Zinc and metalloproteinases 2 and 9: What is their relation with breast cancer?

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Summary

Zinc is the catalytic component of proteins that regulate responses to DNA damage, intracellular signaling enzymes, and matrix metalloproteinases, which are important proteins in carcinogenesis. The objective of this review is to bring current information on the participation of zinc and matrix metalloproteinases types 2 and 9 in mechanisms involved in the pathogenesis of breast cancer. We conducted a literature review, in consultation with the PubMed, Lilacs, and Scielo databases. The zinc and cysteine residues are structural elements shared by all members of the family of matrix metalloproteinases, and these proteins appear to be involved in the propagation of various types of neoplasms, including breast cancer. Moreover, transported zinc is likely to be used for the metalation of the catalytic domain of the newly synthesized metalloproteinases before the latter are secreted. Accordingly, increase in zinc concentrations in cellular compartments and the reduction of this trace element in the blood of patients with breast cancer appear to alter the activity of metalloproteinases 2 and 9, contributing to the occurrence of malignancy. Thus, it is necessary to carry out further studies with a view to clarify the role of zinc and metalloproteinases 2 and 9 in the pathogenesis of breast cancer.

Keywords: zinc, matrix metalloproteinases, breast neoplasms.

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Introduction

Breast cancer is a multifactorial disease, mainly determined by the occurrence of mutations or abnormal activation of genes that control cell growth and proliferation.[1] The mechanisms involved in the genesis of the disease are not yet fully understood. However, it is known that there is an interaction between genetic and environmental factors, and certain nutrients have important roles in the inhibition of cancer or in its development.[2]

Studies have demonstrated the role of micronutrients in anticarcinogenic mechanisms.[3] Zinc, in particular, has been a nutrient of great interest, given that it is a catalytic component in more than 300 enzymes, including those involved in antioxidant defense, for example, metallothionein and Cu/Zn superoxide dismutase.[4]

Zinc also acts as a transcription factor of enzymes involved in the synthesis of DNA and RNA and as a cofactor of proteins that control responses to DNA damage, intracellular signaling enzymes, and matrix metalloproteinases (MMPs), which are proteins involved in the pathogenesis of breast cancer.[5] As such, changes in zinc concentrations may play a significant role in cell dysfunction and proliferation, including the development and progression of this disease.[2]

Gelatinase class MMPs, such as type 2 (MMP-2) and 9 (MMP-9) metalloproteinases, have the ability to degrade collagen IV that makes up the basal lamina, and are probably relevant in the acquisition of the invasive phenotype of malignant neoplasms.[6]

Considering the changes in zinc metabolism in patients with breast cancer and the important relation be-

tween this mineral and MMPs in the progression of this disease, this review intends to provide up-to-date information about the role of zinc and matrix metalloproteinases 2 and 9 in mechanisms involved in the pathogenesis of breast cancer.

Method

A bibliographic search was conducted on the PubMed, Scielo, and Lilacs databases, without any limit on the year of publication, considering the following inclusion criteria: studies that examined the relation between zinc concentrations and the expression of MMPs in patients with breast cancer. The articles were selected in relation to their originality and relevance, considering the rigor and adequacy of the experimental design and the sample number.

The search for bibliographic references was carried out using the following keywords: "zinc," "matrix metalloproteinases," and "breast neoplasms." The bibliographic search covered the following types of studies: randomized or quasi-randomized controlled clinical trials, in vitro studies, case-control studies and review articles.

Zinc and metalloproteinases of the extracellular matrix

MMPs are a family of more than 25 species of proteases that rely on zinc for their catalytic action and are essential for normal tissue remodeling. Metalloproteinases are able to degrade most components of the extracellular matrix and basal membrane, for example, collagen, elastin, and fibronectin. They can also degrade other proteins that are not characteristic of the extracellular matrix, such as growth factors, cytokines, chemokines, and cell surface receptors.[7]

MMPs are classified into five groups: interstitial collagenases (MMP-1, MMP-8, MMP-13 and MMP-18), which cleave fibrillar collagen types I, II and III; gelatinases (MMP-2 and MMP-9), which degrade amorphous collagen and fibronectin; stromalysins (MMP-3, MMP-10 and MMP-11), which act on a variety of extracellular matrix components, including proteoglycans, laminin, fibronectin, and amorphous collagen; membrane type MMPs (MMP-14, MMP-15, MMP-16, MMP-17, MMP-24 and MMP-25), which are proteases associated with the cell surface; and the matrilysins (MMP-7, MMP-12, MMP-20 and MMP-26), which also degrade laminin, fibronectin, and non-fibrillar collagen.[8]

Two structural elements are shared across all members of the family of MMPs. The first is zinc ion, located at the catalytic site of the protein, and necessary for its action; the second element is propeptide, which contains a cysteine residue. These proteases are secreted in the form of a latent precursor or zymogen, usually called pro-MMP, which is activated in the extracellular space.[9]

The activity of MMPs is regulated in several steps, which include transcription, secretion, and activation through proteolytic cleavage, as well as inhibition via endogenous tissue inhibitors of metalloproteinases (TIMPs). Associated with this, it should be noted that certain proteins can stimulate the expression of MMPs, such as EMMPRIN, a plasma membrane-bound glycoprotein that is involved in inflammation and immune response.[10,11]

Gelatinases, in particular, act on various types of extracellular substrates and are important in many biological processes, with the expression of MMP-2 generally constitutive, while MMP-9 may be induced by tumor necrosis factor α (TNF-α), which includes the activation of nuclear factor kappa β (NF-κβ), mitogen-activated protein kinases (MAPK), phosphatidylinositol-3 kinase, and signaling by protein kinase B.[12,13]

In the remodeling process of the extracellular matrix, macromolecules are secreted and form complex protein networks, some of which are specialized in degrading extracellular proteins, contributing to tissue modifications. The remodeling and tissue regeneration process involves the modulation of enzyme mechanisms, which keep the degradation of extracellular matrix harmonious and balanced in several physiological events. Thus, loss of this modulation is deleterious to the functions and structural stability of the tissues, favoring the emergence of pathological processes.[8]

Extracellular matrix metalloproteinases, zinc, and breast cancer

MMPs seem to be involved in the propagation of various types of neoplasms, including breast cancer. In this regard, studies have verified changes in the expression and increased proteolytic activity of these enzymes in invasive and metastatic tumors.[10] The activity of MMPs in the propagation of the tumor is both direct and indirect. In the first case, it promotes the proliferation of neoplastic cells and metastatic dissemination through the degradation of the extracellular matrix and basal membrane, while indirectly it promotes angiogenesis, providing nutrition and dissemination of the tumor.[14]

The first evidence of the involvement of MMPs in cancer came from studies in animal models. Experiments with tumor cells in mice showed that benign tumor cells acquire malignant properties when there is increased expression of these enzymes. On the other hand, it has been verified that when the expression or activity of MMPs is reduced, the malignant cells become less aggressive.[15]

The first role attributed to MMPs in cancer was the induction of metastasis or, more precisely, the creation of a pathway in the extracellular matrix through which the tumor cells pass to colonize distant tissues.[16] However, it has been verified that these enzymes may also change cell proliferation, adhesion, and migration, not only by degrading the extracellular matrix but also by favoring the release of growth factors and the generation of certain cleavage fragments or functional proteins in this space.[17]

Some MMPs are synthesized by tumor cells, such as MMP-7, while others are produced predominantly by stromal cells, including MMP-2 and 9. Tumor cells can also stimulate the surrounding stromal cells and synthesize these enzymes in a paracrine manner via the secretion of interleukins, interferons, EMMPRIN (extracellular inducer of MMPs), and growth factors.[18] MMP-2 and 9 may also be recruited for the membrane of tumor cells in breast cancer.[19,20]

The literature has shown that there is an association between the expression of MMP-9 and a worse prognosis in breast tumors.[21] The first steps of tumor cell invasion, detachment, and migration are influenced by MMPs. The cleavage of laminin-5 by MMP-2 and MMP-14 reveals its matricryptic site (hidden forms of extracellular matrix molecules that can be exposed by structural modifications), favoring cell motility.[22]

Patel et al.[23] evaluated the expression of MMP-2 and 9 and the plasma concentration of these gelatinases in tissue samples with malignant lesions. The authors suggested that the expression of these MMPs could be a useful diagnostic marker in the detection and monitoring of malignant lesions, given that tissue expression of these enzymes was shown to be high in these lesions and in the plasma. Table 1 shows studies that have assessed metalloproteinases in patients with breast cancer.

Zucker et al.[29] demonstrated that the high expression of MMPs, observed mainly in cancerous processes, is due to changes in gene transcription, with the increase of these enzymes leading to a poor prognosis for various types of cancer.[30,31]

A study conducted by Benson et al.[32] evaluated the expression of MMPs in different types of tissues with breast cancer and normal tissues. The results showed that MMPs are regulated differentially in tissues with breast neoplasm. In addition to the possible use of these enzymes as diagnostic markers, the authors highlight their potential as a pharmacological target because they have different substrate specificities that are regulated during the progression of breast cancer, which are important in tumor invasion, metastasis, and angiogenesis.

MMP-9 plays a vital role in the angiogenesis of tumor as it controls the bioavailability of vascular endothelial growth factor (VEGF), which is a potent inducer of an-

TABLE 1 Studies that have assessed metalloproteinases in patients with breast cancer.

Author(s)	Study design	Results
Jinga et al.[24]	Breast tumor in benign and malignant tumor cells	Higher expression of MMP-9 in malignant tumors Positive relation between MMP-9 and tumor diameter
Daniele et al.[25]	Women with breast cancer, and healthy women Sentinel lymph nodes	High serum concentrations of MMP-2 and MMP-9 in women with breast cancer compared to healthy subjects High concentrations of MMP-2 and MMP-9 in sentinel lymph nodes with macrometastases compared to micrometastases and non-metastatic cases
Somiari et al.[26]	Groups with breast cancer, benign disease and group with high and low risk of developing breast cancer	Concentration and activity of MMP-2 were significantly lower in low-risk patients compared to participants in the other groups. Breast cancer patients had high concentration of total MMP-9 in comparison with those with benign disease
Vasaturo et al.[27]	MMPs-2, 3, and 9 in patients with carcinoma and fibroadenoma	Expression of MMP-2 was significantly higher in patients with carcinoma compared to patients with fibroadenoma Plasma concentrations of MMPs-2 and 9 showed a direct and significant correlation with the histological grade of the tumor
Čupić et al.[28]	Primary and recurrent carcinomas	High expression of MMP-9 in primary carcinomas Increased expression of MMP-9 in recurrent carcinomas after 24 months

MMP: metalloproteinases; MMP-2: metalloproteinase 2; MMP-9: metalloproteinase 9.

giogenesis. MMP-9, together with MMP-2, activates transforming growth factor β (TGF-β) signaling to promote the invasion of the tumor, angiogenesis and metastasis.[32]

The role of MMPs during the neoplastic invasion consists of the rearrangement of the extracellular matrix components in order to better accommodate cell migration. Thus, deregulation of these enzymes plays an important role in several stages of the development of breast cancer and in activities dependent on zinc binding to the catalytic site.[33] It is likely that zinc transported to the cellular compartments is used for metalation of the catalytic domain of the MMPs.[34]

As such, the increased concentrations of zinc in cellular compartments and the reduction of this trace element in the blood of breast cancer patients seems to change the activity of the MMPs, contributing to the occurrence of malignant tumors. Another important function of zinc is related to the angiogenesis process, as this mineral increases the expression of MMPs, especially under conditions of hypoxia.[35]

A study conducted by Holanda[36] verified that low concentrations of zinc in the plasma and erythrocytes are positively related to increased plasma concentrations of metalloproteinase 2 in patients with breast cancer. In addition, a significant difference was observed between plasma concentrations of MMP-2 and MMP-9 in these patients compared to the control group.

Taylor et al.[37] and Kelleher et al.[38] highlight the implications of deregulation of zinc homeostasis in the pathogenesis of breast cancer. According to these authors, an increase in the expression of transporters of this mineral occurs in cells with malignant tumors, including metallothionein, Zip5, Zip6, Zip7, Zip8, and Zip10, producing an influx of zinc into the neoplastic cells, suggesting that its accumulation inside the breast tumor induces processes dependent on this mineral, for example, the activation of MMPs.[39]

Lue et al.[40] demonstrated that zinc transporter protein denominated LIV-1 belonging to the Zip transporter family was associated with increased MMP-2 and MMP-9 activity in prostate tumor cells. This protein may play a role in both cell growth, by acting as a zinc transporter, as well as the induction of metastasis, by association with matrix metalloproteinases.[41] It is worth mentioning that this transporter protein is also detected in neoplastic breast tissue.[42]

Zip4 also appears to regulate the activity of metalloproteinases. Zhang et al.[43] found that the overexpression of this zinc transporter protein favored increased activity of MMP-2 and MMP-9 and inducers of angiogenesis in pancreatic cancer cell lines, suggesting that Zip4 may mediate tumor growth through angiogenesis, invasion, and metastasis pathways in these cells. These results suggest the possible involvement of zinc transporter proteins in the activity of MMPs. However, there are no studies on the action of these proteins in the activation of metalloproteinases in neoplastic mammary cells.

In relation to metallothionein, Kim et al.[44] found that the overexpression of the 2A form of this protein is associated with the aggressiveness of the mammary carcinoma by inducing cellular migration and invasion and regulating the expression of MMP-9, through the activation of transcription factor AP-1 (activator protein 1) and NF-κβ. The authors also noted that the reduction in the expression of metallothionein-2A completely inhibited tumor migration and invasion in the MDA-MB-231 cell line. Zitka et al.[45] also demonstrated that the activity of MMP-9 in collagen degradation increases in the presence of metallothionein in vitro, causing a similar effect to that promoted by temperature in the activity of this protein (Figure 1).

In addition, another zinc-dependent protein, known as zinc finger 24 (ZNF24), seems to exert regulatory activity on MMP-2. Jia et al.[46] verified that the deletion of the gene that encodes this protein in primary microvascular endothelial cells significantly decreases migration and tumor invasion by reducing the levels of MMP-2 and impairing the signaling of VEGF receptor 2. However, the authors did not observe effects of ZNF24 on the regulators of MMP-2 activity or its tissue inhibitors.

A study conducted by Huang et al.[47] aimed to investigate whether the activity of ellagic acid, a natural polyphenol found in fruits and nuts, has antiangiogenic effects through the inhibition of MMP-2, and whether this inhibition could be reversed with the addition of zinc chloride. This research verified that ellagic acid can indeed inhibit the activity and secretion of MMP-2 in human vascular endothelial cells, probably mediated by inducing the expression of RECK (reversion-inducing cysteine-rich protein with Kazal motifs). The authors also found that the antiangiogenic effects caused by ellagic acid can be reversed by the addition of zinc, demonstrating the important role of this trace element in the angiogenic process of tumors.

Research has shown the ability to inhibit MMPs by certain substances that have an affinity to zinc, such as lactoferrin. In this regard, Newsome et al.[48] demonstrated that lactoferrin exerts an effect on the proteolytic activity of MMP-2 and other MMPs by removing zinc from the active site of these metalloproteins, which was reversed upon the addition of zinc chloride.

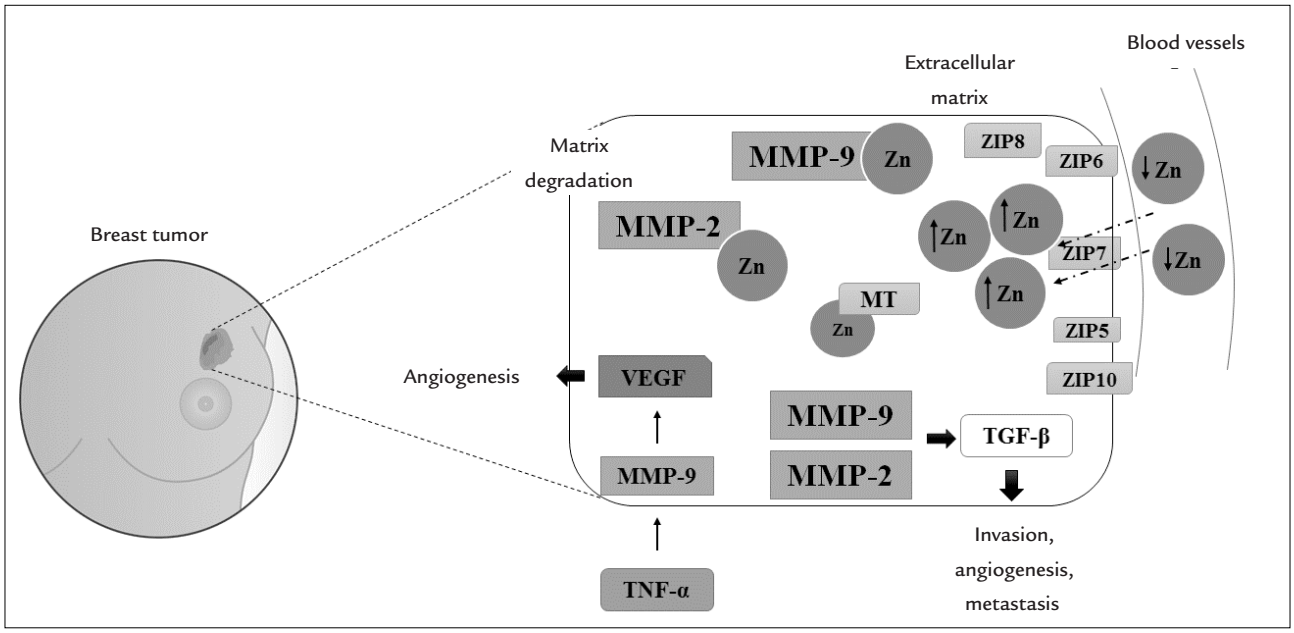

FIGURE 1 Relation between zinc, MMPs, and breast cancer. Zinc compartmentalization within the tumor favors invasion, metastasis, and angiogenesis mediated by matrix metalloproteinases, particularly MMP-2 and MMP-9. The increased zinc in the tumor appears to be due to changes in the expression and activity of its transporter proteins (Zip5, 6, 7, 8, 10, and metallothionein), leading to mineral deficiency in the serum of patients with breast cancer.

MMP-2: matrix metalloproteinase 2; MMP-9: matrix metalloproteinase 9; MT: metallothionein; TGF-β: transforming growth factor β; TNF-α: tumor necrosis factor α; VEGF: vascular endothelial growth factor; Zn: zinc.

Cysteine also appears to inhibit the activity of metalloproteinases due to affinity of zinc for the thiol groups of this amino acid. Therefore, Khrenova et al.[49] observed that the binding of Regasepin 1 to MMP-9 promotes the rearrangement of zinc at the catalytic site of its binding to histidine in order to also bind to two cysteine residues, inhibiting the action of this enzyme. The authors further verified that this drug inhibits MMP-2 because of two replacements in its active site, with cysteine binding.

Thus, considering the complex action of zinc in mechanisms involved in the pathogenesis of breast cancer and its structural role in the activation of MMPs, the inhibition of matrix metalloproteinase activity by removal or chelation of zinc from its active site has been a well-studied therapeutic target in the treatment of cancer. However, new studies that determine the effectiveness of these inhibitors in breast carcinoma are still needed.

Conclusion

There is convincing experimental evidence demonstrating the participation of zinc and matrix MMPs in the pathogenesis of breast cancer. However, although certain mechanisms have been proposed to identify the activity of this mineral and metalloproteinases in the development of tumors, the current information is still quite scarce and inconsistent. It is therefore necessary to carry out further studies on the subject in order to obtain clarification about the influence of the deregulation of zinc homeostasis and the activity of MMPs on the manifestation of breast cancer and its associated disorders.

Conflict of interest

The authors declare no conflict of interest.

Resumo

Zinco e metaloproteinases 2 e 9: qual é a relação com câncer de mama?

O zinco é componente catalítico de proteínas que regulam respostas a danos no DNA, enzimas de sinalização intracelular e metaloproteinases de matriz, proteínas importantes na carcinogênese. O objetivo desta revisão é trazer informações atualizadas sobre a participação do zinco e das metaloproteinases de matriz dos tipos 2 e 9 em mecanismos envolvidos na patogênese do câncer de mama. Realizou-se um levantamento bibliográfico, mediante consulta às bases de dados PubMed, Scielo e Lilacs. O zinco e os resíduos de cisteína são elementos estruturais compartilhados por todos os membros da família das metaloproteinases de

matriz, as quais parecem estar envolvidas na propagação de vários tipos de neoplasias, incluindo o câncer de mama. Além disso, é provável que o zinco transportado seja utilizado para metalação do domínio catalítico das metaloproteinases recentemente sintetizadas antes de serem segregadas. Nesse sentido, o aumento das concentrações de zinco em compartimentos celulares e a redução desse oligoelemento no sangue de pacientes com câncer de mama parecem alterar a atividade das metaloproteinases 2 e 9, contribuindo para a ocorrência de tumor maligno. Assim, faz-se necessária a realização de novos estudos na perspectiva de esclarecer o papel do zinco e das metaloproteinases 2 e 9 na patogênese do câncer de mama.

Palavras-chave: zinco, metaloproteinases da matriz, neoplasias da mama.

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