

MATRIX GLA PROTEIN IN TUMORAL PATHOLOGY

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Abstract

Matrix Gla protein is a vitamin K-dependent protein secreted by chondrocytes and vascular smooth muscle cells. The presence of matrix Gla protein was reported in arterial and venous walls, lungs, kidney, uterus, heart, tooth cementum and eyes. Several studies identified matrix Gla protein in tumoral pathology.

Until recently, it was thought to only have an inhibitory role of physiological and ectopic calcification. New studies demonstrated that it also has a role in physiological and pathological angiogenesis, as well as in tumorigenesis.

The aim of this review is to report the latest findings related to the expression and clinical implications of matrix Gla protein in different types of cancer with an emphasis on cerebral tumors.

Keywords: matrix gla protein, ectopic calcification, angiogenesis, tumorigenesis

Introduction

Matrix Gla protein (MGP), belongs to the vitamin K dependent protein family, which is comprised of both hepatic and extrahepatic proteins. Hepatic proteins are mainly implicated in blood coagulation [1], while, those synthesized outside the liver, have very different functions. The generic attribute, through which they exercise their activity, is the high affinity of their γ -carboxyglutamic acid (Gla) residues for calcium ions. These residues are the result of γ -carboxylation of glutamic acid, a reaction catalyzed by γ -glutamyl carboxylase, in which vitamin K acts as a cofactor [2]. Considering that γ -glutamyl carboxylase is extensively found in the human body, several studies were conducted in order to identify Gla containing proteins.

After the identification of Gla residues in prothrombin and their fundamental role in blood coagulation [3], the focus was turned to the bone. As a result, osteocalcin was purified and found to balance the calcification of bone matrix [4] and MGP was the second Gla containing protein identified in this tissue [5]. Later, MGP was found to be synthesized and secreted in the extracellular matrix by chondrocytes [6] and vascular smooth muscle cells [7].

MGP: structure, localization and role

MGP is an insoluble [5], small protein, with a molecular weight of only 14.7 kD, secreted and localized in the extracellular matrix of chondrocytes or endothelial cells. After the first isolation of MGP from bovine bone [5], a follow up study [8] identified that the mature protein contains 84 amino acid residues and 5 Gla residues. A phosphorylation domain, in the N-terminal end of the signal peptide, contains 3 phosphorylated serine residues. A single, disulfide bond is observed between two conserved cysteines, a characteristic also found in osteocalcin [9]. The N-terminal end also includes the target site for γ -glutamyl carboxylase.

After bone and cartilage, further studies identified MGP in the arterial wall [10], heart, lungs, kidney [11] and uterus [12]. Recently, MGP was found to be expressed in the venous wall [13], tooth cementum [14] and even in trabecular meshwork cells of the eyes [15].

Initially, it was thought that MGP had to undergo reactions of phosphorylation and γ -carboxylation for the sole purpose of binding calcium ions and inhibiting calcification [16]. Later studies showed that MGP has a more vast activity dependent of the phosphorylation-carboxylation status, protein expression and variants. The inactive form of MGP is considered to be a marker of vitamin K status in bone and vasculature [17].

One of the first studies to suggest the role of MGP in preventing ectopic calcification of the cartilage described growth plate mineralization in infants whose mothers were treated with vitamin K antagonist anticoagulants during their pregnancy [6]. The researchers hypothesized that these anticoagulants may cause the inhibition of MGP, consequently leading to the development of foci of mineralization [6]. Later, the calcification inhibitory role of MGP was clearly demonstrated in a study of MGP-deficient mice, resulting in their death by artery wall calcification and consequent rupture of the vessel [18].

In addition, it was demonstrated that MGP has a role in physiological angiogenesis by increasing vascular endothelial growth factor gene expression [19], and more recently in tumor angiogenesis, reporting a direct relationship between MGP expression and tumor vascularization [20]. Although, MGP expression was reported in a variety of cancers, the exact role of this protein in cell differentiation and tumorigenesis is yet to be elucidated.

MGP in tumoral pathology

As stated before, one of the various activities of MGP involves cell differentiation and tumoral development.

The first study to support these implications was published in 1990, when scientists found that breast cancer cells overexpress the MGP gene and raised the possibility that metastasis may be reduced by administering vitamin K antagonists [21]. The same research team later published an article also reporting high MGP expression in primary renal, testicular and prostatic carcinomas, suggesting that it may be associated with tumor progression and metastasis [22].

After these findings, the interest regarding MGP in tumoral pathology has stopped until almost ten years after when, an American research team published a paper in which they reported a ten-fold expression of MGP in ovarian cancer, regardless of the tumor subtype, and suggested it could be a novel marker for diagnosis and treatment for epithelial ovarian cancer [23]. An upregulation of MGP was also exhibited in the precancerous cervical lesions that have a high potential of progression to invasive carcinoma [24].

A group of Chinese researchers identified an overexpression of MGP in gastric cancer specimens, with close relationship to the tumor development and prognosis [25].

Seemingly, the tumoral pathology had been characterized by high levels of MGP, but two studies have shown the contrary. A downregulation of MGP mRNA was found in 79% of colorectal adenocarcinomas compared to normal proximate tissue. Although, no correlation between this loss and tumor progression or differentiation was identified, the low MGP expression could differentiate between normal and malignant colorectal cells [26]. A loss of MGP expression was also described in the progression of lung cancer, in the stage of symptomatic illness [27].

MGP in brain tumors

After summarizing the MGP status in cancers throughout the body, our attention has shifted toward the presence of this protein in brain tumors and calcified foci of the cerebral tissue.

The first data were published in an article concerning bone-related protein mRNA in human meningiomas [28]. They believed that since calcium phosphate deposits in psammoma bodies, bone-related proteins will be expressed in these areas. Northern blotting exhibited an overexpression of MGP mRNA, but this expression did not appear to correlate with the calcification [28].

Later on, another research focused on studying glioblastomas, the most common and malignant brain tumors. According to the World Health Organization, grade II astrocytomas can spontaneously develop in grade III anaplastic astrocytomas or grade IV glioblastomas. The molecular mechanism of this progression is yet to be understood. One study has identified different levels of MGP expression between these three grades [29], reporting significant differences between grade II and grade III astrocytomas, as well as between grade II and grade IV glioblastomas, primary and secondary gliomas, but no difference was found when comparing grade III with grade IV. Further testing showed no gene amplification of MGP in the gliomas, suggesting that other mechanisms are involved [29].

Another study confirmed the overexpression of MGP in glioblastomas and suggested that the upregulation of the protein may lead to a bad prognosis due to increased invasion [30].

Recently, it was hypothesized that MGP may be identified as possible therapeutic targets for glioblastoma multiforme, the most vascularized of brain tumors. The inhibition of MGP resulted in much smaller and less vascularized tumors, indicating the role of MGP in angiogenesis [31].

Conclusions

For many years it was believed that the only role of MGP was that of calcification inhibition. Later, it was demonstrated that it also has a role in physiological and tumoral angiogenesis.

An overexpression of MGP was found in breast cancer, inversely correlated with the prognosis. High levels were also reported in renal, testicular, prostatic, ovarian, and cervical cancers, related to the prognosis and metastasis occurrence. A downregulation of MGP was observed in colorectal and lung cancers.

In the domain of brain tumors, the attention was focused on glioblastomas, in which MGP was found to be overexpressed and correlated with a poor outcome.

Further studies are recommended, as the role of MGP in tumoral pathology is yet to be elucidated.

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