

IMPACT OF GENETIC POLYMORPHISMS IN MMPS ON THE RENAL ALLOGRAFTMansi Bhatt¹ (M.Sc.) and Aneesh Srivastava*¹ (MS, M.Ch.)

Department of Urology & Renal Transplantation, Sanjay Gandhi Postgraduate Institute of Medical Sciences (SGPGIMS), Lucknow, India.

***Corresponding Author: Prof. Aneesh Srivastava**

Department of Urology & Renal Transplantation, Sanjay Gandhi Postgraduate Institute of Medical Sciences (SGPGIMS), Lucknow, India.

Article Received on 01/01/2019

Article Revised on 22/01/2019

Article Accepted on 12/02/2019

ABSTRACT

Renal transplantation (RT) is currently the most effective replacement therapy and believed as a boon for patients with end-stage renal disease (ESRD). The short-term outcomes of transplant have improved significantly, whereas the long term outcomes are still fairly compromised. The role of early acute rejections with their impact on long term graft survival has been widely recognized as one of the most important factor. The Matrix metalloproteinases (MMPs) are traditionally evolved as antifibrotic players in the development and progression of chronic kidney diseases and ESRD in which RT is required. The goal of this review is to highlight the role of MMPs as biomarkers in RT; their impact on the rejection process and therefore longevity of the graft; on the therapeutic regimen and on the delayed graft function. We found that MMP-1, MMP-2, MMP-7, MMP-9 and MMP-20 have impact on renal transplant and allograft rejection. They represent as new mediators involved in acute kidney transplant rejection. MMP-1, MMP-7, MMP-9, and MMP-13 represent as potential molecular allograft rejection markers. MMP-9 was also found associated with delayed graft function. Complementary therapy of allograft rejection and pre-transplant allograft outcome can be predicted due to enhanced allograft survival in mutant allele carriers for MMP-2.

KEYWORDS: Renal transplantation; Allograft rejection; Biomarkers; Delayed Graft Function; Matrix metalloproteinases (MMPs).

1. An Introduction to MMPs

The Matrix metalloproteinases (MMPs) are a large family of zinc-dependent endopeptidases that are collectively capable of proteolyzing all components of the extracellular matrix compartment (ECM).^[1,2] They were first discovered by Gross and Lapierre^[3] when the authors described collagenase activity in metamorphosing tadpoles. Since then, the number of known MMPs as well as their characterized functions has risen dramatically.^[4,5] Thus, MMPs play a multitude of roles in regulating a diverse array of biological processes such as embryonic development, tissue homeostasis, tumorigenesis, and organ fibrogenesis.^[1,6]

MMPs collectively known as matrixins are proteinases that participate in ECM degradation^[7,8] and these are increasingly known to be able to cleave a wide variety of substrates, which range from cell surface receptors and adhesion molecules to growth factors and cytokines. This broad spectrum of substrates enables MMPs to be a critical player not only in regulating ECM remodeling but also in controlling many cell behaviors such as cell proliferation, migration, differentiation, angiogenesis, and apoptosis.^[9,4] MMPs are expressed in both developing and adult kidneys, and they are implicated in regulating nephron formation and the pathogenesis of kidney diseases.^[1] In light of their proteolytic potential,

MMPs are traditionally conceived as antifibrotic players in the development and progression of chronic kidney diseases (CKD) and end-stage renal disease (ESRD) in which renal transplant or some other kind of renal replacement therapies are required.

We therefore attempt to highlight the role of MMPs as biomarkers in Renal Transplant, their impact on the rejection process and therefore longevity of the graft, on the therapeutic regimen and on the delayed graft function in this mini review. In this present study we included the entire positive and the negative studies showing association between Renal Transplantation and MMPs (Please see Table 1). Using the terms (MMPs & Renal Transplantation; MMPs & Renal Allograft Rejection and MMPs & Kidney Transplantation); we searched PubMed for all reports of original research, with English language restriction. We included reports which met the following criteria (1) MMPs in Renal Transplantation between recipients and donors, (2) MMPs in Renal Allograft Rejection, and (3) MMPs in Acute & Chronic Kidney Rejection. These criteria were an absolute requirement for inclusion of a report in the study.

2. MMPs and Kidney Transplantation

Kidney transplantation provides kidney failure patients the best opportunity to live longer and improves their

quality of lives and is currently the most effective replacement therapy for patients with ESRD. Survival after renal transplant is better compared with age matched individuals remaining on the transplant waiting list.^[10,11,12,13] During the last decade, renal allograft survival rates have increased significantly at 1 year after transplant.^[14,15] This is related to improvements in tissue typing, better understanding of immunology of the transplant, the use of more potent immunosuppressive regimens, and better clinical management of recipients preoperatively and postoperatively.^[16,17]

Whereas the short-term outcomes of transplant have improved significantly, the long term outcomes are still fairly compromised.^[18,19] There are many factors which have a significant impact on the overall outcome and the role of early acute rejections with their impact on long term graft survival has been widely recognized as one of the most important. The survey of existing literature revealed that MMPs do actually play a critical role though it was riddled with some controversies. Their role as potential biomarkers during the pre-transplant evaluation of the patient is under evaluation. They have also been found to have evolving role in delayed graft function and complementary therapies in Renal transplant.

3. MMPs in Renal Transplant and Allograft Rejection

Acute and chronic allograft rejection remains to be one of the crucial impediments in successful renal transplantation. Allograft rejection is characterized by coordinated infiltration of T cells and macrophages, which induce the immune-mediated tissue destruction of the allograft, features associated with qualitative and quantitative alterations in the ECM.^[20] The major regulators of ECM turnover are matrix metalloproteinases (MMPs), which represent the major group of zinc-dependent matrix-degrading proteases. Furthermore, MMPs are involved in various pathological conditions associated with cell migration, tissue invasion by lymphocytes and inflammation.^[8,21] In addition, they are also involved in the regulation of the immune response by degradation and activation of several cytokines and chemokines.^[22] Few recent studies have demonstrated increased expression of MMP levels associated with kidney allograft rejection.^[23,24]

Leukocyte invasion and tissue destruction, associated with qualitative and quantitative alterations in the ECM characterizes acute cellular allograft rejection. MMPs that are zinc dependent endoproteinases mainly regulates metabolism of ECM proteins. MMP- 2 and MMP-9 are basement membrane degrading MMPs. These MMPs also facilitate tissue invasion of leukocytes and MMP-2 exerts a direct pro-inflammatory effect upon glomerular mesangial cells.

Alterations in the extracellular matrix compartment and changes in the proliferation rates of various cell types

lead to chronic renal allograft rejection.^[25] Metzincin super family of metallo-endopeptidases, including matrix metalloproteinases (MMPs) controls these features.^[26,27]

While rates of acute rejection (AR) continue to decrease, it remains the strongest predictor of long-term allograft survival.^[28,29,30,31and32] Better understanding of factors predicting AR may contribute to more individualized patient care. Environmental factors associated with AR have been evaluated in the past.^[33,34and35] Similarly, literature discussing genetic predictors of AR has emerged in recent years. Indirect evidence that AR might indeed be associated with genetic factors come from expression studies demonstrating that gene expression profiles between rejecting and non-rejecting kidneys are different.^[36,37]

It therefore appears that, the study of the role of MMPs in transplant rejection process may also lead to novel approaches in the therapy of rejection processes.

4. Members of the Matrixin Family

To date, 28 MMPs have been found in humans^[1], who share a large amount of common structural and functional similarities, however, differ in their substrate specificities.^[38] Matrixins are also found in Hydra^[39] sea urchin,^[40] and Arabidopsis.^[41] The sequence homology with collagenase 1 (MMP-1), the cysteine switch motif PRCGXPD in the propeptide that maintains MMPs in their zymogen form (proMMP), and the zinc-binding motif HEXGHXXGXXH in the catalytic domain are the signatures used to assign proteinases to this family. MMP-23 is the exception, which lacks the cysteine switch motif, but its amino acid sequence of the catalytic domain is related to MMP-1. On the basis of substrate specificity, sequence similarity, and domain organization, vertebrate MMPs can be divided into six groups (collagenases, gelatinases, stromelysins, matrilysins, membrane type, and other).^[42] (See Table1).

4.1. Collagenases

Collagenases have ability to cleave interstitial collagens I, II, and III at a specific site three-fourths from the N-terminus. These enzymes can also digest a number of other ECM and non-ECM molecules. Several MMPs like MMP-1, MMP-8, MMP-13, and MMP-18 (Xenopus) are in this group.

MMP-1 and MMP-13 is from collagenases I and collagenases III respectively and are located on chromosome 11q22.3. MMP-1 and MMP-13 from this group is related to renal transplant and allograft rejection episodes. MMP-1 was increased in patients with acute rejection compared with those with stable graft function and healthy donors.^[43] Likewise, in a study renal transplant recipient groups had higher MMP-13 levels than healthy group.^[44] More positively and negatively associated studies of MMP-1 and 13 with renal transplant are presented in table 2.

Previous *in vitro* studies regarding the effect of Cyclosporine A (CsA) on MMP production gave variant findings^[45, 46,47,48&49] The study by Emingil *et al.* 2010^[44] investigated MMP-13 levels in patients under different immunosuppressive therapies for the first time. In conclusion, the results of the study indicated that CsA and Tacrolimus therapy do not have a significant effect on MMP-13 levels. These results showed that CsA and tacrolimus therapy do not have a significant effect on MMP-13 levels. On the other hand, Emingil *et al.* 2010^[44] have recently found that tacrolimus could slightly but significantly elevate the serum level of MMP-8.^[50] It seems that tacrolimus can *in vivo* up-regulate the systemic serum MMP-8 level and seemingly strengthen the defensive process.^[51,52,53&54] Ong *et al.* 2016^[55], in their study found that the effect of MMP-1 gene polymorphisms on NODAT (New-onset diabetes after transplantation) in renal transplant patients were significantly high after use of Tacrolimus. They also showed that Tacrolimus elevated the serum MMP-1 level and can be the risk factor for NODAT in renal transplant patients.^[56]

4.2. Gelatinases

Gelatinase A (MMP-2) and gelatinase B (MMP-9) belong to this group. They readily digest the denatured collagens, gelatins. These enzymes have three repeats of a type II fibronectin domain inserted in the catalytic domain, which bind to gelatin, collagens, and laminin.^[57] MMP-2 digests type I, II, and III collagens.^[58,59]

4.2.1. MMP-9

MMP-9 is among the biggest members of the MMP family described so far. It is the major structural component of basement membrane.^[60] MMP-9 of the gelatinases subfamily of MMPs has been widely studied in renal transplant models for acute and chronic allograft rejection.^[61,62] MMP-9 (gelatinase B) degrades collagen Types IV and V.^[63] In the kidney, collagen Type IV is present in basal membranes, whereas fibronectin, laminin and collagen Type V constitute the tubulointerstitial matrix.^[63] The MMP-9 gene located on chromosome 20q11-q13 encodes the 92-kDa collagenase IV. In the coding region of the MMP-9 gene, 836A>G in exon 6 (rs17576, Gln279Arg), 1721G>C in exon 10 (rs2250889, Pro574Arg) and 2003G>A in exon 12 (rs17577, Arg668Gln), resulting in missense amino acid substitution and thus influencing the substrate and inhibitor binding capacity.^[64,65] The 836A>G polymorphism in exon 6 of MMP-9, commonly referred to as Q279R, occurs in the coding region within the fibronectin Type II domains that play important roles in substrate binding.^[66] The 1721C>G and 2003G>A polymorphisms, commonly referred to as P574R and R668Q, respectively, are also located in the coding region of the gene, which are in the hemopexin domain and are thought to affect both substrate and inhibitor binding.^[67] Therefore, these polymorphisms potentially alter the protein structure of MMP-9 and may have some

functional relevance and affect an individual's susceptibility to allograft rejection.

The molecular epidemiologic study by Singh *et al.*, 2010^[68] examined the mutant allele carriers (GA+AA) for MMP-9 (2003G>A) SNP in exon 12. The study revealed that this polymorphism was significantly associated with reduced risk for allograft rejection and suggested that the mutant allele carriers for the polymorphism had a beneficial effect and thus, reduced susceptibility for allograft rejection in North Indian cohort of renal transplant recipients. This could serve as an ideal marker to predict pre-transplant allograft outcome. The significantly reduced risk for allograft rejection inferred by mutant allele carriers (GA+AA) for MMP-9 2003G>A in exon 12, suggested that substitution of arginine by glutamine may have resulted in reduced substrate and inhibitor binding and, therefore, reduced MMP-9 expression subsequently resulting in reduced proteolytic cleavage of basement membrane, the major cause of allograft rejection. MMP-9, have been most widely associated with allograft rejection, suggesting a significantly increased gelatinase expression at the time of rejection. Recently, MMP-9 has been suggested to play a critical role in the development of tissue remodeling and fibrosis in the renal allograft.^[62] The distribution of MMPs on the basis of antibody-mediated and cellular rejection suggested a significantly increased risk for cellular rejection in rejecters with variant allele for MMP9 1721C>G in exon 10.^[68] These, findings in the study demonstrated enhanced allograft survival in mutant allele carriers for MMP-9 2003G>A which may offer an opportunity to predict pre-transplant allograft outcome and subsequently be used in complementary therapy of allograft rejection.^[68]

In another landmark study by Ermolli *et al.* 2003,^[69] MMP-9 showed a small but significant increase during the rejection process and appeared to represent as a new mediators involved in acute kidney transplant rejection. Rödder *et al.* 2010^[70] in their study represented MMP-9 as potential molecular AR markers. With regards to the delayed graft function, another studies on MMP9 by Turunen *et al.* 2015^[71] and Kamińska *et al.* 2018^[72] have shown positive association. For some more studies between MMP-9 and renal transplant please see table 2.

4.2.2. MMP-2

MMP-2 of the gelatinases subfamily of MMPs have been widely studied in renal transplant models for acute and chronic allograft rejection.^[61,62] MMP-2 (gelatinase A) predominantly degrades fibronectin and laminin.^[63] The MMP-2 gene encoding 72-kDa collagenase IV is located on chromosome 16q21. MMP-2 (-735 C>T) transition located at a core recognition sequence of Sp1 (CCACC box) leads to a strikingly low promoter activity due to the abolishment of the Sp1 binding site.^[73] MMP-2 has been suggested in increasing gelatinase expression at the time of rejection. It has a critical role in the development of tissue remodeling and fibrosis in the renal allograft.^[62]

In the study by Singh *et al.*, 2010^[68] the mutant allele carriers CT+TT for MMP-2 (-735C>T) SNP was associated significantly with reduced risk for allograft rejection, suggested that T alleles may be associated with reduced MMP-2 expression. MMP-2 (-735C>T) polymorphism had reduced susceptibility for allograft rejection in North Indian cohort of renal transplant recipients, a beneficial effect and could serve as an ideal marker to predict pre-transplant allograft outcome.^[68] The similar findings were also reported by Berthier *et al.* 2006^[74] which suggested increased MMP2 levels in rejected allograft.

Complementary therapy of allograft rejection and pre-transplant allograft outcome can be predicted due to enhanced allograft survival in mutant allele carriers for MMP-2 (-735C>T).^[68] A weak but significant positive correlation was found between increasing Renal Transplant Recipient's age and plasma MMP-2.^[75] MMP-2 is vital for the patient's condition after renal transplantation. The MMP-2 level was found associated with post transplant duration in the transplant recipients and may be critical for graft survival^[76] (See Table 2).

4.3. Stromelysins

Stromelysin 1 (MMP-3) and Stromelysin 2 (MMP-10) both have similar substrate specificities, but in general MMP-3 has a proteolytic efficiency higher than that of MMP-10. Besides digesting ECM components, MMP-3 activates a number of proMMPs, and its action on a partially processed proMMP-1 is critical for the generation of fully active MMP-1.^[77] MMP-11 is known as Stromelysin 3, but due to the sequence and substrate specificity diverges from those of MMP-3, it is usually grouped with "other MMPs".

MMP-3 (Stromelysin 1) and MMP-10 (Stromelysin 2) is located on chromosome 11q22.3. In our review article three studies between MMP-3 and renal transplant were found. One MMP-3 study showed positive association with Renal Transplant^[78] and the other two showed negative association.^[55,43] (See Table2)

4.4. Matrilysins

Matrilysin 1 (MMP-7) and Matrilysin 2 (MMP-26)^[79] also called endometase^[38] are in this group. The Matrilysins have a characteristic feature that they lack of a hemopexin domain. Besides ECM components, MMP-7 processes cell surface molecules such as pro--defensin, Fas-ligand, pro-tumor necrosis factor (TNF)-, and E-cadherin. Matrilysin 2 (MMP-26) also digests a number of ECM components.

MMP7 (Matrilysin 1) and MMP-26 (Matrilysin 2) is located on chromosome 11q22.3. Our present study includes five positively associated studies on MMP7 and acute rejection in renal transplant (Table 2).

4.5. Membrane-Type MMPs

There are six membrane-type MMPs (MT-MMPs): four are type I transmembrane proteins (MMP-14, MMP-15, MMP-16, and MMP-24), and two are glycosylphosphatidylinositol (GPI) anchored proteins (MMP-17 and MMP-25). With the exception of MT4-MMP, they are all capable of activating proMMP-2. These enzymes can also digest a number of ECM molecules, and MT1-MMP has collagenolytic activity on type I, II, and III collagens.^[80] However, we could not find any studies in the area of renal transplantation and these MMPs.

4.6. Other MMPs

Seven MMPs are not classified in the above categories. Metalloelastase (MMP-12) is mainly expressed in macrophages^[81] and is essential for macrophage migration.^[82] Besides elastin, it digests a number of other proteins. MMP-19 was identified by cDNA cloning from liver^[83] and as a T-cell-derived auto antigen from patients with rheumatoid arthritis (RASI).^[84] MMP-20 is also known as Enamelysin; it is primarily located within newly formed tooth enamel and digests Amelogenin. Mutations at MMP-20 cleavage sites causes Amelogenin imperfecta; a genetic disorder caused by defective enamel formation.^[85] MMP-22 was first cloned from chicken fibroblasts^[86] and a human homologue has been identified on the basis of EST sequences. The function of this enzyme is not known. MMP-23, also known as cysteine array MMP and it is mainly expressed in reproductive tissues.^[87] The enzyme has a cysteine-rich domain followed by an immunoglobulin-like domain and lacks the cysteine switch motif in the prodomain and the hemopexin domain. MMP-23 is to be a type II membrane protein which harbors the transmembrane domain in the N-terminal part of the propeptide. Because it has a furin recognition motif in the propeptide, it is cleaved in the Golgi and released as an active enzyme into the extracellular space.^[88] The latest addition to the MMP family is epilysin, or MMP-28, mainly expressed in keratinocytes^[89,90] Expression patterns in intact and damaged skin suggest that MMP-28 might function in tissue hemostasis and wound repair.^[89,90 and 91]

MMP-20 of Enamelysin group is located on chromosome 11q22. MMP-20 gene polymorphism may be used as surrogate markers to predict long-term outcomes after kidney transplantation.^[92] (Table 2)

Table 1: MMPs and their substrates.

MMP	Alternate Names	Selected Substrates	Cytogenetic Location
MMP-1	Collagenase-1	Collagen I, II, III, entactin, perlecan, IGF-BP-2 and -3, pro-IL-1 β , IL-1 β	11q22.3
MMP-2	Gelatinase A	Gelatin, collagen IV, V, XI, laminin, aggrecan, pro-TGF- β , pro-TNF- α , IGFBP-3 and -5	16q21
MMP-3	Stromelysin-1	Aggrecan, laminin, fibronectin, fibrinogen, MCP-1 to -4, pro-MMP-1, -3, -7, -8, -9, -13	11q22.3
MMP-7	Matrilysin	Plasminogen, pro- α -defensin, FasL, pro-TNF- α , E-cadherin, syndecan, pro-MMPs	11q22.3
MMP-8	Collagenase-2	Collagen I-III, VII, X, aggrecan, fibronectin, pro-TNF- α , IGF-BP, MCP-1, angiotensin	11q22.3
MMP-9	Gelatinase B	Gelatin, collagen IV, V, XI, pro-IL-8, Pro-TNF- α , pro-TGF- β , pro-MMP-2, -9, -13	20q11-q13
MMP-10	Stromelysin-2	Gelatin, fibronectin, proteoglycan, pro-MMP-1, -8, -10	11q22.3
MMP-11	Stromelysin-3	Fibronectin, laminin, aggrecan, IGFBP-1	22q11
MMP-12	Metalloelastase	Elastin, fibronectin, laminin, plasminogen, pro-TNF- α	11q22.3
MMP-13	Collagenase-3	Collagen I, II, III, entactin, aggrecan, tenascin, pro-TNF- α , pro-MMP-9, -13	11q22.3
MMP-14	MT1-MMP	Collagen I, II, III, laminin, fibronectin, pro-MMP-2, -13, CD44, tissue transglutaminase	14q11-q12
MMP-15	MT2-MMP	Pro-MMP-2, pro-TNF- α , tissue transglutaminase	16q12-21
MMP-16	MT3-MMP	Collagen III, pro-MMP-2, pro-TNF- α , tissue transglutaminase	8q21
MMP-17	MT4-MMP	Gelatin, fibronectin, fibrin, pro-MMP-2, ADAMTS-4, TIMPs, pro-TNF- α	12q24.33
MMP-18	Collagenase-4	Collagen I, II, III	
MMP-19	Stromelysin-4	Collagen IV, gelatin, laminin	12q14
MMP-20	Enamelysin	Amelogenin, aggrecan, cartilage oligomeric matrix protein (COMP)	11q22
MMP-21		Gelatin, α -1-antitrypsin	
MMP-23		May be similar to Stromelysins and collagenases	1p36
MMP-24	MT5-MMP	Pro-MMP-2	20q11.2
MMP-25	MT6-MMP	Collagen IV, gelatin, fibrin, fibronectin, pro-MMP-2 and -9, TIMPs, uPAR	
MMP-26	Matrilysin-2	Collagen IV, fibronectin, fibrin, fibrinogen, pro-MMP-9	
MMP-27		Gelatin, casein	
MMP-28	Epilysin	Neural cell adhesion molecule (NCAM), casein	

Table 2: Summary of the reports indicating the presence and absence of association between MMPs and Renal Transplant.

MMPs	Enzymes	Positive Studies	Negative Studies
MMP-1	Collagenase-1	N=40, MMP-1 was significantly elevated ^[95]	N=309 ^[55]
		N=30, MMP-1 was increased in patients with acute rejection compared with those with stable graft function and healthy donors ^[43]	
MMP-2	Gelatinase A	There was a weak but significant positive correlation MMP-2, N=150 ^[75]	[96]
		N=150, significantly associated ^[97]	
		^[98] N=24	^[99] N=150
			^[100] N=87
		N=46, The expression of either MMP-2 was significantly increased in the renal allografts of the recipients ^[101]	N=40, Serum MMP-2 ^[43]
		N=309 ^[55]	N=150 ^[94]
		N=41 ^[102]	
		Mutant alleles for MMP-2 (-735C>T) were associated with reduced risk for allograft rejection and improved allograft survival in North Indian transplant recipients and could serve as an ideal	

		marker to predict pre-transplant allograft outcome, N=306 ^[68] ^[103]	
		MMP-2 may be critical for graft survival. ^[76] N=152	
MMP-3	Stromelysin-1	N=16, MMP3 was significant ^[78]	N=309 ^[53]
			N=40 ^[43]
MMP-7	Matrilysin	MMP7 contributes to transplant tolerance may help in the development of new strategies to improve long-term graft outcome ^[104] ^[104, 105]	
		N=235, Polymorphisms of MMP7 gene may be surrogate marker to predict long-term outcomes after kidney transplantation ^[92]	
		N=25 ^[95]	
		N=10, MMP-7 represents potential molecular Acute Rejection marker ^[70]	
MMP-9	Gelatinase B	N=45, MMP-9 was associated with delayed graft function ^[71]	N=150 ^[97]
		N=102 ^[106]	
		N=10, MMP-9 represents potential molecular Acute Rejection marker ^[70]	[96]
		N=150, Renal transplant recipients compared with healthy volunteers (control group) showed significantly increased MMP-9 levels ^[99]	
		N=102, ^[106]	
		N=24, ^[98]	
		N=87, ^[100]	
		N=150, MMP-9 was increased in RTR compared with controls ^[94]	
		N=306, Mutant alleles for MMP-9 (2003G>A) is associated with reduced risk for allograft rejection and improved allograft survival in North Indian transplant recipients and could serve as an ideal marker to predict pre-transplant allograft outcome ^[68]	
		MMP-9 is involved in protecting the transplant kidney from preservation injury ^[103]	
		During the rejection process, MMP-9 showed significant increase so concluded that MMP-especially MMP-9-appear to represent new mediators involved in acute kidney transplant rejection. ^[69]	
		N=33, MMP9 was related with delayed graft function. ^[72]	
MMP13	Collagenase-3	Patient groups had higher MMP-13 levels than healthy group ^[44]	
MMP20	Enamelysin	N=235, Polymorphisms of MMP20 gene may be surrogate markers to predict long-term outcomes after kidney transplantation ^[92]	

N= number of cases (recipients)

1. DISCUSSION

In the present review the activity of MMPs involved in the Renal transplantation and allograft rejection was studied. Our study revealed that gelatinases especially MMP9 and MMP2 play major role in renal transplantation and allograft rejection. The several studies included in our review suggested that MMP-1, MMP-7, MMP-9, and MMP-13 represent as promising molecular Allograft Rejection markers and MMP-9, particularly was also found associated with delayed graft function.^[72]

Likewise, Singh *et al.* 2010^[68] in their study have shown that polymorphism in MMP9 and MMP2 have significant association with allograft rejection in North Indian population. Alexander *et al.* 2010^[93] included most of the genes as genetic predictors of acute renal

transplant rejection in their study except MMPs. They did not included MMPs as genetic predictors of acute rejection in their review article. Mazanoskwa *et al.* 2011^[94] observed increased MMP-2 concentrations in renal transplant recipients, experiencing chronic humoral rejection. MMPs are proteolytic enzymes involved in degradation of extracellular matrix and basement membrane and play important roles in the progression of CKD.

In summary, the tight regulation of the MMP system is essential for normal renal development. MMPs are usually considered to be protective due to their antifibrotic activities, but this view is too simplistic and too optimistic. Increased levels of MMPs are usually associated with disease activity and the influx of inflammatory cells. It is now becoming widely accepted

that MMPs are not just involved in ECM degradation, but are precise proteolytic processing enzymes that are involved in development, homeostasis of the extracellular environment, and control of innate immunity.^[4]

We are exploring more MMPs through an ongoing study on MMP2 and MMP9 in renal transplant recipients. It appears that, the investigation of the role of MMPs in allograft rejection may lead to better understanding and subsequently newer approaches to combat rejection process. In this way, we hope that more interesting discoveries can be brought and we can have a more specific and accurate understanding of their function in the human body.

2. CONCLUSION AND PERSPECTIVES

MMP-1, MMP-2, MMP-7, MMP-9 and MMP-20 have been found to have impact on renal transplant and allograft rejection. They represent as new mediators involved in acute kidney transplant rejection. However, their exact role in the process of rejection still remains unclear and needs further exploration.

Most of the studies in our review show that MMP-1, MMP-7, MMP-9, and MMP-13 represent as promising potential molecular Acute Rejection markers.

MMP-9 was found associated with delayed graft function.^[72]

Complementary therapy of allograft rejection and pre-transplant allograft outcome can be predicted due to enhanced allograft survival in mutant allele carriers for MMP-2.

More research based on larger samples size, genome-wide association analysis, rigorous study design and appropriate statistical methods using modern bioinformatics tools is required in this important area.

ACKNOWLEDGEMENTS

Research fellowship to author Mansi Bhatt by UPCST, Uttar Pradesh is gratefully acknowledged.

Funding The funding for the study was provided by Council of Science and Technology, Uttar Pradesh, Government of India.

REFERENCES

1. Catania, J. M.; Chen, G.; Parrish, A. R., Role of matrix metalloproteinases in renal pathophysiology. *American journal of physiology. Renal physiology*, 2007; 292(3): F905-11.
2. Parks, W. C.; Wilson, C. L.; Lopez-Boado, Y. S., Matrix metalloproteinases as modulators of inflammation and innate immunity. *Nature reviews. Immunology*, 2004; 4(8): 617-29.
3. Gross, J., How tadpoles lose their tails: path to discovery of the first matrix metalloproteinase. *Matrix biology : journal of the International Society for Matrix Biology*, 2004; 23(1): 3-13.
4. Morrison, C. J.; Butler, G. S.; Rodriguez, D.; Overall, C. M., Matrix metalloproteinase proteomics: substrates, targets, and therapy. *Current opinion in cell biology*, 2009; 21(5): 645-53.
5. Visse, R.; Nagase, H., Matrix metalloproteinases and tissue inhibitors of metalloproteinases: structure, function, and biochemistry. *Circulation research*, 2003; 92(8): 827-39.
6. Pardo, A.; Selman, M., Matrix metalloproteinases in aberrant fibrotic tissue remodeling. *Proceedings of the American Thoracic Society*, 2006; 3(4): 383-8.
7. Nagase, H.; Woessner, J. F., Jr., Matrix metalloproteinases. *The Journal of biological chemistry*, 1999; 274(31): 21491-4.
8. Sternlicht, M. D.; Werb, Z., How matrix metalloproteinases regulate cell behavior. *Annual review of cell and developmental biology*, 2001; 17: 463-516.
9. Gialeli, C.; Theocharis, A. D.; Karamanos, N. K., Roles of matrix metalloproteinases in cancer progression and their pharmacological targeting. *The FEBS journal*, 2011; 278(1): 16-27.
10. Wolfe, R. A.; Ashby, V. B.; Milford, E. L.; Ojo, A. O.; Ettenger, R. E.; Agodoa, L. Y.; Held, P. J.; Port, F. K., Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. *The New England journal of medicine*, 1999; 341(23): 1725-30.
11. Oniscu, G. C.; Brown, H.; Forsythe, J. L., Impact of cadaveric renal transplantation on survival in patients listed for transplantation. *Journal of the American Society of Nephrology : JASN*, 2005; 16(6): 1859-65.
12. Riano-Galan, I.; Malaga, S.; Rajmil, L.; Ariceta, G.; Navarro, M.; Loris, C.; Vallo, A., Quality of life of adolescents with end-stage renal disease and kidney transplant. *Pediatric nephrology*, 2009; 24(8): 1561-8.
13. Schnuelle, P.; Lorenz, D.; Trede, M.; Van Der Woude, F. J., Impact of renal cadaveric transplantation on survival in end-stage renal failure: evidence for reduced mortality risk compared with hemodialysis during long-term follow-up. *Journal of the American Society of Nephrology : JASN*, 1998; 9(11): 2135-41.
14. Hariharan, S.; Stablein, D. E., Improvements in long-term renal transplant graft survival. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*, 2005; 5(3): 630-1. author reply, 632-3.
15. Hariharan, S.; Johnson, C. P.; Bresnahan, B. A.; Taranto, S. E.; McIntosh, M. J.; Stablein, D., Improved graft survival after renal transplantation in the United States, 1988 to 1996. *The New England journal of medicine*, 2000; 342(9): 605-12.

16. Jorga, A.; Johnston, A., Novel therapies in transplantation. *Expert opinion on investigational drugs*, 2005; 14(3): 295-304.
17. Womer, K. L.; Kaplan, B., Recent developments in kidney transplantation--a critical assessment. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*, 2009; 9(6): 1265-71.
18. Karthikeyan, V.; Karpinski, J.; Nair, R. C.; Knoll, G., The burden of chronic kidney disease in renal transplant recipients. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*, 2004; 4(2): 262-9.
19. Meier-Kriesche, H. U.; Schold, J. D.; Kaplan, B., Long-term renal allograft survival: have we made significant progress or is it time to rethink our analytic and therapeutic strategies? *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*, 2004; 4(8): 1289-95.
20. Norman, J. T.; Lewis, M. P., Matrix metalloproteinases (MMPs) in renal fibrosis. *Kidney international. Supplement*, 1996; 54: S61-3.
21. McCawley, L. J.; Matrisian, L. M., Matrix metalloproteinases: they're not just for matrix anymore! *Current opinion in cell biology*, 2001; 13(5): 534-40.
22. Garton, K. J.; Gough, P. J.; Raines, E. W., Emerging roles for ectodomain shedding in the regulation of inflammatory responses. *Journal of leukocyte biology*, 2006; 79(6): 1105-16.
23. Yamani, M. H.; Starling, R. C.; Young, J. B.; Cook, D.; Yu, Y.; Vince, D. G.; McCarthy, P.; Ratliff, N. B., Acute vascular rejection is associated with up-regulation of vitronectin receptor (alpha_vbeta₃), increased expression of tissue factor, and activation of the extracellular matrix metalloproteinase induction system. *The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation*, 2002; 21(9): 983-9.
24. Berthier, C. C.; Lods, N.; Joosten, S. A.; van Kooten, C.; Leppert, D.; Lindberg, R. L.; Kappeler, A.; Raulf, F.; Sterchi, E. E.; Lottaz, D.; Marti, H. P., Differential regulation of metzincins in experimental chronic renal allograft rejection: potential markers and novel therapeutic targets. *Kidney international*, 2006; 69(2): 358-68.
25. Racusen, L. C.; Solez, K.; Colvin, R. B.; Bonsib, S. M.; Castro, M. C.; Cavallo, T.; Croker, B. P.; Demetris, A. J.; Drachenberg, C. B.; Fogo, A. B.; Furness, P.; Gaber, L. W.; Gibson, I. W.; Glotz, D.; Goldberg, J. C.; Grande, J.; Halloran, P. F.; Hansen, H. E.; Hartley, B.; Hayry, P. J.; Hill, C. M.; Hoffman, E. O.; Hunsicker, L. G.; Lindblad, A. S.; Yamaguchi, Y.; et al., The Banff 97 working classification of renal allograft pathology. *Kidney international*, 1999; 55(2): 713-23.
26. Lovett, D. H.; Johnson, R. J.; Marti, H. P.; Martin, J.; Davies, M.; Couser, W. G., Structural characterization of the mesangial cell type IV collagenase and enhanced expression in a model of immune complex-mediated glomerulonephritis. *The American journal of pathology*, 1992; 141(1): 85-98.
27. Turck, J.; Pollock, A. S.; Lee, L. K.; Marti, H. P.; Lovett, D. H., Matrix metalloproteinase 2 (gelatinase A) regulates glomerular mesangial cell proliferation and differentiation. *The Journal of biological chemistry*, 1996; 271(25): 15074-83.
28. Almond, P. S.; Matas, A.; Gillingham, K.; Dunn, D. L.; Payne, W. D.; Gores, P.; Gruessner, R.; Najarian, J. S., Risk factors for chronic rejection in renal allograft recipients. *Transplantation*, 1993; 55(4): 752-6; discussion, 756-7.
29. Kamoun, M., Cellular and molecular parameters in human renal allograft rejection. *Clinical biochemistry*, 2001; 34(1): 29-34.
30. Massy, Z. A.; Guijarro, C.; Wiederkehr, M. R.; Ma, J. Z.; Kasiske, B. L., Chronic renal allograft rejection: immunologic and nonimmunologic risk factors. *Kidney international*, 1996; 49(2): 518-24.
31. Matas, A. J.; Gillingham, K. J.; Payne, W. D.; Najarian, J. S., The impact of an acute rejection episode on long-term renal allograft survival (1/2). *Transplantation*, 1994; 57(6): 857-9.
32. Ramanathan, V.; Goral, S.; Helderman, J. H., Renal transplantation. *Seminars in nephrology*, 2001; 21(2): 213-9.
33. Mahalati, K.; Belitsky, P.; Sketris, I.; West, K.; Panek, R., Neoral monitoring by simplified sparse sampling area under the concentration-time curve: its relationship to acute rejection and cyclosporine nephrotoxicity early after kidney transplantation. *Transplantation*, 1999; 68(1): 55-62.
34. Nickerson, P.; Jeffery, J.; Gough, J.; Grimm, P.; McKenna, R.; Birk, P.; Rush, D., Effect of increasing baseline immunosuppression on the prevalence of clinical and subclinical rejection: a pilot study. *Journal of the American Society of Nephrology : JASN*, 1999; 10(8): 1801-5.
35. van Saase, J. L.; van der Woude, F. J.; Thorogood, J.; Hollander, A. A.; van Es, L. A.; Weening, J. J.; van Bockel, J. H.; Bruijn, J. A., The relation between acute vascular and interstitial renal allograft rejection and subsequent chronic rejection. *Transplantation*, 1995; 59(9): 1280-5.
36. Flechner, S. M.; Kurian, S. M.; Head, S. R.; Sharp, S. M.; Whisenant, T. C.; Zhang, J.; Chismar, J. D.; Horvath, S.; Mondala, T.; Gilmartin, T.; Cook, D. J.; Kay, S. A.; Walker, J. R.; Salomon, D. R., Kidney transplant rejection and tissue injury by gene profiling of biopsies and peripheral blood lymphocytes. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*, 2004; 4(9): 1475-89.

37. Sarwal, M.; Chua, M. S.; Kambham, N.; Hsieh, S. C.; Satterwhite, T.; Masek, M.; Salvatierra, O., Jr., Molecular heterogeneity in acute renal allograft rejection identified by DNA microarray profiling. *The New England journal of medicine*, 2003; 349(2): 125-38.
38. Park, H. I.; Ni, J.; Gerkema, F. E.; Liu, D.; Belozarov, V. E.; Sang, Q. X., Identification and characterization of human endometase (Matrix metalloproteinase-26) from endometrial tumor. *The Journal of biological chemistry*, 2000; 275(27): 20540-4.
39. Leontovich, A. A.; Zhang, J.; Shimokawa, K.; Nagase, H.; Sarras, M. P., Jr., A novel hydra matrix metalloproteinase (HMMP) functions in extracellular matrix degradation, morphogenesis and the maintenance of differentiated cells in the foot process. *Development*, 2000; 127(4): 907-20.
40. Lepage, T.; Gache, C., Early expression of a collagenase-like hatching enzyme gene in the sea urchin embryo. *The EMBO journal*, 1990; 9(9): 3003-12.
41. Maidment, J. M.; Moore, D.; Murphy, G. P.; Murphy, G.; Clark, I. M., Matrix metalloproteinase homologues from *Arabidopsis thaliana*. Expression and activity. *The Journal of biological chemistry*, 1999; 274(49): 34706-10.
42. Parsons, S. L.; Watson, S. A.; Brown, P. D.; Collins, H. M.; Steele, R. J., Matrix metalloproteinases. *The British journal of surgery*, 1997; 84(2): 160-6.
43. Rodrigo, E.; Lopez-Hoyos, M.; Escallada, R.; Fernandez-Fresnedo, G.; Ruiz, J. C.; Pinera, C.; Cotorruelo, J. G.; Zubimendi, J. A.; de Francisco, A. L.; Arias, M., Circulating levels of matrix metalloproteinases MMP-3 and MMP-2 in renal transplant recipients with chronic transplant nephropathy. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association*, 2000; 15(12): 2041-5.
44. Emingil, G.; Afacan, B.; Tervahartiala, T.; Toz, H.; Atilla, G.; Sorsa, T., GCF and serum myeloperoxidase and matrix metalloproteinase-13 levels in renal transplant patients. *Archives of oral biology*, 2010; 55(10): 719-27.
45. Bolzani, G.; Della Coletta, R.; Martelli Junior, H.; Martelli Junior, H.; Graner, E., Cyclosporin A inhibits production and activity of matrix metalloproteinases by gingival fibroblasts. *Journal of periodontal research*, 2000; 35(1): 51-8.
46. Tipton, D. A.; Stricklin, G. P.; Dabbous, M. K., Fibroblast heterogeneity in collagenolytic response to cyclosporine. *Journal of cellular biochemistry*, 1991; 46(2): 152-65.
47. Sugano, N.; Ito, K.; Murai, S., Cyclosporin A inhibits collagenase gene expression via AP-1 and JNK suppression in human gingival fibroblasts. *Journal of periodontal research*, 1998; 33(8): 448-52.
48. Yamada, H.; Nishimura, F.; Naruishi, K.; Chou, H. H.; Takashiba, S.; Albright, G. M.; Nares, S.; Iacopino, A. M.; Murayama, Y., Phenytoin and cyclosporin A suppress the expression of MMP-1, TIMP-1, and cathepsin L, but not cathepsin B in cultured gingival fibroblasts. *Journal of periodontology*, 2000; 71(6): 955-60.
49. Dannewitz, B.; Edrich, C.; Tomakidi, P.; Kohl, A.; Gabbert, O.; Eickholz, P.; Steinberg, T., Elevated gene expression of MMP-1, MMP-10, and TIMP-1 reveal changes of molecules involved in turn-over of extracellular matrix in cyclosporine-induced gingival overgrowth. *Cell and tissue research*, 2006; 325(3): 513-22.
50. Emingil, G.; Afacan, B.; Tervahartiala, T.; Toz, H.; Atilla, G.; Sorsa, T., Gingival crevicular fluid and serum matrix metalloproteinase-8 and tissue inhibitor of matrix metalloproteinase-1 levels in renal transplant patients undergoing different immunosuppressive therapy. *Journal of clinical periodontology*, 2008; 35(3): 221-9.
51. Sorsa, T.; Tjaderhane, L.; Kontinen, Y. T.; Lauhio, A.; Salo, T.; Lee, H. M.; Golub, L. M.; Brown, D. L.; Mantyla, P., Matrix metalloproteinases: contribution to pathogenesis, diagnosis and treatment of periodontal inflammation. *Annals of medicine*, 2006; 38(5): 306-21.
52. Owen, C. A.; Hu, Z.; Lopez-Otin, C.; Shapiro, S. D., Membrane-bound matrix metalloproteinase-8 on activated polymorphonuclear cells is a potent, tissue inhibitor of metalloproteinase-resistant collagenase and serpinase. *Journal of immunology*, 2004; 172(12): 7791-803.
53. Gueders, M. M.; Balbin, M.; Rocks, N.; Foidart, J. M.; Gosset, P.; Louis, R.; Shapiro, S.; Lopez-Otin, C.; Noel, A.; Cataldo, D. D., Matrix metalloproteinase-8 deficiency promotes granulocytic allergen-induced airway inflammation. *Journal of immunology*, 2005; 175(4): 2589-97.
54. Kuula, H.; Salo, T.; Pirila, E.; Tuomainen, A. M.; Jauhainen, M.; Uitto, V. J.; Tjaderhane, L.; Pussinen, P. J.; Sorsa, T., Local and systemic responses in matrix metalloproteinase 8-deficient mice during *Porphyromonas gingivalis*-induced periodontitis. *Infection and immunity*, 2009; 77(2): 850-9.
55. Ong, S.; Kang, S. W.; Kim, Y. H.; Kim, T. H.; Jeong, K. H.; Kim, S. K.; Yoon, Y. C.; Seo, S. K.; Moon, J. Y.; Lee, S. H.; Ihm, C. G.; Lee, T. W.; Chung, J. H., Matrix Metalloproteinase Gene Polymorphisms and New-Onset Diabetes After Kidney Transplantation in Korean Renal Transplant Subjects. *Transplantation proceedings*, 2016; 48(3): 858-63.
56. Ghisdal, L.; Baron, C.; Le Meur, Y.; Lionet, A.; Halimi, J. M.; Rerolle, J. P.; Glowacki, F.; Lebranchu, Y.; Drouet, M.; Noel, C.; El Housni, H.; Cochaux, P.; Wissing, K. M.; Abramowicz, D.; Abramowicz, M., TCF7L2 polymorphism associates with new-onset diabetes after transplantation.

- Journal of the American Society of Nephrology : JASN*, 2009; 20(11): 2459-67.
57. Allan, J. A.; Docherty, A. J.; Barker, P. J.; Huskisson, N. S.; Reynolds, J. J.; Murphy, G., Binding of gelatinases A and B to type-I collagen and other matrix components. *The Biochemical journal*, 1995; 309(1): 299-306.
 58. Aimes, R. T.; Quigley, J. P., Matrix metalloproteinase-2 is an interstitial collagenase. Inhibitor-free enzyme catalyzes the cleavage of collagen fibrils and soluble native type I collagen generating the specific 3/4- and 1/4-length fragments. *The Journal of biological chemistry*, 1995; 270(11): 5872-6.
 59. Patterson, M. L.; Atkinson, S. J.; Knauper, V.; Murphy, G., Specific collagenolysis by gelatinase A, MMP-2, is determined by the hemopexin domain and not the fibronectin-like domain. *FEBS letters*, 2001; 503(2-3): 158-62.
 60. Wilson, C. L.; Matrisian, L. M., Matrilysin: an epithelial matrix metalloproteinase with potentially novel functions. *The international journal of biochemistry & cell biology*, 1996; 28(2): 123-36.
 61. Lenz, O.; Elliot, S. J.; Stetler-Stevenson, W. G., Matrix metalloproteinases in renal development and disease. *Journal of the American Society of Nephrology : JASN*, 2000; 11(3): 574-81.
 62. Inkinen, K. A.; Soots, A. P.; Krogerus, L. A.; Lautenschlager, I. T.; Ahonen, J. P., Fibrosis and matrix metalloproteinases in rat renal allografts. *Transplant international : official journal of the European Society for Organ Transplantation*, 2005; 18(5): 506-12.
 63. Johnson, T. S.; Haylor, J. L.; Thomas, G. L.; Fisher, M.; El Nahas, A. M., Matrix metalloproteinases and their inhibitions in experimental renal scarring. *Experimental nephrology*, 2002; 10(3): 182-95.
 64. Hu, Z.; Huo, X.; Lu, D.; Qian, J.; Zhou, J.; Chen, Y.; Xu, L.; Ma, H.; Zhu, J.; Wei, Q.; Shen, H., Functional polymorphisms of matrix metalloproteinase-9 are associated with risk of occurrence and metastasis of lung cancer. *Clinical cancer research : an official journal of the American Association for Cancer Research*, 2005; 11(15): 5433-9.
 65. Wu, J.; Zhang, L.; Luo, H.; Zhu, Z.; Zhang, C.; Hou, Y., Association of matrix metalloproteinases-9 gene polymorphisms with genetic susceptibility to esophageal squamous cell carcinoma. *DNA and cell biology*, 2008; 27(10): 553-7.
 66. O'Farrell, T. J.; Pourmotabbed, T., Identification of structural elements important for matrix metalloproteinase type V collagenolytic activity as revealed by chimeric enzymes. Role of fibronectin-like domain and active site of gelatinase B. *The Journal of biological chemistry*, 2000; 275(36): 27964-72.
 67. Murphy, G.; Knauper, V., Relating matrix metalloproteinase structure to function: why the "hemopexin" domain? *Matrix biology : journal of the International Society for Matrix Biology*, 1997; 15(8-9): 511-8.
 68. Singh, R.; Srivastava, P.; Srivastava, A.; Mittal, R. D., Matrix metalloproteinase (MMP-9 and MMP-2) gene polymorphisms influence allograft survival in renal transplant recipients. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association*, 2010; 25(10): 3393-401.
 69. Ermolli, M.; Schumacher, M.; Lods, N.; Hammoud, M.; Marti, H. P., Differential expression of MMP-2/MMP-9 and potential benefit of an MMP inhibitor in experimental acute kidney allograft rejection. *Transplant immunology*, 2003; 11(2): 137-45.
 70. Rodder, S.; Scherer, A.; Korner, M.; Eisenberger, U.; Hertig, A.; Raulf, F.; Rondeau, E.; Marti, H. P., Meta-analyses qualify metzincins and related genes as acute rejection markers in renal transplant patients. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*, 2010; 10(2): 286-97.
 71. Turunen, A. J.; Lindgren, L.; Salmela, K. T.; Kyllonen, L. E.; Andersson, S.; Pesonen, E., Matrix Metalloproteinase-9 and Graft Preservation Injury in Clinical Renal Transplantation. *Transplantation proceedings*, 2015; 47(10): 2831-5.
 72. Kaminska, D.; Koscielska-Kasprzak, K.; Mazanowska, O.; Zabinska, M.; Bartoszek, D.; Banasik, M.; Chudoba, P.; Lepiesza, A.; Gomulkiewicz, A.; Dziegiel, P.; Krajewska, M.; Polak, W.; Klinger, M., Pretransplant Immune Interplay Between Donor and Recipient Influences Posttransplant Kidney Allograft Function. *Transplantation proceedings*, 2018; 50(6): 1658-1661.
 73. Price, S. J.; Greaves, D. R.; Watkins, H., Identification of novel, functional genetic variants in the human matrix metalloproteinase-2 gene: role of Sp1 in allele-specific transcriptional regulation. *The Journal of biological chemistry*, 2001; 276(10): 7549-58.
 74. Berthier, C.; Marti, H. P., Metzincins, including matrix metalloproteinases and meprin, in kidney transplantation. *Swiss medical weekly*, 2006; 136(49-50): 789-94.
 75. Mazanowska, O.; Zabinska, M.; Koscielska-Kasprzak, K.; Kaminska, D.; Banasik, M.; Krajewska, M.; Madziarska, K.; Zmonarski, S. C.; Chudoba, P.; Biecek, P.; Boratynska, M.; Klinger, M., Advanced age of renal transplant recipients correlates with increased plasma concentrations of interleukin-6, chemokine ligand 2 (CCL2), and matrix metalloproteinase 2, and urine concentrations of CCL2 and tissue inhibitor of metalloproteinase 1. *Transplantation proceedings*, 2014; 46(8): 2640-3.
 76. Chang, H. R.; Kuo, W. H.; Hsieh, Y. S.; Yang, S. F.; Lin, C. C.; Lee, M. L.; Lian, J. D.; Chu, S. C., Circulating matrix metalloproteinase-2 is associated

- with cystatin C level, posttransplant duration, and diabetes mellitus in kidney transplant recipients. *Translational research : the journal of laboratory and clinical medicine*, 2008; 151(4): 217-23.
77. Suzuki, K.; Enghild, J. J.; Morodomi, T.; Salvesen, G.; Nagase, H., Mechanisms of activation of tissue procollagenase by matrix metalloproteinase 3 (stromelysin). *Biochemistry*, 1990; 29(44): 10261-70.
78. Hu, X.; Ren, L.; Yin, H.; Zhang, X., Signal transducer and activator of transcription 1 and matrix metalloproteinase 3 genetic expression and clinical significance on urothelial tumors after renal transplantation. *Transplantation proceedings*, 2010; 42(7): 2534-7.
79. Uria, J. A.; Lopez-Otin, C., Matrilysin-2, a new matrix metalloproteinase expressed in human tumors and showing the minimal domain organization required for secretion, latency, and activity. *Cancer research*, 2000; 60(17): 4745-51.
80. Ohuchi, E.; Imai, K.; Fujii, Y.; Sato, H.; Seiki, M.; Okada, Y., Membrane type 1 matrix metalloproteinase digests interstitial collagens and other extracellular matrix macromolecules. *The Journal of biological chemistry*, 1997; 272(4): 2446-51.
81. Shapiro, S. D.; Kobayashi, D. K.; Ley, T. J., Cloning and characterization of a unique elastolytic metalloproteinase produced by human alveolar macrophages. *The Journal of biological chemistry*, 1993; 268(32): 23824-9.
82. Shipley, J. M.; Wesselschmidt, R. L.; Kobayashi, D. K.; Ley, T. J.; Shapiro, S. D., Metalloelastase is required for macrophage-mediated proteolysis and matrix invasion in mice. *Proceedings of the National Academy of Sciences of the United States of America*, 1996; 93(9): 3942-6.
83. Pendas, A. M.; Knauper, V.; Puente, X. S.; Llano, E.; Mattei, M. G.; Apte, S.; Murphy, G.; Lopez-Otin, C., Identification and characterization of a novel human matrix metalloproteinase with unique structural characteristics, chromosomal location, and tissue distribution. *The Journal of biological chemistry*, 1997; 272(7): 4281-6.
84. Kolb, C.; Mauch, S.; Peter, H. H.; Krawinkel, U.; Sedlacek, R., The matrix metalloproteinase RASI-1 is expressed in synovial blood vessels of a rheumatoid arthritis patient. *Immunology letters*, 1997; 57(1-3): 83-8.
85. Li, W.; Gibson, C. W.; Abrams, W. R.; Andrews, D. W.; DenBesten, P. K., Reduced hydrolysis of amelogenin may result in X-linked amelogenesis imperfecta. *Matrix biology : journal of the International Society for Matrix Biology*, 2001; 19(8): 755-60.
86. Yang, M.; Kurkinen, M., Cloning and characterization of a novel matrix metalloproteinase (MMP), CMMP, from chicken embryo fibroblasts. CMMP, Xenopus XMMP, and human MMP19 have a conserved unique cysteine in the catalytic domain. *The Journal of biological chemistry*, 1998; 273(28): 17893-900.
87. Velasco, G.; Pendas, A. M.; Fueyo, A.; Knauper, V.; Murphy, G.; Lopez-Otin, C., Cloning and characterization of human MMP-23, a new matrix metalloproteinase predominantly expressed in reproductive tissues and lacking conserved domains in other family members. *The Journal of biological chemistry*, 1999; 274(8): 4570-6.
88. Pei, D.; Kang, T.; Qi, H., Cysteine array matrix metalloproteinase (CA-MMP)/MMP-23 is a type II transmembrane matrix metalloproteinase regulated by a single cleavage for both secretion and activation. *The Journal of biological chemistry*, 2000; 275(43): 33988-97.
89. Marchenko, G. N.; Strongin, A. Y., MMP-28, a new human matrix metalloproteinase with an unusual cysteine-switch sequence is widely expressed in tumors. *Gene*, 2001; 265(1-2): 87-93.
90. Lohi, J.; Wilson, C. L.; Roby, J. D.; Parks, W. C., Epilysin, a novel human matrix metalloproteinase (MMP-28) expressed in testis and keratinocytes and in response to injury. *The Journal of biological chemistry*, 2001; 276(13): 10134-44.
91. Saarialho-Kere, U.; Kerkela, E.; Jahkola, T.; Suomela, S.; Keski-Oja, J.; Lohi, J., Epilysin (MMP-28) expression is associated with cell proliferation during epithelial repair. *The Journal of investigative dermatology*, 2002; 119(1): 14-21.
92. Han, S. S.; Lee, H.; Oh, Y. J.; Lee, J. P.; Kim, S.; Ha, J.; Kim, S. J.; Park, M. H.; Kim, Y. S.; Kim, D. K., Identification of the effects of aging-related gene-matrix metalloproteinase on allograft outcomes in kidney transplantation. *Transplantation proceedings*, 2013; 45(6): 2158-64.
93. Goldfarb-Rumyantzev, A. S.; Naiman, N., Genetic predictors of acute renal transplant rejection. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association*, 2010; 25(4): 1039-47.
94. Mazanowska, O.; Kaminska, D.; Krajewska, M.; Zabinska, M.; Kopec, W.; Boratynska, M.; Chudoba, P.; Patrzalek, D.; Klinger, M., Imbalance of metalloproteinase/tissue inhibitors of metalloproteinase system in renal transplant recipients with chronic allograft injury. *Transplantation proceedings*, 2011; 43(8): 3000-3.
95. Hirt-Minkowski, P.; Marti, H. P.; Honger, G.; Grandgirard, D.; Leib, S. L.; Amico, P.; Schaub, S., Correlation of serum and urinary matrix metalloproteinases/tissue inhibitors of metalloproteinases with subclinical allograft fibrosis in renal transplantation. *Transplant immunology*, 2014; 30(1): 1-6.
96. Racca, M. A.; Novoa, P. A.; Rodriguez, I.; Della Vedova, A. B.; Pellizas, C. G.; Demarchi, M.; Donadio, A. C., Renal dysfunction and intragraft proMMP9 activity in renal transplant recipients with interstitial fibrosis and tubular atrophy. *Transplant*

- international : official journal of the European Society for Organ Transplantation*, 2015; 28(1): 71-8.
97. Mazanowska, O.; Zabinska, M.; Koscielska-Kasprzak, K.; Kaminska, D.; Krajewska, M.; Banasik, M.; Madziarska, K.; Zmonarski, S. C.; Chudoba, P.; Biecek, P.; Boratynska, M.; Klinger, M., Increased plasma matrix metalloproteinase-2 (MMP-2), tissue inhibitor of proteinase-1 (TIMP-1), TIMP-2, and urine MMP-2 concentrations correlate with proteinuria in renal transplant recipients. *Transplantation proceedings*, 2014; 46(8): 2636-9.
 98. Wagrowska-Danilewicz, M.; Danilewicz, M., Aberrant tubulointerstitial immunoeexpression of matrix metalloproteinases MMP-2, MMP-9 and tissue inhibitor of matrix proteinase-2 (TIMP-2) in acute cellular rejection of human renal allograft. *Polish journal of pathology : official journal of the Polish Society of Pathologists*, 2008; 59(4): 189-94.
 99. Mazanowska, O.; Kaminska, D.; Krajewska, M.; Banasik, M.; Zabinska, M.; Koscielska-Kasprzak, K.; Biecek, P.; Chudoba, P.; Patrzalek, D.; Boratynska, M.; Klinger, M., Increased plasma tissue inhibitors of metalloproteinase concentrations as negative predictors associated with deterioration of kidney allograft function upon long-term observation. *Transplantation proceedings*, 2013; 45(4): 1458-61.
 100. Kwiatkowska, E.; Domanski, L.; Bober, J.; Safranow, K.; Romanowski, M.; Pawlik, A.; Kwiatkowski, S.; Ciechanowski, K., Urinary Metalloproteinases-9 and -2 and Their Inhibitors TIMP-1 and TIMP-2 are Markers of Early and Long-Term Graft Function After Renal Transplantation. *Kidney & blood pressure research*, 2016; 41(3): 288-97.
 101. Kopecky, R. T.; Frymoyer, P. A.; Witanowski, L. S.; Thomas, F. D.; Wojtaszek, J.; Reinitz, E. R., Prospective peritoneal scintigraphy in patients beginning continuous ambulatory peritoneal dialysis. *American journal of kidney diseases : the official journal of the National Kidney Foundation*, 1990; 15(3): 228-36.
 102. Wanga, S.; Ceron, C. S.; Delgado, C.; Joshi, S. K.; Spaulding, K.; Walker, J. P.; Song, S.; Olson, J. L.; Lovett, D. H., Two Distinct Isoforms of Matrix Metalloproteinase-2 Are Associated with Human Delayed Kidney Graft Function. *PloS one*, 2015; 10(9): e0136276.
 103. Moser, M. A.; Arcand, S.; Lin, H. B.; Wojnarowicz, C.; Sawicka, J.; Banerjee, T.; Luo, Y.; Beck, G. R.; Luke, P. P.; Sawicki, G., Protection of the Transplant Kidney from Preservation Injury by Inhibition of Matrix Metalloproteinases. *PloS one*, 2016; 11(6): e0157508.
 104. Jovanovic, V.; Dugast, A. S.; Heslan, J. M.; Ashton-Chess, J.; Giral, M.; Degauque, N.; Moreau, A.; Pallier, A.; Chiffolleau, E.; Lair, D.; Usal, C.; Smit, H.; Vanhove, B.; Soullillou, J. P.; Brouard, S., Implication of matrix metalloproteinase 7 and the noncanonical wingless-type signaling pathway in a model of kidney allograft tolerance induced by the administration of anti-donor class II antibodies. *Journal of immunology*, 2008; 180(3): 1317-25.
 105. Ho, J.; Rush, D. N.; Krokhin, O.; Antonovici, M.; Gao, A.; Bestland, J.; Wiebe, C.; Hiebert, B.; Rigatto, C.; Gibson, I. W.; Wilkins, J. A.; Nickerson, P. W., Elevated Urinary Matrix Metalloproteinase-7 Detects Underlying Renal Allograft Inflammation and Injury. *Transplantation*, 2016; 100(3): 648-54.
 106. Zhao, Y. G.; Shi, B. Y.; Qian, Y. Y.; Bai, H. W.; Xiao, L.; He, X. Y., Clinical significance of monitoring serum level of matrix metalloproteinase 9 in patients with acute kidney allograft rejection. *Transplantation proceedings* 2015; 47(2): 319-22.