



Utilizing the Knowledge of Role of Matrix Matrixmetalloproteinases Along with Tissue Inhibitors of Matrix Metalloproteinases in Various Gynaecological Disorders with Great Emphasis on Preeclampsia, PCOs Along with Gynaecological Malignancies-A Systematic Review

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Research Article

Volume 6 Issue 4

Received Date: October 04, 2021

Published Date: November 02, 2021

DOI: [10.23880/oajg-16000223](https://doi.org/10.23880/oajg-16000223)

Abstract

Our insight has escalated over the past decade regarding the understanding of Molecular mechanisms underlying the generation of preeclampsia, with us reviewing the role of epigenetics in the development of preeclampsia along with intra uterine growth restriction (IUGR) generation. Matrix Metalloproteinases (MM's) MMP's represent calcium-based zinc-endopeptidases that belong to the metzincin superfamily possessing a lot of functions like a physiological part in tissue morphogenesis, cell migration along with angiogenesis as well as in pregnancy in invasion along with migration of trophoblast besides spiral artery remodeling. Matrix Metalloproteinases (MMP), cytokines, growth factors have a role in physiological events like embryo implantation, trophoblast invasion as well as migration along with decidualization with studies documented that blastocysts are direct generators of MMP2. Thus here we decided to conduct a systematic review on the role of Matrix Metalloproteinases (MMP's) along with their inhibitors, namely the, Tissue inhibitors of Matrix Metalloproteinases (TIMPs) in gynaecological disorders specifically in generation of preeclampsia along with IUGR; in women with Polycystic Ovarian Syndrome(PCOS); besides in spontaneous abortion along with generation of various cancers of the whole body but main emphasis on gynaecological cancers. Hence utilizing the search engine Thus we utilized Pubmed, MEDLINE, Google Scholar, Scopus, Embase, Web of Sciences, Cochrane library search engines where we utilized the MeSH terms like MMP's in pregnancy physiological roles; pathological in preeclampsia, IUGR; miRs in these disorders; spontaneous abortion; gynaecological disorders like PCOS; gynaecological cancer along with association of certain MIR's abnormal in IUGR that were linked to certain gliomas along with MMP'S and IUGR and further utilization of MMP inhibitors clinically, besides that since no efficacious therapy available other therapies like role of extracellular vesicles (ECV's) that target combined miR'S that are altered and associated with MMP's in various pathologies and effectively we can treat those disorders from 1970 till January 2021 till date. We found a total of 500 articles out of which we selected 145 articles for this review following evaluation of cross references. No meta-analysis was done. Here we provide an insight on how this knowledge on molecular mechanisms interactions of MMP's, TIMP's micro RNA'S might get utilized in generating therapies to prevent or treat preeclampsia, IUGR, various gynaecological malignancies developing extracellular vesicles carrying miR;s targeting specific MMP's in particular disease or malignancy.

Keywords: Matrix Metalloproteinases; TIMPs; Preeclampsia; IUGR; miRs; Gynaecological cancer; ECV's; PCOS

Abbreviations: IUGR: Intra Uterine Growth Restriction; MMP: Matrix Metalloproteinases; TIMP: Tissue Inhibitors of Matrix Metalloproteinases; PCOS: Polycystic Ovarian Syndrome; ECV: Extracellular Vesicles; ECM: Extracellular Matrix; VSM: Vascular Smooth Muscle; CVS: Cardio Vascular; TNF α : Tumor Necrosis Factor Alpha; TGF β : Transforming Growth Factor β ; T2DM: Type 2 Diabetes Mellitus; RPL: Recurrent Pregnancy Loss; TACE: Trophoblasts Cause an Enhanced; GCM: Glial Cell Missing; MHC: Major Histocompatibility Complex; SIUGR: Selective Intra Uterine Growth Restriction.

Introduction

MMPs represent a family of zinc-based endoproteases possessing lot of parts in tissue refashioning and breakdown

of different proteins in the extracellular matrix (ECM). MMPs facilitate cell proliferation, migration, along with differentiation besides playing a part in cell apoptosis, angiogenesis, tissue repair, along with immune response. MMPs might further influence bioactive molecules on the cell surface and manipulate different cellular in addition to signaling pathways. Changes in MMP expression in addition to activity take place in normal biological events like during pregnancy, wound healing, nevertheless, have also been seen in cardiovascular diseases like atherosclerosis, aneurysms and varicose veins, musculoskeletal disorders such as osteoarthritis and bone resorption, and in various cancers. MMPs have also been believed to be involved in tumor propagation along with invasiveness.

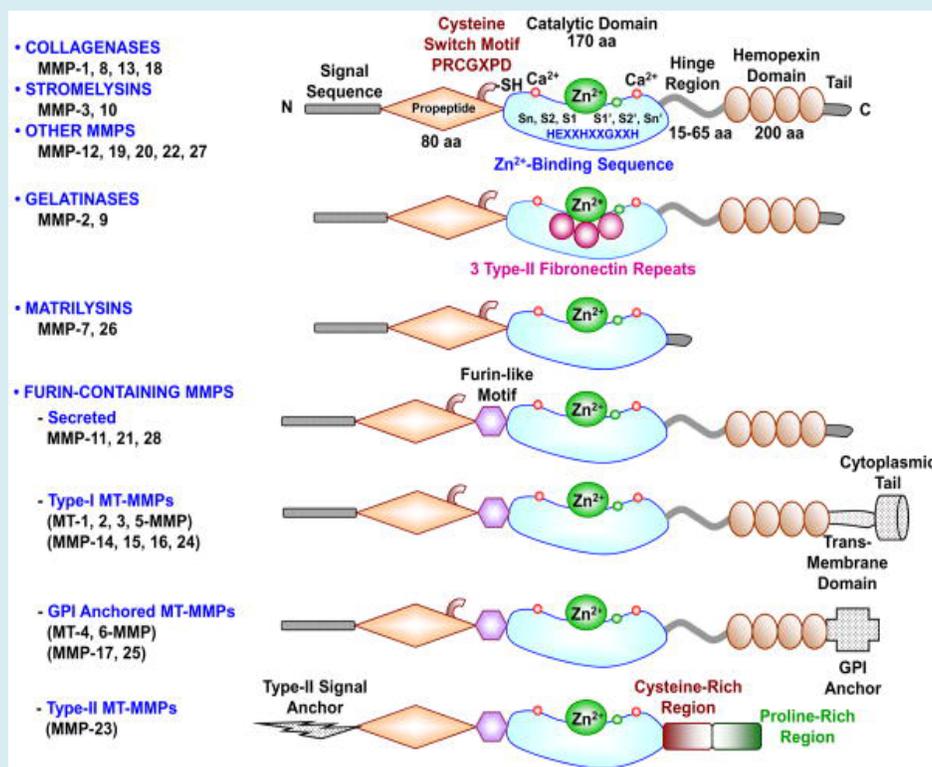
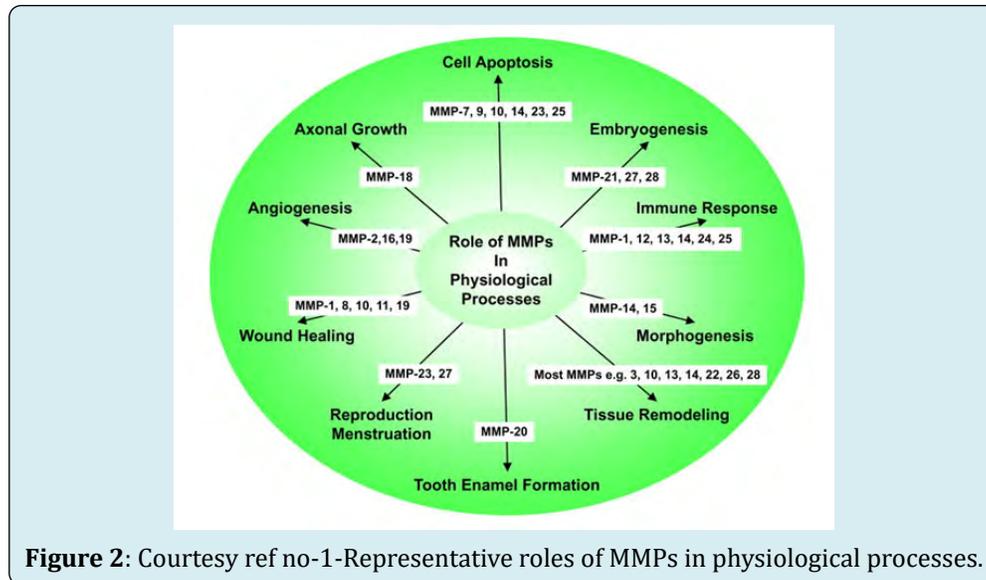


Figure 1: Courtesy reference no-1-Major MMPs subtypes and their structure. A typical MMP consists of a propeptide, a catalytic metalloproteinase domain, a linker peptide (hinge region), and a hemopexin domain. The propeptide has a cysteine switch motif PRCGXP whose cysteine sulfhydryl ($-SH$) group chelates the active site Zn^{2+} , keeping the MMP in the latent pro MMP zymogen form. The catalytic domain contains the Zn^{2+} binding motif HEXXHXXGXXH, two Zn^{2+} ions (one catalytic and one structural), specific S1, S2,...Sn and S1', S2',...Sn' pockets, which confer specificity, and two or three Ca^{2+} ions for stabilization. Some MMPs show exceptions in their structures. Gelatinases have 3 type-II fibronectin repeats in the catalytic domain. Matrilysins have neither a hinge region nor a hemopexin domain. Furin-containing MMPs such as MMP-11, 21 and 28 have a furin-like pro-protein convertase recognition sequence in the propeptide C-terminus. MMP-28 has a slightly different cysteine switch motif PRCGVTD. Membrane-type MMPs (MT-MMPs) typically have a transmembrane domain and a cytosolic domain. MMP-17 and -25 have a glycosylphosphatidylinositol (GPI) anchor. MMP-23 lacks the consensus PRCGXP motif, has a cysteine residue located in a different sequence ALCLLPA, may remain in the latent inactive proform through its type-II signal anchor, and has a cysteine-rich region and an immunoglobulin-like proline-rich region.



Classically, MMPs possess a propeptide sequence, a catalytic metalloproteinase domain along with catalytic zinc, a hinge region or linker peptide, besides a hemopexin domain. Usually classification of MMPs is done depending on their substrates along with the organization of their structural domains into collagenases, gelatinases, stromelysins, matrilysins, membrane-type (MT)-MMPs, and other MMPs. MMPs are liberated by lot of cells that include fibroblasts, vascular smooth muscle (VSM) and leukocytes. MMPs are controlled at the level of mRNA expression and by activation of their latent zymogen form. MMPs are often liberated as inactive pro MMP form which is cleaved to the active form by various proteinases that are other MMPs. MMPs result in the breakdown of ECM proteins like collagen along with elastin, nevertheless, could affect endothelial cell function in addition to VSM cell migration, proliferation, Ca²⁺ signaling along with contraction. MMPs participate in tissue remodeling at the time of different physiological events like angiogenesis, embryogenesis, morphogenesis along with wound repair, besides in pathological conditions like myocardial infarction, fibrotic disorders, osteoarthritis, along with cancer. Escalation in specific MMPs could participate in arterial remodeling, aneurysm generation, venous dilation along with lower extremity venous disorders. MMPs further participate in leukocyte infiltration along with tissue inflammation. MMPs have been documented in cancer, and enhanced MMP amounts have been correlated with tumor propagation along with invasiveness. MMPs can be controlled by endogenous tissue inhibitors of metalloproteinases (TIMPs), and the MMP/TIMP ratio often determines the extent of ECM protein breakdown along with tissue remodeling. MMPs have been posited to be biomarkers for a lot of pathological conditions along with getting evaluated as potential therapeutic targets in different cardiovascular (CVS) along with musculoskeletal

disorders in addition to cancer [1] (Figures 1 & 2). Thus here we decided to conduct a systematic review on the role of Matrix Metalloproteinases (MMP's) along with their inhibitors, namely the, Tissue inhibitors of Matrix Metalloproteinases (TIMPs) in gynaecological disorders specifically in generation of preeclampsia along with IUGR; in women with Polycystic Ovarian Syndrome(PCOS); besides in spontaneous abortion along with generation of various cancers of the whole body but main emphasis on gynaecological cancers.

Methods

Hence utilizing the search engine we utilized Pubmed, MEDLINE, Google Scholar, Scopus, Embase, Web of Sciences, Cochrane library search engines we utilized the MeSH terms like MMP's in pregnancy physiological roles; pathological in preeclampsia, IUGR; miR's in these disorders; spontaneous abortion; gynaecological disorders like PCOS; gynaecological cancer along with association of certain miR's abnormal in IUGR that were linked to certain gliomas along with MMP'S and IUGR and further utilization of MMP inhibitors clinically, besides that since no efficacious therapy available other therapies like role of extracellular vesicles (ECV's) that target combined miR'S that are altered and associated with MMP's in various pathologies and effectively we can treat those disorders from 1970till January 2021 till date.

Results

We found a total of 500 articles out of which we selected 145 articles for this review following evaluation of cross references. No meta-analysis was done.

Matrix Metalloproteinases (MMP's), Tissue Inhibitors of Matrix Metalloproteinases (TIMPs) as well as Gynaecological Abnormalities

Metalloproteinases and TIMPs are normally expressed in variety of tissues. Nevertheless, it has been documented that at the time of generation of variety of human diseases, metalloproteinases 1, 2, 3, 7, 8, 9, 13, and 14 get overexpressed

in particular tissues. These tissues are the kidneys, liver, colon, placenta, intestines, stomach, bladder, pancreas, ovary, uterus, along with bone marrow, among others. TIMPs have varying expression in particular tissues like the breast, brain, lungs, liver, kidneys, colon, skin, ovaries, and heart. In these tissues, TIMP-1 is overexpressed, TIMP-3 is under expressed, and TIMP-2 and TIMP-4 can be either under expressed or over expressed [2] Figure 3.

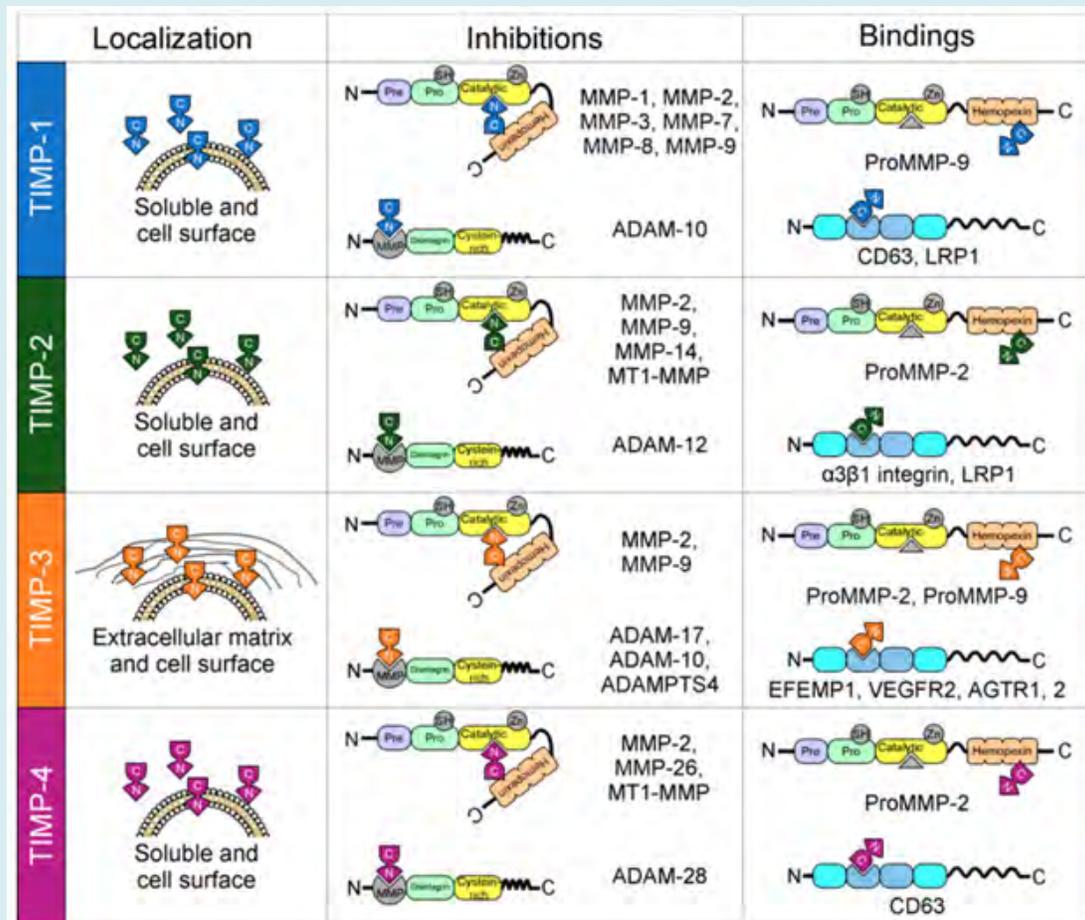


Figure 3: Courtesy ref no-2-Localization and interactions between tissue inhibitors of matrix metalloproteases (TIMPs) and matrix metalloproteases (MMPs). All TIMPs are secreted, but only TIMP-3 is incorporated into the matrix. Structurally, TIMPs are comprised of two domains that pack side-by-side (N-terminal and C-terminal domains). The N-terminal domain is sometimes referred to as the “inhibitory domain”. TIMP-1 inhibits MMP-1–3 and MMP-7–9; TIMP-2 inhibits MMP-2, MMP-9, MMP-14, and membrane-type matrix metalloproteases 1 (MT1-MMP); TIMP-3 inhibits MMP-2 and MMP-9; and finally, TIMP-4 inhibits MMP-2, MMP-26, and MT1-MMP. In addition, TIMPs interact with the proforms of MMPs in a non-inhibitory manner, and they also have functions independent of MMP inhibition by directly binding to cell surface receptors (TIMP-1 to CD63; TIMP-2 to $\alpha 3\beta 1$ integrin and LRP1; TIMP-3 to EFEMP1, VEGFR2 and AGTR1,2; and TIMP-4 to CD63).

Matrix Metalloproteinases (MMP), cytokines, growth factors have a role in physiological events like embryo implantation, trophoblast invasion as well as migration along with decidualization with studies documented that blastocysts are direct generators of MMP2 [3]. Of the cytokines

implicated in decidualization, IL-11, that is generated by stromal as well as epithelial cells along with escalated by IL-1 α , Tumor necrosis factor alpha (TNF α), transforming growth factor β (TGF β), that get stimulated the generation of human endometrium [4]. Besides the implicated cytokines,

escalated amounts of MMPs, like MMP-2, MMP-3 as well as MMP-9 that get expressed in the deciduas are correlated with an enhancement of trophoblast invasion [5]. The existence of MMPs In addition to gonadotropin chorionic hormone as well as VEGF, aids in manipulations of the endometrium which are needed for human implantation to take place, In addition to a part in the avoidance of aberrant placental generation of the placenta [5,6].

MMP, along with TIMP regulate the area along with refashioning of polycystic ovarian tissue, besides being correlated with a lot of physiological as well as pathological events. The appropriate balance among MMPs as well as their inhibitors have a big part in the structural along with functional vascular alterations of women possessing complicated pregnancies [7].

Polycystic Ovarian Syndrome (PCOS)

PCOS represents the commonest condition of endocrine initiation in women from reproductive age. Its clinical expression usually are oligo or anovulation, hyperandrogenism (clinical/biochemical) along with the existence of polycystic ovaries In addition to its association with insulin resistance (IR), Type 2 diabetes mellitus (T2DM), obesity, cardiovascular disease (CVD), along with escalated cancer chances [8]. PCOS represents the commonest etiologies of anovulatory infertility, implicating 6-10% of premenopausal women. Adrenal In addition to pituitary diseases need to be ruled out prior to diagnosing it along with the counting of primordial follicles is further significant [9]. It has significant incidence in younger women, as well as might get underdiagnosed in view of greater amount of follicles. Although its etiology is not fully clarified, proof exists that a genetic factor which influences patients at the time of oogenesis [10]. The escalated amount of androgens In addition to LH generation, that represses the generation of SHBG, along with stimulation of adrenal as well as androgens generation correlated with anovulatory cycles [11]. Evaluation of MMP-2 along with MMP-9 expression in the ovaries was conducted in certain studies [12,13]. Follicular atresia In addition to generation of follicular cysts is the hallmark of histological properties of PCOS. MMP-9 is associated with an imbalance in the escalated reconstruction of the ovarian follicles as well as walls, resulting in irregular ovulation, Follicular occlusion In addition to escalated stromal tissue [14]. TIMP-1, TIMP-2 as well as TIMP-3 are present in the stroma along with teak of developing follicles. Besides serum amounts of MMP-9, MMP-9: TIMP-1 ratios are significantly > in women with PCOS as compared to healthy women [15]. Changes in balance among serum amounts of MMPs as well as TIMP in women with PCOS has got documented recently. Implying that a reduction in serum TIMP amounts, along with proportions of MMP-9 to TIMP-1 as well as MMP-2 to

TIMP-2 escalate significantly [16]. TIMP-1 amounts might specifically depict both systemic chronic inflammatory along with immune responses. Escalated amounts of MMP-8, along with MMP-8: TIMP-1 ratio in saliva along with serum appear to be more accentuated in women with PCOS, In addition to getting augmented by gingival inflammation [17]. Besides that studies have documented that testosterone (T) amounts associated positively with the percentage of MMP-9 to TIMP-1 besides correlating negatively with TIMP-2 [18]. One can presume that enhanced androgens liberation can change the balance of MMPs, along with TIMP in the ovaries under physiological situations, causing propagation of fibrosis in women with PCOS [19]. Suppression of the MMP-9: TIMP-1 ratios might have a significant manipulative actions on progesterone (P) liberation [20]. Conversely, other studies have demonstrated that the amounts of TIMP-3 mRNA is significantly less in PCO ovaries. These changes seen in the liberation as well as/or distribution of type IV collagen along with TIMP-3 point the implication of basement membrane (BM) in the pathogenesis of PCOS [21]. Escalated amounts of TIMP-1 have got observed in PCOS patients, as well as women who get pregnant possess greater amounts of TIMP-1 [22].

Spontaneous Abortion

Spontaneous Abortion (SA) by definition is the expelling of fetal products prior to getting viable at the gestation age (GA) of 22 wks or at the time the fetus weighs 50gm (usually among the 6th-10th wk of pregnancy [23]. Maximum SAs take place in women among 20-45 yrs age, with the peak occurring at the ages of 40-44 yrs (90%) [24].

The basic etiology of SA are maternal, ovofetal along with implantation factors [25]. As far as implantation is considered, the early loss of fetus gets enhanced when implantation takes >10 days, but other 20% of cases take place once trophoblast refuses to implant. The commonest issues taking place among 0-10 wk GA associate with fertilization or malformations in the fetus secondary to chromosomal aberrations [26]. There are disorders that stop the right generation of the fetus, like systemic maternal disease, infections congenital abnormalities in the reproductive system, or psychosomatic alterations [27]. Clinical presentation of SA are haemorrhage in the deciduas secondary to implantation failure, causing expulsion of the products (14-22 wks GA). Retention within the cavity might also take place prior to 8-14 wks of GA or rupture of membranes (ROM), with the expulsion of the fetus but not placenta, that persists in the uterine wall along with resulting in significant haemorrhage [9].

Human pregnancy needs haemostasis for avoiding haemorrhage, along with normal placentation, decidualization, as well as modulation of spiral arteries. The upregulation of MMP as well as cytokines are directly

correlated with spontaneous preterm birth [28]. MMP, along with TIMP signalling In addition to their pleiotropic actions are needed for a normal pregnancy [29]. The MMP, along with TIMP expression is needed at the time of trophoblast invasion gets guided by trophoblast cells. MMP-9 that gets expressed by trophoblast cells present in the embryo, as well as TIMP-3 expressed by maternal uterine cells, are the major enzymes implicated in the invasion of trophoblast cells in the endometrium, being necessary for the implantation events along with proper generation of embryos [30]. MMP-2 generation starts at the initiation of gestation, with its major function being trophoblast bed invasion [31]. Upregulation of MMP-9, MMP-2, as well as TIMP-2 has a part in spontaneous pregnancy termination, mostly prior to 12 wks of GA [32]. Anumba, et al. observed that enhanced TIMP-2 in women with history of recurrent pregnancy loss (RPL), correlated its aberrant implantation along with generation of the placenta, besides being an anticipatory marker for the same [33]. Expression of MMP mRNA along with MMP-9: TIMP-3 mRNA ratio also have a correlation with SA [30]. Invasive capacity exhibited by EVT's is given partly to regulation of extracellular matrix degradation mediated by matrix metalloproteinases (MMP's) like MMP-2 and MMP-9. Differential expression of these MMP's and their tissue inhibitors (TIMPs) has been related to histone H3K9/27me3 [34]. Impairment of TIMP-1 expression correlates with infertility as well as early pregnancy loss [35]. Decidual stromal cells expressing CD82 upregulate the expression of TIMP-1 via an autocrine method along with inhibition of first trimester trophoblast cells invasiveness partially via $\beta 1$ integrin /MAPK signalling pathway [36].

Preeclampsia (PE)

Preeclampsia (PE) as part of the hypertensive Disorder of pregnancy (HDP), is believed to be a serious complication worldwide. It has the properties of new onset hypertension in the 2nd part of pregnancy in correlation with proteinuria or thrombocytopenia, renal insufficiency, dysfunctional liver function, pulmonary oedema as well as cerebral or visual symptoms. These symptoms are secondary to poor placentation which causes vascular impairment along with main cardiovascular complications [37]. MMP's get correlated with implantation of the embryo along with invasion of the trophoblast into the endometrium as well as inner myometrium. Thus impairment of MMP action is associated with aberrant placentation along with vascular impairment as observed in PE [38]. In the early few wks of pregnancy MMP's start making a proper surroundings in the placental bed. The amount of MMP-2 and MMP-9 get sustained all through pregnancy with the major action being to act at the time of implantation In addition to conduct invasion of the trophoblast (MMP-9) along with the sustenance of of the placental bed (MMP-2) [39]. This

invasion of the trophoblast cells gets guided by autocrine as well as paracrine stimuli from the uterine along with trophoblast cells. Additionally, various molecules having influence in PE generation like proteinases, cytokine as well as growth factors have a part in markedly shallow invasion of the trophoblast observed during pathophysiology of PE, resulting in impairment along with inefficient remodeling of the spiral arteries, hence decreasing blood flow to the intervillous space resulting in systemic hypertension along with fetal hypoxia [40]. Plaks, et al. Evaluated a mouse model of PE had inactivation of maternal as well as embryonic MMP-9, revealing a need for adequately balanced MMP-9 activation in normal placentation [41]. Reduction in MMP-2 and MMP-9 expression /activation results in altered perfusion of the fetal-placental unit resulting in the liberation of factors within the maternal circulation along with the formation of endothelial dysfunction [42]. Enhanced MMP-2 activation/amount in patients with PE have been documented in studies, since it can facilitate Platelet aggregation, vascular refashioning membrane In addition to the liberation of vasoactive peptides like endothelin1. These amounts have been demonstrated to get modulated via vascular endothelial growth factors (VEGF) [43]. There is an enhancement of MMP-1 in patients with PE, although without enhanced TIMP-1. It is implicated in the breakdown of vascular collagen type1, that enhances vascular permeability promoting edema as well as proteinuria, that are properties seen in patients with PE. There is a stretch association among their neutrophils activation, along with vascular impairment observed in PE; like a part in leukocytes migration along with vascular impairment similarly its expression gets stimulated by activated neutrophils that also produce ROS along with TNF α [44]. The amounts of MMP in the urine specifically MMP-2 have been hypothesized as being anticipating biomarkers for patients having great risk for PE among 12-16 wks GA. This demonstrates that an imbalance that is present in MMPs during pregnancy can influence the vasculature at both structural along with functional status with discernible alterations taking place along with clinical signs onset [45]. The regulated expression along with appropriate balance among MMPs, along with TIMP, that decides the net MMP activity, thus control the invasive capacity of placental trophoblasts are key for sustenance of normal placentation [46]. Generally, the reason that this disequilibrium can result in the generation of pathological disorders particularly, at the time of pregnancy, this balance disturbance influences the trophoblastic invasive cascade [31]. TIMP-1 represents an endogenous inhibitor of MMP-9 which might influence the responsiveness of HDP to treatment [47]. Levels of TIMP-1 are enhanced in PE [48]. Placentas Evaluated from pregnant women diagnosed with PE have demonstrated that at the transcriptional level, the aberrant expression of TIMP-1 can result in inadequate trophoblast invasion along with superficial placentation [49]. Nevertheless, rest of studies

have demonstrated that decreased MMP-1 amounts in the umbilical serum placenta, In addition to decidua in pregnant women who had PE generation [50], Levels of TIMP-2 are further greater in women generating a hypertensive Disorder of pregnancy [51] Nevertheless, a particular part of TIMP-2 in PE generation needs to be clarified . TIMP-3 expression is significantly decreased in placentas of PE women, since TIMP-3 is an endogenous inhibitor of TACE, In addition to down regulation of TIMP-3 activity in trophoblasts cause an enhanced TACE expression as well as consequently TNF- α generation [52]. Histone deacetylases facilitate trophoblast cells migration along with trophoblast by repression of TIMP-promoter via histone hypoacetylation [53]. Moreover studies demonstrated that TIMP-3 promoter might be hypo methylated placentas of PE women, pointing that epigenetic changes might be linked with decreased trophoblast invasion [54]. Hypomethylated as well as placental particular TIMP-3 might be a potential marker for the early diagnosis of PE in maternal plasma. In case of PE escalated circulating TIMP-4 as compared to those in healthy pregnant women, along with these amounts are associated with clinical parameters of the disease. Rest of the studies have demonstrated that plasma TIMP-4 amounts are not changed prior to the presentation of clinical symptoms ,hence they are not good anticipators of PE generation [55]. It has been pointed that polymorphisms in TIMP-4 protect from the PE generation [56] along with TIMP-4 is a downstream target of the transcription factors glial cell missing (GCM)which might associate the sequences of decreased GCM 1 guided trophoblast differentiation to histological as well as functional components of imbalanced placentation in robust PE cases [57].

MMP along with TIMPs in Cancer

Cancer is a big cost for the caregivers in society, being a main etiology for mortality as well as morbidity althrough world. MMP along with TIMPs have a significant part in lot of stages of tumor generation. Disturbance in the balance among MMP along with TIMPs has been believed to be responsible for the propagation of Cancer [58].

To begin with, MMPs had been believed to take part in the initiation of metastases, in view of the disruption of the physical barriers which are the ECM In addition to the BM collagen. Nevertheless, at present insight is there that MMPs participate in all steps required for tumor propagation, implicating a lot of biological functions like the modulation of signalling pathways, the control of cytokines implicated in the immune response along with tumor growth (Specifically by developing angiogenesis and hence the cancer spread) [58]. MMP activity escalates in view of their part in refashioning of the ECM, the control of biological functions, along with the cytokines along with growth factors viability. Based on the MMP implicated in the tissue site where the tumor is present,

they can further tumor repressive actions, like an e.g given by MMP-8 as well as MMP12, that have been appreciated as antitumor MMP's [59]. MMP-11 influences a double action on tumors. MMP-11 facilitates cancer generation by inhibition of apoptosis along with escalation of invasion of cancer cells. Conversely, in case of animal models, MMP-11 has a negative part against cancer generation by repression of metastases [60]. It is significant to emphasize on the double action since MMP-11 might work as an important tumor biomarker in cancer for tumor staging, prognostic evaluation, monitoring of recurrence at the time of follow up, regards to immunotherapy, along with for early detection.

The event of pre metastases generation of a predetermined site is determined by refashioning of the ECM. MMPs are implicated in the liberation of soluble factors implicated in extra cellular recruitment In addition to expression of growth factor receptors in metastatic cells. These growth factors are VEGFR2, in Bone marrow (BM) obtained haematopoietic progenitor cells. MMP-9 has been seen to be overexpressed by endothelial cells as well as myeloid cells [61]. Tumor cell metastases is promoted by pre metastatic niches pre represented by BMDC along with Type IV collagen in the BM. This kind of collagen is liberated by a primary tumor in response to the hypoxic situations in the tumor surroundings, where BMDC's breakdown Type IV collagen via the expression of MMP-2 that aids in invasion as well as metastases growth [62].

Although lots of MMP inhibitors got generated maximum were a flop ,pointing that still lots has to be deciphered as far as the correlation of MMPs with cancer is concerned. Despite the negative factors lot of experts in this arena are persisting with the trying to generate useful anti MMP drugs [63].

The TIMP family inhibits the proteolytic action of various MMPs implicated in the invasion of tumors as well as metastases, Nevertheless, TIMPs can also take part in tumor growth, apoptosis along with angiogenesis [64]. All TIMPs get liberated but only TIMP-3 gets incorporated into the matrix. The glycosylation of TIMP-3, escalates its affinity for glycan-bound MMPs. Abnormalities of glycosylation is generally common in cancer [65]. Besides TIMP-3 antagonizing Matrix Metalloproteinases activity along with repress tumor growth, angiogenesis, the invasion of tumors as well as metastases [66], TIMP-3 possesses other functions not associated with MMP inhibition, like the apoptosis stimulation [67] along with inhibition of endothelial cell motility as well as proliferation [68,69]. As compared to TIMP-1 up regulation, there is lot of proof that TIMP-3 silencing occurs in a lot of human cancers [70].

Various authors demonstrated that silencing of the TIMP-3 gene is correlated with a good prognosis in various kinds

of cancer [71-74]. Additionally, other than its MMP inhibition function, it is also clear that TIMP-1 facilitates cell growth, along with proliferation besides inhibiting apoptosis, along with is possibly implicated in the control of angiogenesis. enhanced amounts of TIMP-1 mRNA along with TIMP-1 protein are observed in various kinds of cancers, as well as various clinical studies have demonstrated a positive correlation of raised TIMP-1 protein with a poor prognosis or tumor propagation in lung, brain prostate, can have both pro as well as anti tumoral actions. as compared to the constant along with reverse patterns of TIMP-1 along with TIMP-3, separate trends have been documented for TIMP-2 along with TIMP-4 in ovarian cancer that might be secondary to heterogeneity of the kinds along with stages of cancer [75]. TIMP- reduces cell proliferation, neo angiogenesis, along with tumor growth. The overexpression signalling proliferation decrease of TIMP-2, both have been reported in relation to a lot of clinical studies of breast, lung, gastric as well as colorectal cancer. Similarly of TIMP-2, silencing by epigenetic means via promoter hyper methylation in prostate cancer [76]. Expression of TIMP-2 points towards a good prognosis in certain kinds of cancers [77,78]. Conversely clinical studies demonstrate a correlation of greater TIMP-2 amounts with poor prognosis [79]. Akin to TIMP-2, observations have been there that TIMP-4 is up/down regulated in a variety of cancers. Studies in breast as well as prostate cancer have demonstrated an escalation in TIMP-4 in the early stages of the disease at the end during the invasive stages. Correlations with other TIMP's, lesser documentation of alterations in TIMP-4 have been seen [80-82].

Degranulation of TIMP results in a disturbed balance in key signals that start the pathways which result in the classical cancer steps of maintained signalling of proliferation, escape from growth repressors along with resistance to cell death, that aids in replicative immortality [75].

Currently, no particular changes known to be implicated in the propagation of cancer, like i) proliferation ii) survival iii) angiogenesis iv) aiding in replicative immortality v) invasion/migration along with vi) immunity escape [83], show that MMP along with TIMPs are implicated in the event of invasion along with metastases [84].

1) Control of Cell Growth

MMP-1, MMP-2, MMP-3 along with MMP-7 can regulate the growth of tumor cells by modes like liberation of precursors of growth factors which are attached to the cell membrane, manipulating the bioavailability of growth factors along with controlling cell proliferation signals [85]. MMPs inhibit tumor growth via the activation of transforming growth factor beta (TGF β) as well as formation of proapoptotic molecules [84]. TIMP's are thought to have a lot of cellular

functions, Specifically, the comparing actions of inhibiting tissue breakdown enzymes along with facilitating cellular growth [86]. TIMP-1 as well as TIMP-2 escalates the amount of Ras-GTP, Nevertheless, they utilize separate signalling pathways. TIMP-1 utilizes the tyrosine kinase/MAPK, signalling pathways, whereas TIMP-2 signalling utilizes protein kinase A, that has a direct role in the generation of Ras/phosphoinositide-3 - kinase (PI3-K) Complex [87]. Certain studies have pointed that the influence of TIMP-2 on cellular growth is brought about by its binding to MMP-2 on the Cell surface along with consequent activation of extra cellular-regulated-kinase (ERK) $\frac{1}{2}$ [88]. Nevertheless, TIMP-2 has separate functions as well as characteristics which are not dependent on its protease inhibitor activity. These characteristics are the activation of Shp-1 protein tyrosine phosphatase activity along with inhibition of tyrosine kinase receptor signalling by binding to $\alpha 3 \beta 1$ integrin on the cell surface. This mode of receptor in activation causes inhibition of growth factor-modulated proliferation of both tumor (fibroblast along with endothelial cell) as well as normal cells [77]. TIMP-2 further inhibits growth by activating adenylate cyclase, escalating intracellular cyclic adenosine monophosphate (cAMP) amounts as well as activating the SH2 tyrosine phosphatase-1 (SHP-1) protein, that decreases the activity of growth factor receptors along with inhibits the activation of MAPK [89].

2) Control of Apoptosis

MMP-7 along with ADAM10 imparts antiapoptotic activity to cancer cells by cleavage of the Fas ligand from the Cell surface [90]. Further this antiapoptotic activity of MMPs gets regulated by proteolytic detachment of proteins correlated to the tumor linked major histocompatibility complex (MHC) Class 1. TIMP-1 inhibits apoptosis [91]. It binds to the CD63 receptor as well as crosstalks with the $\beta 1$ subunit of integrins [92]. Subsequently the TIMP-1/CD63/ $\beta 1$ integrin complex constitutively activates the survival signals via the activation of focal adhesion kinase (FAKs), PI3-K, along with ERK [93,94]. TIMP-3 binds to ECM following liberation, that aids it to regulate peri cellular proteolysis via its robust inhibition of MMP, ADAM, along with ADAMTS [95]. Certain studies hypothesized that the antiapoptotic activity of TIMP-3 occurs secondary to inhibition of TACE (ADAM17) with the subsequent stabilization of TNF receptors [96]. Other evaluation corroborated that TIMP-3 stabilizes 3 unique receptors [-TNF receptor1, FAS along with TNF related apoptosis inducing ligand receptor1 (TRAIL 1) [97].

3) Control of Angiogenesis

Angiogenesis is necessary for tumor propagation. MMPs, mainly MMP-2, MMP-3, MMP-10, MMP-11, MMP-1, MMP-8, along with MMP-13, possess 2 functions in this event, facilitating in beginning (but simultaneously, they possess

a role in inhibition of angiogenesis [98,99]. MMPs start angiogenesis via breakdown of type IV collagen in the BM, Specifically MMP-9, that liberates angiogenic factors like VEGF, fibroblast growth factors b(FGF-b), which are bound to the ECM [100]. On the other hand MMPs further inhibit the event of angiogenesis by facilitating the cleavage of type XVIII collagen, generating andotanine along with liberation of urokinase type plasminogen activator receptors which are bound to the cell surface that are needed for the invasion from endothelial cells to fibrin [101]. At present it has been determined that all the 4 TIMPs possess antiangiogenic action [102]. Possibly TIMP-1 is implicated in the control of angiogenesis, though this is still a controversial topic [103]. TIMP-2's antiangiogenic action is brought about via crosstalk with $\alpha 3\beta 1$ integrin. As per studies over expression of TIMP-2 inhibited tumor growth along with angiogenesis by the up regulation of MAPK kinase phosphatase1, that dephosphorylates p38 MAPK, a molecule implicated in the proliferation along with migration of endothelial cells [104]. Additionally, TIMP-2 improves RECK expression that is a membrane-anchored protein possessing inhibitory action for mainly MMP-2, MMP-9, MMP-14, along with ADAM-10 [105], This antiangiogenic action TIMP-2 got localized to an area of a sequence of C terminal domain [106]. That might be the site of crosstalk with $\alpha 3\beta 1$ integrin. TIMP-3, similarly is a robust inhibitor of angiogenesis by binding directly to VEGFR2 along with blocks the VEGF action on endothelial cells [107]. Further TIMP-3, binds to angiotensin II type 2 receptor, along with overexpression of TIMP-3. In addition to angiotensin II type 2 receptor has additive inhibition of angiogenesis [108]. Little proof exists that crosstalk among endothelial cells along with pericytes, stimulates the expression of TIMP-3 in pericytes. TIMP-3 from this area in addition to TIMP-2 expressed in endothelial cells, takes part in vascular stabilization via inhibition of various MMPs In addition to ADAMs [109] along with probably by crosstalk with VEGFR2 [14].

4) Control of Invasion along with Metastases

Progression of tumor takes place by a lot of processes in which cell motility along with migration combine with proteolysis, tumor cell proliferation at the newer area, along with angiogenesis, besides being correlated with crosstalk of cells with the ECM [110]. MMPs are implicated in cell invasion along with migration that is correlated with the later generation of colonies in earlier anticipated areas. Basically utilizing the aid of MMP-2, along with MMP-9, they succeed in breaking down of Type IV collagen of the BM, and hence get into the blood along with lymphatic vessels [111].

The overexpression of every TIMP within cancer lines inhibits the migration of these cancer lines via migration, invasion, metastases along with consequent growth [8]. Various MMP-s possess the capacity for cleaving cell adhesion

molecules like cadherins, that bring about cell-cell contact along with integrins [112]. TIMP-1 represents an inhibitor of ADAM-10 along with TIMP-3 is the only inhibitor of ADAM-17. The overexpression of these TIMPs inhibits NOTCH signalling [80]. Certain transcription factors like TWIST 1 along with SNAIL bring about a switch in the expression of cadherin (like E- cadherin loss or N- cadherin gain) which promotes motility along with cell depolarization. SNAIL results in stimulation of TIMP-3 along with akin to that though independent of the metalloproteinases inhibitory function, the expression of TIMP-1 stimulates TWIST 1 to negatively control E- cadherin in cancer cells [113], whereas upregulation of this cadherin is induced via TIMP-2 .In case of fibroblasts ,the lack of TIMP-1 [114] as well as TIMP-3 [115] interferes with the action of cadherin along with cell-cell contact. Akin to that, the lack of TIMP-3 results in abnormal cellular distribution of E- cadherin along with associated β -catenin signalling [115]. Proof is there to demonstrate the liberation of TIMP-1, TIMP-3,or TIMP-4 inhibits the invasive event, whereas the liberation of TIMP-2 escalates this event [115]. Despite the TIMP-1-Metalloproteinase balance could regulate the matrix alignment, density along with rigidity, the proof corroborating this posit is minimal. Lysyl oxidase (LOXL) that crosslinks the collagen fibrils facilitates tumor cell motility [116]. Deletion of LOXL2 in cancer cells reduces the invasion along with TIMP-1 amounts. The generation of a metastatic niche is thought to be dependent on particular components of the ECM which are tenascin 2004:48:proteins [117], along with the overexpression of the isoforms of tenascin changes the expression of TIMP-3 along with MMPs [118].

5) Control along with Surveillance via Immune System

MMPs possess a significant part in immunity escape along with activation again of TGF β , by which it indirectly controls the action of T lymphocytes. Implication of this is that in cancer tumor MMPs can indirectly influence the function of leukocytes, since chemokines are the direct MMP targets which avoid these molecules from working like chemo-attractants [119]. In the tumor evolution aberrations of cell proliferation along with death signals In addition to, inflammation which facilitates the tumor along with the pleiotropic cytokine TNF- β having the capacity to start these events .Akin to the physiological inhibitor of ADAM-17, TIMP-3, besides controlling TNF binding to the membranes against the systemic TNF, it also controls its2 receptors (TNFR1 as well as TNFR2) that are liberated into the blood. Lack of TIMP-3 results in escalatation of TNF signalling along with the inflammatory response secondary to the dysregulated action of ADAM-17 [120]. TIMP-3 is necessary for restricting inflammation. TIMP-3 deletion might escalate IL-6 generation through the TNF- α nuclear factor κ B (NF κ B) axis [121].

6) Control of Inhibitory Signals for Growth

Trying to find the part of MMPs along with cancer propagation via proteolysis has aided in the generation of drug inhibitors of these enzymes [122]. To begin with, the transcription of MMPs gets inhibited, that persists in blocking the pathway which guides the transduction that initiates signals, like MAPK pathway along with ERK pathway, hence sending nuclear factors for inhibition of the expression of MMPs [396]. TIMPs can be controlled at the transcriptional level of different cytokines along with growth factors, causing tissue particular constitutive, or inducible expression. TIMP-1 expression that encodes genes can be controlled by TGF β . Rest of inhibitors (TIMP-2 along with TIMP-4) have lesser proneness to the actions of cytokines [123]. Overexpression of particular miR's robustly escalating the start along with propagation of cancer via repression of TIMP proteins. miR-221 along with/or miR-222 can act on TIMP-3, stimulating drug resistance In addition to promoting cellular growth in various kinds of cancer via ADAM-10 along with ADAM-17 based signalling [75]. TIMP-3 repression is brought about by members of the family members of miR-181. Intriguingly it has been demonstrated that TGF β , whose action is controlled by TIMPs, stimulate miR-181 via SMAD4 [75]. The miRs implicated in inflammatory diseases, like miR-21 stimulate the silencing of TIMP-3 [124]. miR-196 causes repression of TIMP In addition to escalates the expression of MMP-1 In addition to MMP-9 indirectly via mitochondrial protein nucleoside diphosphate kinase 4 (NME4) along with N-terminal kinase of June[120]. The miRNA-TIMP axis has been posited as a treatment target for vicious or drug resistant human cancers. Hence new insight regarding the part of MMPs along with TIMPs in all stages of cancer propagation In addition to tumor surroundings could open new directed strategies regards to cancer therapy in the form of adjuvant treatments in early or advanced disease stages [125]. Although here our aim had been to discuss with regards to gynaecological malignancies, this is applicable for all body malignancies.

Utilization of MMP and TIMP Inhibition for Therapy

With the insight with regards to biology of MMP along with the control resulted in the generation of basic as well as preclinical experimental work in animal models besides clinical research in patients with any kind of pathologies involving gynaecological, other fields along with inflammatory problems but maximum was in cancer. These studies have mainly laid concentration on MMPs, in view of thoughts that their aetiology is related to changes in significant physiological modes which result in aberrant angiogenesis, apoptosis along with immune modulatory action, thus aiding in growth of tumor as well as/or metastases [126]. Pharmacological industry gave monetary

support for research with regards to the generation of broad spectrum MMP inhibitors, nevertheless, the exact physiology in addition to biology of MMP's, besides how they have evolved with regards to time along with control by separate molecules are not clear. Clinical trials did not get the anticipated outcomes, deteriorating the prognosis of disease, in view of delivery in advanced stages resulting in side effects like musculoskeletal toxicity [126]. Currently it is known that MMP's participate in physiological events like embryogenesis, angiogenesis, tissue remodeling, bone generation, wound healing, Mammary involution, promotion of liberation of signalling molecules, cell migration, activation of signalling molecules along with immunity [126]. The following are the MMP inhibitors In addition to the treatments which work against MMP's are detailed here.

Hydroxamate Dependent Inhibitors

The initial molecules that got generated were hydroxamate dependent inhibitors. Their bases is on the structure of collagen along with mainly implicate compounds that possess a backbone that have been fashioned to simulate the normal peptide substrate of the wanted MMP's along with a group which chelates the catalytic Zn^{2+} ion. They decrease the aid of the remaining of the compounds to the inhibitor-enzyme binding event, thus aiding widespread inhibition. Certain examples of this kind of drug are marimastat, ilomastat as well as batimastat. Of these batimastat was the first MMP inhibitors to enter clinical trials, In addition to that it was demonstrated to inhibit various MMP's, that are MMP-1, MMP-2, MMP-7, along with MMP-9 showing antitumor actions in animal models of human ovarian cancer, colorectal cancer ,melanoma along with haemangioma. Marimastat was observed to be inefficacious besides resulting in musculoskeletal side effects in a randomized phase III trial for metastatic breast cancer cases which were stable or responding following first line chemotherapy. The reason for the musculoskeletal pain is believed to be secondary to the inhibition of ADAM as well as ADAMTS family members, that are ADAM17. Usually MMP inhibitors have been found to be delivered very late for making any change, since basic work was conducted in early stages of the disease as well as Clinical work was meant to be a last resort in the therapy of terminally ill patients [126].

Newer Hydroxamate Dependent MMP Inhibitors Formation

These ones have been formed to have greater specificity, with a view of reducing the side effects. MMI270, MMI-166, PD-166793, ABT-770, cipemastat, along with prinomastat. MMI-166 represents a selective inhibitor of MMP-2, MMP-9, along with MMP-14. PD-166793, prinomastat as well as ABT-770 were generated to prevent binding to the "shallow

pocket' of MMP-1, dependent on the thought (at that particular time) that MMP-1 sparing inhibitors might not result in musculoskeletal side effects. Cipemastat, that inhibits MMP-1, TIMP-3, along with MMP-9, was utilized for the therapy of rheumatoid arthritis (RA), as well as osteoarthritis, although it could not avoid the propagation of joint damage.

Non - Hydroxamate Dependent MMP Inhibitors

Hydroxamic acid are usually metabolically labile but there exist a lot of other zinc -binding groups which are stable. Reverse Hydroxamates as well as non hydroxamate inhibitors, like carboxylates, hydroxy carboxylates, sulfhydryls. Phosphoric acid derivatives as well as hydantoin got generated to prevent the drawbacks linked to with the 1st generation MMP inhibitors, like metabolic inactivation, besides the chelation of metals of rest of metalloproteins [126]. MMP structure has been illustrated with the aid of crystallography along with novel inhibitors have been fashioned with different peptidomimetic as well as non peptidomimetic backbone, structures. Rebamastat, which is a thiol zinc-binding groups, represents a wide spectrum MMP inhibitor; nevertheless, a phase II trial for early stage Breast Cancer, besides a phase III trial in nonsmall cell lung carcinoma both documented side effects [126]. Tanomastat was shown to have problems with the dosing along with timing of delivery linked to disease propagation, besides the effectiveness of this agent was demonstrated to be variable, with controversial outcomes being derived based on the timing of delivery [79]. Ro28-2653 inhibits MT -MMP, MT3-MMP, MMP2, MMP8 as well as MMP9 yet spares MMP-1 along with ADAM17 activity. Various promising experimental work in animal models has shown its antitumor along with anti angiogenic action but they did not move to Clinical trials [126]. Robust inhibitors of MMP-13 as well as MMP-12 got generated utilizing the alternate zinc -binding group hydantoin. Various biphenyl sulphonamide carboxylate MMP inhibitors got fashioned for therapy of osteoarthritis via inhibition of MMP-13. Tetracycline antibiotics, like doxycycline along with minocycline, possess innate MMP inhibitory ability. Doxycycline has been indicated for the therapy of periodontal disease as well as is the only collagenase inhibitor that has got approval from US Food and Drug Administration (FDA) for any kind of human disease [126].

Alternate Binding Sites Getting Targeted

For decreasing the off target actions seen in clinical trials, besides preventing wide MMP inhibition in view of a big structural homology of the various MMPs. Current work has shifted from targeting the catalytic area to alternate ones that have been lesser conserved sites. Besides the Zn²⁺

ion in their catalytic area, MMPs have subsites (S) labeled as unprimed or primed. The P'-S1' crosstalk is the major factor that determines the affinity of inhibitors along with cleavage positions of peptide substrates. Like extension of the P1 substituent was utilized to obtain selectivity of MMP-13 above the markedly homologous MMP-2. The utilization of NMR along with X-ray crystallography techniques in addition to, computational strategies that aid in modeling of drug-protein Crosstalk with Non-Hydroxamate dependent MMP inhibitors which bind to sites other than catalytic. Lot of these inhibitors showed good MMP-13 selectivity which lead to decreased clinical symptoms when evaluated in a mouse model of RA as well as osteoarthritis. The combined techniques with computational anticipation showed hidden areas in the MMP structure, that cannot get utilized to form a rational fashioning of novel molecular effectors as well as therapeutic targets [126].

Treatment which is Antibodies Based

These molecules possess great selectivity besides having lot of functional blocking antibodies. Selectively they target membrane anchored MMPs. The markedly selective antibody-dependent MMP-14 inhibitor DX-2400 has demonstrated antitumor anti angiogenic, along with anti invasive characteristics, besides blocking MMP-14- based pro- MMP-2 processing. MMP-14 inhibitory antibodies have got successfully evaluated in vivo and in vitro. Depending on the 3-D structure as well as amino acid sequence of MMP-13, that is a neutralizing antibody which binds to the active form of MMP-13, without binding the latent form or to other MMPs was generated [126].

Endogenous Inhibitors of MMP Function-A

Polymyxin-conjugated α -2 macroglobulin is a big serum protein which controls MMP function. MMP's are embedded within the macroglobulin, hence avoiding the MMP's from coming across large substrates. Polymyxin-conjugated α -2 macroglobulin showed protective action in mouse models of sepsis, with this action being correlated with binding to along with neutralizing inflammatory cytokines; MMP inhibition has not got evaluated [126].

Theoretically TIMPs represent the basis for another innovative class of MMP inhibitor, nevertheless, they have hardly been thought of. They have been utilized in model system's to give key clues regarding the effectiveness of MMP inhibitors in various diseases. Nevertheless, TIMPs besides inhibiting MMPs, in particular cases they can indirectly facilitate MMP action. Like, domain- particular overexpression of TIMP-2 as well as TIMP-3 illustrated the independent functions of TIMPs at the time of generation [126].

Despite TIMPs have been believed in present treatment approaches for the control of MMPs, in particular in various diseases, no success. Propagation has got attained in this field, that is probably in view of the fact that certain diseases share akin pathways or modes of action where MMPs as well as TIMP-3 intervene besides not playing common parts. Usual events of the MMPs various diseases are inflammation, cell death, along with migration, of rest. Getting insights regarding subtleties of MMP biology is not enough, hence it is essential to think of crucial points to enhance understanding in this particular area of study.

Discussion

Despite detailing the etiopathogenesis by which MMPs and TIMPs modulate various obstetric and gynaecological diseases like PCOD, IUGR, preeclampsia, spontaneous abortion and newer roles in DUB, Endometriosis in addition to various aspects of cancer manipulation the limitations of this study is that although a lot of MMP inhibitors have been developed yet no satisfactory agent has been generated thus far, with their complications being the limiting factor. Nevertheless, getting this insight is significant in the sense that with newer advances and knowledge with regards to the extracellular Vesicles (ECV's) one can generate innovative therapies of supplying a particular MiRNA, other substances and as per desire modulate as per the etiopathogenesis of the diseases via the ECVs and hence might aid in cancer regulation besides placentation abnormality etc.

Conclusion

Till date, no precise treatment dependent on MMP inhibition has become available for the Clinical utilization in chronic diseases, hence newer approaches are required for proper utilization of the advantages by the understood modes of MMPs as well as TIMP-3. The inhibition of MMP liberation as well as/or function in the right place with the aim of giving a better quality of life (Q.O.L) to those patients with an illness linked to the impairment of control of MMPs implicated in maximum diseases might be beneficial. It is essential to keep conducting research for evaluation of the part played by in maximum diseases like in MMP-2 along with MMP-9. The functions of MMPs are tough to anticipate as already known, Nevertheless, by having insight regards to mode by which they work for deterioration of diseases, can be advantageous, besides working in form of treatment, as bio-markers, along with risk anticipators of diseases. It is clarified here how much heterogeneity in the status of TIMPs based on the various diseases, since they vary in the kinds of crosstalk that they go through various MMPs along with independently of MMPs. Nevertheless, a generalized escalation of in TIMP-1 along with generalized silencing of TIMP-3 can be seen as the the disease advances along with

deterioration of prognosis occurs. Extra studies are essential for the particular evaluation of these endogenous inhibitor in various chronic diseases. Alternate strategy to the treatment of MMP-associated diseases could get utilized for engineering of TIMPs possessing limited inhibitory specificities. Further widening of our horizon on the particular part of MMPs as well as TIMP-3 via studies along with evaluation of the MMPs actions at the post translational level, in view of maximum studies in the literature have only analyzed transcriptional action, with little insight on intracellular actions of MMPs to know the relevant functions of pathological significance which could yield greater knowledge on the various parts played by MMPs as well as TIMP-3 in the various diseases. Moreover it is essential to carry out greater in vivo work to illustrate the functions of MMPs as well as TIMP-3, since it is not currently possible to illustrate how these are controlled/impairment of control, besides finding which substrates interfere in various events. More Evaluation is needed for finding the actions of MMPs under pathological along with non pathological disorders.

Further recently Timokhina et al conducted a retrospective study that included 92 pregnant women at a gestational age of 26-38 weeks, of which the principal group consisted of 61 patients with severe PE. They divided the principal group into two subgroups: the first subgroup was named the severe early-onset preeclampsia (EO-PE) group and consisted of 30 pregnant women. The second group was designated the severe late-onset preeclampsia (LO-PE) group, comprising 31 patients. They determined the plasma concentrations of MMPs 2 and 9 in the groups with an ELISA. They observed that in the group of PE patients with both EO-PE and LO-PE, the amount of MMP-2 was significantly higher as compared to the women undergoing normal pregnancy; besides that they did not find any significant variation on comparison of the amounts of MMP-2 in the subgroups with EO-PE as well as LO-PE. Evaluation of the amounts of MMP-9 in EO-PE and LO-PE subgroups illustrated ameliorated amounts of MMP-9 in both groups relative to the control group. Further they observed a decreased amount of MMP-9 in the EO-PE group as compared to the LO-PE group. Thus concluding that the significantly escalated amounts of MMP-2 in women-both in the EO-PE and LO severe PE subgroups-reason out the participation of this enzyme in endothelial impairment in the second stage of severe PE. A decrease in MMP-9 in the EO-PE group validated the participation of MMP-9 in the event of spiral artery transformation [127].

Earlier we have reviewed role of prokineticins in reproduction [128] Su MT, had documented the role of miR-346 and miR-582-3p in controlling EG-VEGF expression and trophoblast invasion via matrix metalloproteinases 2 and 9 [129]. Further earlier we had reviewed the role of epigenetics in Preeclampsia, and recently the role of Extracellular Vesicles

(ECV's), in human reproduction and how we can utilize their cargo like miRNA's in treating various metabolic diseases like DM, and similarly might utilize them for targeting miR's along with MMP's in Preeclampsia [130-132].

Ding et al. revealed that miR-519-d-3p suppresses invasion and migration of trophoblast cells via targeting MMP2 [133].

Further members of the placenta-specific miRNA cluster C19MC, including miR-519d, are secreted by fetal trophoblast cells within extracellular vesicles (EVs). Earlier we have reviewed the role of ECV's in human reproduction besides their roles in carrying different microRNA's besides proteins, lipids and nucleic acids in their cargo [131,132]. Recently Chaiwangyen et al. demonstrated that trophoblast-derived EVs can be internalized by the autologous trophoblast and surrounding maternal immune cells, resulting in coordination of cellular responses. The study of functions and targets of placental miRNAs in the donor and recipient cells might aid in getting insight of the immune tolerance that is necessary in pregnancy. Here, they documented that miR-519d-3p levels were associated positively with cell proliferation and negatively with migration in trophoblastic cell lines. Inhibition of miR-519d-3p in JEG-3 cells increases caspase-3 activation and apoptosis. PDCD4 and PTEN are targeted by miR-519d-3p in a cell type-specific manner. Transfection of trophoblastic cell lines with miR-519d mimic results in secretion of EVs containing elevated levels of this miRNA (EVmiR-519d). Autologous cells enhance their proliferation and decrease their migration ability when treated with EVmiR-519d. NK92 cells incorporate EV-delivered miR-519d-3p at higher levels than Jurkat T cells. EVmiR-519d increases the proliferation of Jurkat T cells but decreases that of NK92 cells. Altogether, miR-519d-3p regulates pivotal trophoblast cell functions, can be transferred horizontally via EVs to maternal immune cells and exerts functions therein. Vesicular miRNA transfer from fetal trophoblasts to maternal immune cells may contribute to the immune tolerance in pregnancy [134]. Besides other authors have shown how ECV's might be used in other disorders [135].

Moreover Selective intrauterine growth restriction (sIUGR) is a disorder of monochorionic (MC) twin pregnancies. However, the underlying mechanism remains largely unknown. Trophoblast cells are the major component of the placenta. Dysfunction of trophoblast cells is associated with placental dysfunction. In their earlier study, Wenetal [136] identified miR-338-5p is down regulated in placenta tissues sharing larger twins of sIUGR. In the present study, they aimed to investigate the role of miR-338-5p in trophoblast cells and explored its target. Their results further indicated that miR-338-5p was down regulated in placental tissues supporting larger twins of sIUGR, whereas

epidermal growth factor-containing fibulin-like extracellular matrix protein 1 (EFEMP1) was upregulated. Moreover, miR-338-5p overexpression suppressed the growth and invasion of trophoblast cells. Importantly, results from luciferase reporter assay demonstrated that miR-338-5p bound on the 3'-UTR of EFEMP1. miR-338-5p suppressed the growth and invasion of trophoblast cells via targeting EFEMP1. Further, miR-338-5p/EFEMP1 might disrupt the function of trophoblast cells via inhibiting the phosphorylation of AKT [136].

Earlier Li et al. had evaluated the differential expression of same miR-338-5p of the sa miR-338-5p in gliomas and the role of miR-338-5p in glioma cell invasion via its potential target gene TSHZ3 encoding Teashirt zinc finger homobox 3, predicted by bioinformatics, and matrix metalloproteinase 2 (MMP2), the key pro-invasive protease overexpressed in gliomas. Quantitative real-time reverse transcription PCR (qRT-PCR) and Spearman correlation analysis were used to determine differential expressions of miR-338-5p and TSHZ3 in astrocytic gliomas of different grades (n = 35) and glioblastoma cell lines (U87 and U251) in comparison to non-neoplastic brain (NNB) tissues (n = 6). Western blotting was used to determine the protein levels of TSHZ3 and MMP2 in glioblastoma cell lines and Matrigel invasion assay to examine the role of miR-338-5p in cell invasiveness. The results demonstrated that the expression of miR-338-5p, normalized to hsnRNA U6, was significantly higher in grade III and IV gliomas and glioblastoma cell lines in contrast to that in NNB and grade II gliomas, whereas TSHZ3 expression, normalized to GAPDH, was inversely related to miR-338-5p (R = -0.636, P < 0.01). Luciferase assays showed TSHZ3 to be a target gene of miR-338-5p. In both U87 and U251 cells, miR-338-5p mimics increased MMP2 and invasiveness of the cells. Overexpression of ectopic TSHZ3 suppressed the cell invasiveness and attenuated the pro-invasive effect of miR-338-5p mimics. Overall, their results demonstrated that miR-338-5p has a function in promoting glioma cell invasion by targeting TSHZ3 suppression on MMP2. In conclusion, miR-338-5p is a possible potential biomarker for the diagnosis and target for therapy of high-grade glioma [137].

This intricate insight has resulted in not only treating tumours, utilizing ECV's, but intricate knowledge of molecular modes like MMPs with micro RNA interaction might aid in developing therapies by delivering ECV's from particular microRNA implicated in the pathogenesis of diseases like preeclampsia, IUGR, besides lot of malignancies [138].

Moreover how curcumin might be participating in endometriosis treatment was by targeting MMP2 as well as 9, besides further melatonin might target by attacking MMP3 along with apoptotic pathways [139-142].

Further Grzechocinska et al. demonstrated how there was an absence of association among lack of correlation between proMMP-2 along with MMP-2 amounts point that separate pathway of their activation in AUB. ProMMP-2 is up regulated by estradiol and down regulated by progesterone while MMP-2 levels increase with the length of bleeding [143]. This way with knowledge given by Johanns et al with regards to Cellular uptake of proMMP-2:TIMP-2 complexes by the endocytic receptor megalin/LRP-1, with earlier knowledge on how low-density lipoprotein receptor-related protein-1 (LRP-1) mediates the clearance of a complex between the zymogen form of MMP-2 (proMMP-2) and tissue inhibitor of metalloproteinases, TIMP-2, in HT1080 human fibrosarcoma cells. Here they demonstrated that, in BN16 rat yolk sac cells, proMMP-2: TIMP-2 complex is endocytosed through a distinct LRP member, megalin/LRP-2. Addition of receptor-associated protein (RAP), a natural LRP antagonist, caused accumulation of endogenous proMMP-2 and TIMP-2 in conditioned. They concluded that megalin/LRP-2 can efficiently mediate cell-surface binding and endocytosis of proMMP-2: TIMP-2 complex. Therefore megalin/LRP-2 can be considered as a new actor in regulation of MMP-2 activity, an enzyme crucially involved in many pathological processes. Thus more and more insight is being developed regarding targeting DUB with various MMP pathways [144]. Further Yohan et al showed how targeting the MMP-14/MMP-2/integrin $\alpha_v\beta_3$ axis with multispecific N-TIMP2-based antagonists might be utilized for cancer therapy thus utilizing the newer MMP-14 or membrane type 1 (MT-1-MMP) axis [145].

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