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Review Article

ROLES OF MATRIX METALLOPROTEINASES (MMPS) IN CANCER PROGRESSION: A REVIEW

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ABSTRACT

Matrix metalloproteinases (MMPs) contain a multigene group of the zinc-dependent extracellular matrix (ECM) renovating endopeptidases involved in pathological processes, for example, carcinogenesis. In such way, their development accepts an important role in tumor improvement and the multistep procedure of invasion and metastasis, including proteolytic degradation of ECM, change of the cell-cell and cell-ECM communications, movement, and angiogenesis. The concealed introduction of the present mini-review is that MMPs can proteolytically process substrates in the extracellular milieu and, in this way, promote tumor progression. In this review it was clear that certain individuals of the MMP family apply revoking roles at different stages amid cancer progression, depending among various factors on the tumor stage, tumor site, enzyme localization, and substrate profile. MMPs are subsequently pleasant to therapeutic intervention by natural inhibitors and synthetic.

Keywords: Cytotoxicity potency, cell adhesion, proliferation, migration, prognosis, cancer progression, metastasis, cell invasion, and apoptosis.

INTRODUCTION

The tumor is portrayed as the over-proliferation of cells and it is a critical reason for mortality around the world[1]. Recent years of biomedical examination reveal a huge measure of data on the molecule occasions that occur during carcinogenesis and signaling pathway taking part in tumor migration. The molecule components of the mind-boggling transaction between the cancer microenvironment assume an indispensable role in this process[2]. Over 50 years ago the discovery of the dangerous property of nitrogen mustards on hematopoietic cells activated research on the advancement of cytotoxic operators for the treatment of cancer. The underlying guarantee of these medications in the administration of hematological and extra uncommon malignancies has not been supported and cure of the more typical epithelial malignancies when metastatic remains an elusive goal[2, 3].

A significant number of the current chemotherapeutic agents have been found because of screening the mixes for cytotoxic potency in vitro against murine or potentially human malignancy cells or in-vivo against rodent growth models. With our better comprehension of the sub-molecule premise of growth, there is presently enthusiasm towards target coordinated medication treatments. The aims being to create specialists that can be modulated or inhibit specific molecular targets recognized as being essential for malignancy development, among the different perspectives on the membrane proteins which are considered as a key target. Over-expressed membrane proteins/receptors are winding up progressively key in cancer cell treatment. The utilization of a targeted on way to deal with treat harm appears to be sensible. In any case, this requires a detailed characterized of growth to determine cell susceptibility. A portion of the promising targets for consideration is the plasma membrane proteins, including the tyrosine kinase, which regulates cell proliferation, adhesion, migration and they are the key factors in tumor pathogenesis. The presence of the membrane proteins in the outside of the cell will be to a great degree available to drugs and the membrane proteins associated with cancer progression are discussed below.

MATRIX METALLOPROTEINASES (MMPs)

Matrix metalloproteinases are zinc-dependent endopeptidases, which are established protein complex assuming a key role in growth progression. MMPs are expansion up to its typical physiological capacities, for example, angiogenesis, morphogenesis, and tissue repair. The MMPs are well-known mediators of cancer metastasis and invasion by breaking down the barriers of connective tissues. In spite of the fact that there have been a vast huge of reports on the responsibility of MMPs in metastasis, angiogenesis, and invasion of different cancers, its role in prostate malignancy progression has not been systematically studied.

At the development stages of carcinogenesis, cancer cells partake in numerous relationship with the tumor microenvironment including extracellular matrix (ECM), growth factors, cytokines, endothelial cells, fibroblasts, macrophages, mast cells, neutrophils, pericytes, and adipocytes[2,4,5]. Four critical components related to cancer to be specific, migration, invasion, metastasis and angiogenesis are dependent on the surroundings of the microenvironment. Basic molecules associated with this methodology are MMPs in light of the fact that they corrupt different cell adhesion molecules, subsequently regulating cell-cell and cell-ECM interactions. Late examinations demonstrated that the individuals from the MMP family apply for distinctive roles at various stages of cancer progression. Specifically, MMP may promote or inhibit malignancy improvement depending upon different factors, for example, cancer stages, tumor sites like primary, metastasis, enzyme localization, and a substrate.

MMPs and cancer invasion

The ECM is a functioning structure that arranges the direct of the cells by interfacing with them. The proteolytic development of MMPs is required for a tumor cell to corrupt physical barriers in the midst of nearby expansion and intravasation at adjacent veins, invasion, and extravasation. During tumor invasion, MMPs are localized at the specific cell surface structure and is called as invadopodia, which is essential for their ability to promote invasion and these structures converse to the site where active ECM degradation occurs. Invadopodia use transmembrane invadopodia-related proteinases, including MMP 14, a few individuals from the ADAM family and likewise released and inactivated MMPs at the site, for example, MMP 2 and 9 to degenerate an arrangement of ECM macromolecules and encourages cell invasion[6].

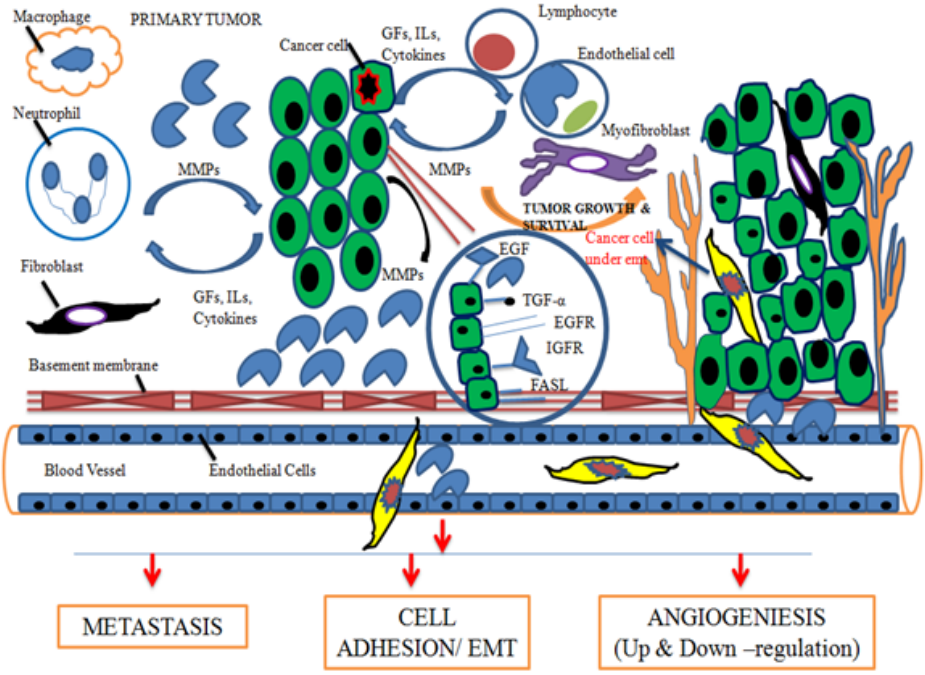

Fig. Important roles of MMPs in cancer progression.

MMPs and cancer cell proliferation

There are different systems by which MMPs add to cancer cell multiplication. In particular, they can change the bioavailability of growth factors and the function of cell-surface receptors by including ADAM family. Individuals from the MMP and ADAM families can release cell membrane precursor of a few growth factors, for example, insulin-like growth factors (IGFs) and the epidermal growth factor receptor (EGFR) ligands that promote multiplication. A few MMPs (MMP 1, 2, 3, 7, 9, 11 and 19) and ADAM 12 separate IGF-binding proteins that disregard the bioavailability of the growth factor[7, 8]. EGFR, a mediator of cell duplication, is captured in growth progression since it is over-expressed in over 33% of all solid malignancy[9]. During tumor progression, extended shedding of the membrane secured ligands of EGFR, including heparin-binding EGF (HB-EGF), transforming growth factor (TGF)-α and amphiregulin was seen with the action of MMP 3, 7, ADAM 17 or ADAM 10[10,11]. MMPs and ADAM like manner control proliferation signals through integrins on the ground that the shedding of E-cadherin achieves β-catenin translocation deeply, prompting cell multiplication[12]. It is basic to observe the inactive proform of TGF-β, a fundamental biomolecule included growth is proteolytically activated by MMP 2, 9, 14 of comparatively[13, 14].

MMPs and apoptosis of cancer cell

Matrix-degrading enzymes are in charge of both apoptotic and anti-apoptotic action. MMPs and ADAMs, particularly MMP 7 and ADAM 10, exhibit anti-apoptotic signals to malignancy cells by separating "Fas ligand", a transmembrane stimulator of the passing receptor "Fas" from the cell surface. This proteolytic progression inactivates "Fas" receptor and prompts assurance from apoptosis and chemoresistant from the cancer cells or raises apoptosis to the neighboring cells depending upon the system[15,16,17]. Proteolytic shedding of cancer-related major histocompatibility proteins complex class-I (MHC-I) related proteins by ADAM 17 may suppress nature killer (NK) cell-mediated cytotoxicity towards growth cells[18]. Remarkably, MMPs may contribute against apoptotic effect by actuating in an indirectly the serine/threonine kinase Akt is called as protein kinase B through the signaling falls of EGFR and IGFR[9,19]. MMPs likewise promote apoptosis, without a doubt with an indirect change in ECM composition[20].

MMPs in cancer angiogenesis and vasculogenesis

MMPs show a dual function in malignancy vasculature by acting both as positive and negative controllers of angiogenesis, which depends upon the time reason for expression amid cancer angiogenesis, vasculogenesis and the convenience of the substrates. MMP families that affect tumor angiogenesis are generally MMP 2, 9, and in addition 14, and to a lesser degree by MMP 1 and 7[21]. For tumor cells to proceed to develop and for the migration, it is important to form new blood vessels. The initial step in this procedure is to eliminate the physical obstructions by ECM degradation and thusly to produce pro-angiogenic factors. Without a doubt, MMP 9 appreciates the angiogenic switch since it assembles the bioavailability of basic factors related to this procedure. For example, vascular endothelial growth factor (VEGF), is a most potent mediator of malignancy vasculature and basic fibroblast growth factor (bFGF) by degrading the extracellular parts, for example, collagen type IV, XVIII and perlecan correspondingly[22,23,24,25]. The angiogenic amend is

firmly controlled by MMPs in light of the way that they can in likewise down-regulate the formation of blood vessels through the generation of corruption parts that inhibit angiogenesis by using the atoms. For example, tumstatin, endostatin, angiostatin, and endorepellin, which are made by methods for cleavage of type IV, XVII collagen, plasminogen, a dormant precursor of a serine proteinase plasmin, and perlecan[25,26,27,28].

MMPs in cell adhesion, migration and epithelial to mesenchymal transition

Cell development is exceedingly related to the proteolytic action of MMPs and ADAMs, which are controlling the dynamic ECM-cell and cell-cell communications along with migration. At first, the generation of tryptic peptides by methods for degradation of ECM molecules, for example, collagen type IV and laminin-5, promotes the migration of malignancy cells[22,29]. A few integrins expect a dynamic part in the control of cell migration since they can fill in as substrates for MMPs[30]. Overexpression of a few MMPs (MMP 2, 3, 9, 13, and 14) has been connected with epithelial to mesenchymal transition (EMT), an exceedingly apportioned and essential procedure of morphological progress. Amid this occasion, epithelial cells effectively/successfully down-regulates cell-cell adhesion systems, lose their extremity, and obtain a mesenchymal phenotype with decreased intercellular associations and expanded migratory capacity[31]. The correspondence between the cells is upset by the shedding of E-cadherin by ADAM 10, prompting disturbed cell adhesion and acceptance of EMT, trailed by extended cell migration. MMP 1 and 7 additionally appear to add to this morphological progress by cutting E-cadherin[32]. Late investigations revealed the implications of MMP 28 in the proteolytic initiation of TGF-β, and able inducer of EMT, driving EMT[33,34]. It is worth to observe the association amongst hyaluronan and its genuine cell surface receptor CD44, which achieves the enactment of signaling molecules, for example, Ras, Rho, PI-3 kinases, and AKT, subsequently advancing cancer progression. A present report declared that hyaluronan advances malignancy cell migration and expanded lattice metalloproteinase release, which especially expanded the active type of MMP 2, through Rho kinase-mediated signaling[35].

MMPs and immune surveillance

The immune system of the host is capable of recognizing and attacking malignancy cells by enlisting tumor-specific T-lymphocytes, NK cells, neutrophils, and macrophages. Instead of these, the tumor cells develop getting away mechanism using MMPs to acquire immunity. MMPs shed interleukin-2 receptor-α with the cell surface of T-lymphocytes, along these lines suppressing their proliferation[36]. Also, TGF-β, act as a critical silencer of T-lymphocyte functions against tumor cells, in response to MMP active[37]. So additionally, MMPs decrease tumor cell affectability to NK cells by making a bioactive part from α 1-proteinase inhibitor[38]. Different examinations showed the capacity of MMPs in separating the few individuals from CC-β and CXC-α chemokines subfamilies or to control their assembly, affecting leukocyte penetration and migration[39,40].

CONCLUSION

MMPs have well-established complex and vital roles in cancer progression. In any case, all around, the agents targeting on MMPs demonstrated poor execution in clinical trials, rather than their promising action in different preclinical models. In particular, for certain cancer types, especially those where the stroma is an essential member of carcinogenesis, the inhibition of MMPs is ended up being more effective. Moreover, the time span of targeting on MMPs differ depends upon the stage of cancer, due to the expression profile, and additionally, the activity of MMPs isn't the same in the early stage compared to advanced cancer disease. Late investigations exhibit that individuals of the MMP family apply for different roles at different steps of cancer progression.

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