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Clinical and prognostic role of matrix metalloproteinase-2, -9 and their inhibitors in breast cancer and liver diseases: A review

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ABSTRACT

Matrix metalloproteinases are a family of zinc endopeptidases with proteolytic activity against the extracellular matrix components. In particular, two members of this family named Gelatinase A and B, as amply documented in the literature, play a key role in the process of tumor growth/metastasis in breast and hepatocellular carcinoma. Their activity is regulated by Tissue Inhibitor of metalloproteinases-1 and −2, which are the physiological inhibitor of Gelatinases A and B respectively. The aim of this review is to determine the current understanding of the clinical and prognostic role of Metalloproteinases-2 and −9 and their inhibitors in the course of breast cancer and liver diseases. Forty-one articles were selected from PubMed by entering the following keywords: liver diseases, breast cancer, MMP-2, TIMP-2; all articles were read and notes were made regarding the number of enrolled patients, pathology, measures, results and these data were used to write this review. Over-expression of both gelatinases is associated with the relapse of disease, metastasis, shorter overall survival in breast cancer and hepatocellular carcinoma and invasion and progression to tumors in chronic liver diseases, and MMPs/TIMPs ratio could be useful in the follow-up of these patients.

1. Introduction

1.1. Breast cancer

Breast cancer is more common in women and accounts for 25% of all cancers affecting this gender. The number of cases of breast cancer has increased significantly since the 1970s, with the changes in lifestyle in the western world. It currently affects 1 in 10 women and is the leading cause of cancer mortality in women around the world, with a mortality rate of 17% of all deaths due to cancer. In Italy there are about 37,000 diagnosed cases, or 152 of every 100,000 women. Incidence increases with age. The disease is rare in men (Parkin et al., 2005).

One of the crucial events associated with the primary tumor in the breast is the formation of metastases. The formation of a metastasis is an extremely complex process, described as a "cascade tumour". In fact, during this process some cancer cells lose their normal cell-cell contact, beyond the basement membrane (MB) they advance in the surrounding stroma and, after crossing the vascular endothelium pass into the bloodstream; through this tissue they reach the stroma and form a metastatic nucleus (Egeblag and Werb, 2002).

Unfortunately, there is no effective therapy at present for the treatment and prevention of metastasis, therefore, the analysis of the role of molecules that have a key role in the prognosis of this malignancy becomes indispensable.

The malignant tumor progression is a multi-step process in which normal cells undergo genetic alterations, lose the normal proliferative control, invade and colonize the surrounding tissue and away from target organs. The synthesis and release of proteolytic enzymes capable of degrading the MB and the extracellular matrix (ECM) are the first step of the process of metastatic invasion: as a result of proteolytic degradation of the ECM in fact endothelial cells begin to migrate through the degraded matrix (Talvensaari-Mattila et al., 1998); there follows a proliferation of endothelial cells, the second step, stimulated by various growth factors including Vascular Endothelial Growth Factor (VEGF), which acts as an

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angiogenic factor (Westermarck and Kahari, 1999). At the same time, a smaller cell cohesion and minor cell-matrix adhesion occurs that causes the spread of cancer cells. The MMP-2 and MMP-9 are involved in many stages of development and tumor progression: primary tumor growth, angiogenesis, tumor cell extravasation and intravasione, migration, invasion of metastatic organ secondary cells, beginning and maintaining tumor growth in metastatic site. In addition, they can also suppress tumor progression by acting with proteolytic cleavage, on many bioactive substrates. The final effect, therefore, depends to a large extent by the general context of the microenvironment that promotes malignant transformation. They are generally associated with malignant phenotype, invasion, progression and poor survival. They are synthesized by tumor cells but also from the stroma. It is believed that cancer cells can stimulate the stromal cells of the tumor to synthesize gelatinase in a paracrine manner through the secretion of interleukins, interferon and growth factors. After the local secretion can reach the bloodstream and find themselves in the various body fluids.

Numerous studies have emphasized the importance of matrix metalloproteinases (MMPs), and in particular of MMP-2, MMP-9 and their inhibitors, whose role is relevant in breast cancer and metastasis and these are the subject of this review.

1.2. Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver. With a progressive increase in incidence, it represents the fifth most common cancer worldwide in men and the seventh in women. In the United States, HCC related to infection with the hepatitis C virus (HCV) has become the most significant cause of death, and in the last two decades its incidence has tripled with a 5-year survival substantially stable at around 12% (McGlynn et al., 2001; Srivatanakul et al., 2004). In Italy, HCC incidence and mortality occupies an intermediate position on the global scale being the seventh leading cause of cancer death, with about 5000 deaths (or about 3% of all cancer deaths) a year (Malvezzi et al., 2009).

The clinical outcome of patients with HCC is very poor; diagnosis is usually established late, treatment is generally unsatisfactory and death often occurs within a few years. With the exception of AFP, there are currently no biomarkers specific and sensitive enough to detect HCC at an early phase, and even fewer are useful and predictive biomarkers in response to loco-regional treatment and therefore to overall survival.

In HCC and liver diseases, a key role is played by the remodelling of the extracellular matrix, a complex, multistep process involved both in physiological and pathological states and therefore linked to the proper mechanisms of wound healing in processes of tumor invasion and metastasis. All these conditions have in common an excessive proteolytic activity explicated by enzymes degrading the matrix such as MMP-2 (Burt, 1993).

1.3. The structure of matrix metalloproteinases

MMPs belong to the family of zinc-dependent endopeptidase. The first member of this family was described in 1962, after the degradation of the collagen triple helix in the process of reabsorption of the tadpole tail during metamorphosis was observed. Up to now, at least 23 types of MMPs have been described, implicated in numerous physiological processes such as reproduction, fetal development and wound healing and in numerous pathological processes, including the invasion of tumor cells and metastasis, tissue degradation and inflammatory processes of various organs (Bissell and Radisky, 2001; Sternlicht and Werb, 2001; Stetler-Stevenson, 1990).

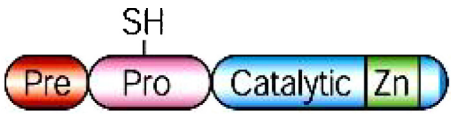

Fig. 1. Basic structure of metalloproteinases. Image idea illustrated in Caleidoscopio Italy 2009 (74).

Fig. 2. Gelatinases A and B. Structure image idea illustrated in Caleidoscopio Italy 2009 (74).

The proteolytic enzymes belonging to the family of MMPs are capable of degrading in vitro essentially all components of the ECM and on the basis of efficiency of proteolysis of the matrix components and the composition domains in the family are divided into four main classes: Gelatinase (MMP-2, MMP-9), collagenase (MMP-1, MMP-8, MMP-13), stromelysins (MMP-3, MMP-10, MMP-12) and membrane metalloprotease (MT1-MMP, MT2-MMP, MT3 –MMP, MT4-MMP).

From the structural point of view each family member is made from an amino terminal pro peptide, a catalytic domain (which has at least two calcium ions and two zinc ions) and a C terminal domain structurally similar to haemopexin (Woessner, 1991; Birkedal-Hansen et al., 1993). All members of the MMPs family demonstrate a structural homology and can be considered as derivatives of the five domain structure of the collagenase enzyme with either addition or deletion of domain. The pro-peptide N- terminal domain consists of a sequence of about 80 highly conserved amino acids PRCG(V/N) PD, in which cysteine is present to coordinate the Catalytic Zinc in latent form (Fig. 1); this binding serves to maintain the inactive state of the enzyme (pro-enzyme), excluding the H_2O molecules. In the process known as “cysteine switch” this bond is broken and the enzyme switches to “active” (Van Wart and Birkedal-Hansen, 1990). The catalytic domain contains highly conserved sequences, a motif that binds zinc (HEXXHXXGXXH), and a methionine residue that forms a particular structure called Met-Turn (Bode et al., 1993).

Glutamate and aspartate rich sequences at the N- and C- terminal ends of this domain are thought to represent calcium binding motifs. The active site is always constituted by a Zn^{2+} atom coordinated with three histidines and one molecule of H_2O; in the inactive form of the H_2O molecule this is replaced by a Cys, which belongs to the pro-peptide domain. The gelatinases A and B (MMP-2 and MMP-9) contain additional three tandem repeats of a fibronectin type-II like sequence inserted into their catalytic domain which, as several researchers suggest, confers affinity to the gelatin substrate (Fig. 2). The C-terminal haemopexin like domain determines the substrate specificity of the various classes of MMPs; this bond, in fact, has a functional role in substrate binding and/or interaction with TIMP. It is linked to the catalytic domain by a short proline rich hinge region (Sanchez-Lopez et al., 1993).

1.3.1. Gelatinases

The gelatinases (known as collagenase type IV), are the molecules characterized by high proteolytic efficiency to gelatin which it is a degradation product of collagen molecules. They family contains two members, 72 kDa type IV collagenase or gelatinase-A (MMP-2) and 95 kDa or gelatinase-B (MMP-9). Both contain, with respect to other MMPs, an additional sequence inserted into a loop of the catalytic domain. This sequence assumes the conformation of type II, found in fibronectin. MMP-2 and MMP-9