agents isolated from broccoli. The anti-cancer properties of these compounds have been demonstrated in a number of malignancies, including prostate, breast, skin and liver cancers (5-9). Previous reports suggest that quercetin is an anti-oxidant and anti-inflammatory compound (10,11). Others have indicated that sulforaphane acts as a potential HDAC inhibitor and an inducer of various pro-apoptotic molecules (12-14). Sulforaphane was also found to inhibit prostate tumor growth and lung metastasis in a melanoma model (15,16).

Matrix metalloproteinases (MMPs) are extracellular matrix proteins known to play a crucial role in normal physiological processes, such as embryogenesis, wound healing, morphogenesis, reproduction, tissue resorption and remodeling, and in pathological processes, such as inflammation, arthritis, cancer, cardiovascular and pulmonary diseases; hence, they are considered therapeutic targets (17,18). Certain MMPs act as tumor suppressors, whereas others act as tumor promoters. MMP-9 is expressed mostly by stromal cells in a tumor environment, although cancer cells do express MMP-9 at low levels (19,20). MMP-9 efficiently degrades native type IV and V collagens, fibronectin, ectactin and elastin. The regulation of MMP-9 activation is more complex than that of other MMPs, as most cells in general do not express the constitutively active form of MMP-9. Rather, its activity is...
Osteopontin: a potentially important therapeutic target in cancer


Introduction: Cancer is an extremely complex disease and most cancer treatments are limited to chemotherapy, radiation and surgery. The progression of tumours towards malignancy requires the interaction of various cytokines, growth factors, transcription factors and effector molecules. Osteopontin is a cytokine-like, calcium-binding, extracellular matrix-associated member of the small integrin-binding ligand, N-linked glycoprotein (SIBLING) family of proteins. It plays an important role in determining the oncogenic potential of various cancers. The role of osteopontin in various pathophysiological conditions suggests that the alteration in post-translational modification result in different functional forms that might change its normal physiological functions.

Areas covered: Osteopontin-based anticancer therapy, which may provide a new insight for the effective management of cancer.

Expert opinion: A better understanding of the signalling mechanism by which osteopontin promotes tumorigenesis may be useful in crafting novel osteopontin-based anticancer therapy. The role of osteopontin in promoting cancer progression is the subject of in depth investigation and thus targeting osteopontin might be a suitable therapeutic approach for the treatment of cancer.

Keywords: angiogenesis, metastasis, osteopontin, prognostic marker, targeted therapy, tumour-stroma interaction

Expert Opin. Ther. Targets (2011) 15(9):1113-1126

1. Introduction

Cancer is a multistage genetic and epigenetic disease in which a group of normal cells transform into highly malignant cells that are self sufficient in growth signals, insensitive to antigrowth signals, overcome replicative senescence, evade apoptosis, induce angiogenesis and activate invasion and metastasis [1]. The progress in research during recent decades has added two more emerging hallmarks, reprogramming of energy metabolism and evading immune destruction during the process of cancer progression [2]. Tumour progression is a complex process with a finely tuned interaction between tumour and its microenvironment composed of multiple distinct cell types that secrete a wide array of molecules, which act through autocrine and paracrine mechanisms.

Osteopontin is an extracellular matrix (ECM)-associated, cytokine-like, non-collagenous, sialic acid rich phosphoglycoprotein [3-5]. Osteopontin regulates normal physiological processes, including bone resorption, wound healing, tissue remodeling, immunological responses and vascularization, and various
Semaphorin 3A Suppresses Tumor Growth and Metastasis in Mice Melanoma Model

Goutam Chakraborty1*, Santosh Kumar1*, Rosalin Mishra1*, Tushar V. Patil2, Gopal C. Kundu1*

1 National Center for Cell Science (NCCS), NCCS Complex, Pune, India, 2 Department of Histopathology, YCM Hospital, Pune, India

Abstract

Background: Recent understanding on cancer therapy indicated that targeting metastatic signature or angiogenic switch could be a promising and rational approach to combat cancer. Advancement in cancer research has demonstrated the potential role of various tumor suppressor proteins in inhibition of cancer progression. Current studies have shown that axonal sprouting inhibitor, semaphorin 3A (Sema 3A) acts as a potent suppressor of tumor angiogenesis in various cancer models. However, the function of Sema 3A in regulation of melanoma progression is not well studied, and yet to be the subject of intense investigation.

Methodology/Principal Findings: In this study, using multiple in vitro and in vivo approaches we have demonstrated that Sema 3A acts as a potent tumor suppressor in vitro and in vivo mice (C57BL/6) models. Mouse melanoma (B16F10) cells overexpressed with Sema 3A resulted in significant inhibition of cell motility, invasiveness and proliferation as well as suppression of in vivo tumor growth, angiogenesis and metastasis in mice models. Moreover, we have observed that Sema 3A overexpressed melanoma clone showed increased sensitivity towards curcumin and Dacarbazine, anti-cancer agents.

Conclusions: Our results demonstrate, at least in part, the functional approach underlying Sema 3A mediated inhibition of tumorigenesis and angiogenesis and a clear understanding of such a process may facilitate the development of novel therapeutic strategy for the treatment of cancer.

Introduction

Melanoma or malignancies of melanocytic tissues have been identified as one of the most malignant cancer in the United States and around the world. In the year 2010, more than 68,130 new cases of melanoma have been reported in the United States with a result of 8,700 deaths [1]. Malignant progression of cancer cells depends on intrinsic crosstalk between several factors, overexpression of various oncogenic molecules and loss of function of tumor suppressor genes. Therefore, understanding the mechanisms of various tumor suppressor genes in regulation of cancer progression and their possible role in cancer therapeutics is under intense investigation. Semaphorins have been originally known as a large family of evolutionary conserved axonal guidance molecules [2,3]. The role of semaphorins in various physiological as well as pathophysiological processes including cell migration, regulation of immune response, angiogenesis and cancer have recently been studied [4]. Among various semaphorins, selected members of semaphorin 3 (Sema 3) family are involved in suppression of tumor progression and have been considered as potent tumor suppressors [5]. Loss of expressions of Sema 3B and Sema 3F gene (deletion of chromosome 3p21.3 in human) have been shown to associate with lung cancer progression [6–8]. On the other hand, overexpression of these molecules inhibits tumor cell proliferation and in vivo tumor growth [9–12]. Moreover, Semaphorin 3A (Sema 3A), another member of this family is shown to inhibit angiogenesis and acts as tumor suppressor [13–16].

Sema 3A is originally described as a secretory protein with potent axonal repulsive activity [17,18]. Polleux et al have identified the chemoattractive effect of Sema 3A on cortical apical dendrites [19] and shown that Sema 3A acts as a crucial regulatory molecule for neuronal development. However, Serini et al have observed a significant vascular defect in Sema 3A null mice [16]. In this study, we have deciphered the function of Sema 3A beyond brain, and demonstrated that this protein could play an important role in melanoma growth. Knockdown of endogenous Sema 3A significantly induce in vitro migration of human breast cancer cell and indicated that Sema 3A may act as a potent tumor suppressor [20]. Overexpression of Sema 3A attenuates invasion and matrigel adhesion of human prostatic cancer cells [21]. Moreover, loss of Sema 3A inhibitory loop in hormone-refractory human prostatic cancer has been recently identified by tissue microarray analysis.