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Prostatic Semino-Micro Protein: A Recent Macrophage Chemoattractant and a Promising Target for Allograft Rejection Therapy

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Abstract

Renal allograft injury is considered a major challenge for both nephrologists and pathologists. Macrophage infiltration has been recognized as being involved in the process of renal allograft rejection. The chemokine ligand 2 - chemokine receptor 2 (CCL2-CCR2) axis is one of the pathways that attracts macrophages to the site of injury. Prostatic semino-micro protein (PSMP) is a recently discovered chemo attractant for macrophages that has chemokine ligand 2 (CCL2) affinity for chemokine receptor 2 (CCR2). By promoting inflammation and fibrosis, PSMP could be a promising predictor of allograft function and the development of rejection. Targeting PSMP could be a future antibody therapy that could delay the process of renal allograft rejection.

Keywords: Macrophages, Chemokines, Renal Allograft Rejection, PSMP.

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1. Introduction

Renal transplantation has become standard clinical practice over the past few decades. Avoiding hemodialysis or peritoneal dialysis has a significant impact on reducing mortality and improving patients' quality of life [1]. Renal allograft rejection, clinical or subclinical is the major causes of kidney allograft loss. Increasing evidence focused on the profound meaning of innate immune cells, such as natural killer (NK) cells, macrophages, and neutrophils [2]. The kidney contains a complex array of phagocytes with macrophage and antigen-presenting cell characteristics [3]. The key role of macrophages in promotion of tissue injury has recently questioned by many researchers through mapping process of macrophage development and function during different types and phases of graft rejection [4]. Recruitment of macrophages largely directed by chemokine's and their cognate receptors [5]. PSMP is a recently discovered chemokine that has an affinity for CCR2. CCL2, a well-known ligand of CCR2 had reported to be expressed on monocytes and macrophages [6]. The CCL2-CCR2 axis is currently the most well-studied chemokine pathway in many diseases [7]. Term 'chemokine' refers to a large family of structurally homologous proteins that stimulate movement of leukocytes and regulate their migration from blood to tissues [8].

Chemokines are classified into four families, based on the number and location of the N-terminal cysteine residues. The first two families are the CC chemokines, where residues are adjacent, and the CXC family, whose residues are separated by one amino acid. A small number of chemokines have a single cysteine (C family), or two cysteines separated by three amino acids (CX3C) [9]. Chemokines can mediate their activities through G-protein–coupled receptors having a characteristic seven-transmembrane structure and transduce their signals to the inside of the cell through heterotrimeric G-proteins [10-11]. Inflammatory chemokine abundance, distribution, and activity will be controlled by their interactions with extracellular matrix, proteases, and other proteins within the tissue, and by scavenging via conventional and atypical chemokine receptors [12]. Chemokine receptors, in turn, are differentially expressed on all leukocytes. The receptor occupancy of its respective chemokine immediately initiates intracellular responses [13], such as increasing cytoplasmic calcium and activation of protein kinase C. Changes in the cytoskeleton as well as the polymerization of the actin and myosin filaments were observed, resulting in increased cell motility. These signals also alter the conformation of cell surface integrin, increasing the affinity of them with their ligands [11].

1.1. PSMP structure

Sequence homology analysis of PSMP shows that PSMP is homological to β-micro semino protein, for which

MSMP was named. The mature PSMP protein contains CXC and CC motifs in 10 cysteines, which is different with the characteristic sequences contained in classical chemokine structures. PSMP shows no homology to any known chemokines, including CCL2 and CCL8 [14].

1.2. The role of PSMP in renal allograft rejection

A recent study carried out by Zhan *et al.* revealed that the expression level of PSMP in patients with chronic active antibody-mediated rejection (CAAMR) is strongly increased, and this increase is significantly correlated with the number of infiltrating CD68+ macrophages [15]. A recent study by song *et al.*, reported that overexpressed human PSMP in the mouse kidney could reverse the improvement of kidney injury in a CCR2-dependent manner [16].

1.3. The role of PSMP in other organ injury

Several studies have shown that the PSMP may play an essential role in inflammation and tumor progression. Pei *et al.*, reported that PSMP promoted dextran sodium sulfate (DSS)-induced colitis in mice by chemo-attracting Ly6Chi monocytes through CCR2 [17]. IL-1β, the damage-associated molecular pattern (DAMP) molecules IL-33 and HMGB-1 could induce mouse primary hepatocytes to produce PSMP. PSMP could recruit inflammatory macrophages through CCR2 to infiltrate and promote M2-type polarization of macrophages and directly activate hepatic stromal cells, ultimately promoting the progression of liver fibrosis. Moreover, the expression of PSMP was markedly increased in human cirrhotic and HCC-adjacent liver tissue. A promising reduction in liver fibrosis development (in vivo) was established by using PSMP antibodies. These findings indicated that PSMP antibodies may be potential therapeutic agents for liver fibrosis [18]. PSMP secreted by ovarian cancer cells induced by hypoxia could promote angiogenesis through the MAPK signaling pathway [19]. Also, CD5L, EGFL6, and PSMP contribute to the progression of ovarian cancer, and preclinical data indicate that the inhibition of these proteins by their antibodies, RNAi, and/or aptamers can reduce tumor growth and reverse adaptive resistance in ovarian cancer [20]. In prostate cancer tissues, results demonstrated that PSMP secreted by the tumor cells promoted the growth and survival of prostate cancer cells and induced epithelial mesenchymal transition by directly stimulating tumor cells. [21].

1.4. CCL2-CCR2 pathway in macrophage activation

One of the first discovered chemokines was CCL2 (C-C motif ligand 2), also called monocyte chemoattractant protein-1 (MCP-1). CCL2 is found mainly in mononuclear cells, endothelial cells, and fibroblasts. CCL2 binds mainly to CCR2, a major factor driving leukocyte infiltration and other immune cells that stimulate inflammation. The CCL2-CCR2 axis is currently the most well-studied chemokine pathway in many diseases [22]. CCL2 is hardly detectable in normal human kidneys, but its expression increases in kidneys from patients with acute renal transplant rejection, indicating its involvement in macrophage infiltration and renal graft damage [22]. Also, CCL2 has been shown to play a role in numerous kidney diseases, such as IgA nephropathy, membranous nephropathy, glomerulosclerosis, autosomal dominant polycystic kidney disease, lupus nephritis, GBM-induced nephritis, ANCA-associated renal vasculitis, and diabetic nephropathy [23]. It has been shown that CCR2 is responsible for Ly6Chi monocyte recruitment and the regulation of bone marrow-derived fibroblasts in kidneys subjected to ureteral obstruction [24]. CCR2 deficiency led to decreased Th17-related cytokine production, an immune response profile associated with nephropathy, progressive fibrosis, and decreased the production of VEGF, a molecule directly related to renal fibrosis [25]. CCR2 and its ligands have become therapeutic targets of interest for biopharmaceutical companies [26-28].

1.5. Macrophages and graft rejection

Macrophages have a critical role in acute and chronic allograft rejection [29-32] noticed that patients performed post transplantation biopsy at one year and three years with lower macrophage score had a significantly higher estimated glomerular filtration rate compared with those with higher macrophage score (Group I (CD68<400/mm) with 87±29 mL/min vs. Group II (CD68>400/mm); 64± 19 mL/min, p= 0.014) Toki *et al.*, 2014). [31-33] [31-33] [31-33] [31-33] [30-32] Also, Bergler, found that patients with poor clinical outcome (reflected by significantly elevated creatinine values and a significantly shortened graft survival) up to month 36 after transplantation had a significantly increased macrophage infiltration ($p < 0.0001$) [34] [34] [34] [34] [33] (Bergler 2016). In addition, Bräsen *et al.*, found out that CD68 macrophage marker density significantly contributes to the prediction of allograft function and is associated with a significantly lower GFR [35]. Moreover, Azad *et al.*, and his colleagues found that macrophage score in protocol biopsies 6 months following transplant predicted histological damage at 24 months after transplant with sensitivity of 91.6% and specificity of 83%. They suggested that the macrophage score could be applicable as a "rule-out test" for long-term graft loss. That is, patients with low macrophage scores may be candidates for less aggressive immunosuppression, limiting the treatment-related side effects. [36].

1.6. Macrophage polarization

The macrophages' destiny relies on various environmental conditions that fuel polarization to any of classically triggered pro-inflammatory M1 immune response or anti-inflammatory M2 response. M1 or M2 polarization is a precisely regulated process comprising several keys signaling pathways, transcriptional epigenetic and post-transcriptional regulatory networks [2]. M1 macrophages, also called "classically activated macrophages," tend to be proinflammatory cells secrete proinflammatory cytokines, such as IL-1, IL-6, tumor necrosis factor-α (TNF-α), and IL-23. M1 macrophages are also capable of eradicating bacterial, fungal, or viral infections. These cells are polarized following stimulation with interferon-γ (IFN-γ), lipopolysaccharides (LPS), TNF-α, granulocyte-macrophage colony-stimulating factor (GM-CSF) and engagement of Toll-like receptors (TLRs) by microbial products. This subset characterized by high expression of inducible nitric oxide synthase (iNOS) [4]. Although M1 macrophages contribute to anti-infection responses, their sustained activation, particularly under sterile inflammatory conditions, leads to tissue injury [37]. M2 macrophages, which are also described as "alternatively activated macrophages," possess anti-inflammatory functions and can facilitate wound healing, angiogenesis, phagocytosis, fibrosis, and inflammation resolution.

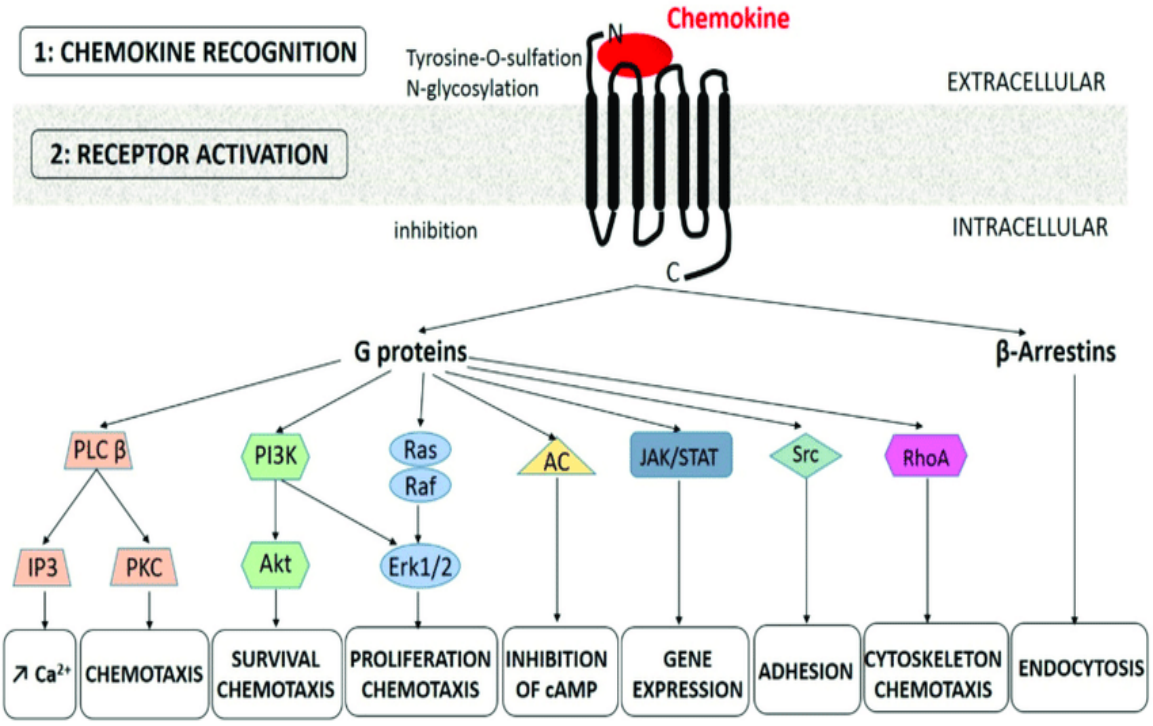

Figure 1. Chemokine-receptor interaction and the activation of downstream signaling pathways. Two main interactions between chemokines and their receptors are generally accepted: The N-terminal region of the chemokine binds in the pocket of the receptor transmembrane helical domain, while the N-terminal region of the receptor binds to a structural loop of the chemokine**.** Evidence for more interactions has been reported. Posttranslational modifications in the N-terminus part of chemokine receptor, such as tyrosine-O-sulfation and N-glycosylation, can affect this first binding step. A second activation step then occurs that stabilizes the receptor in an active conformation**.** AC: Adenylate cyclase, C: C terminus part, IP3: Inositol trisphosphate, JAK/STAT: Janus kinase/signaling transducer and activator of transcription, Erk: Extracellular signal-regulated kinase, N: N terminus part, C: C terminus part, PI3K: Phosphoinositide 3-kinase, PKC, Protein kinase C, PLC: Phosphoinositide-specific phospholipase C [38].

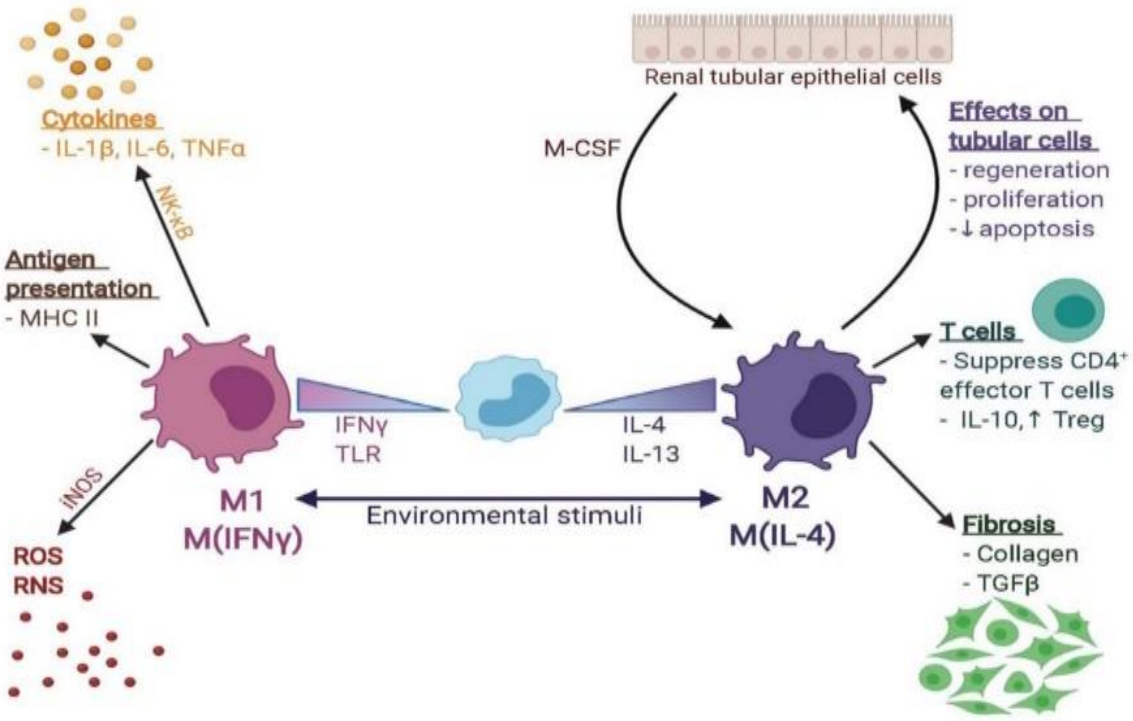

Figure 2: Macrophage polarization occurs on a continuum. At one end of the spectrum is the proinflammatory M1 phenotype, or M (IFNγ) macrophages. M1 macrophages are generated by exposure to IFNγ or TLRs. The effector functions of M1 macrophages include the production of cytokines (such as IL-1β, IL-6, and TNFα). M2 macrophages, or M (IL-4), are generated by exposure to IL-4/IL-13 and have reparative and anti-inflammatory functions [4].

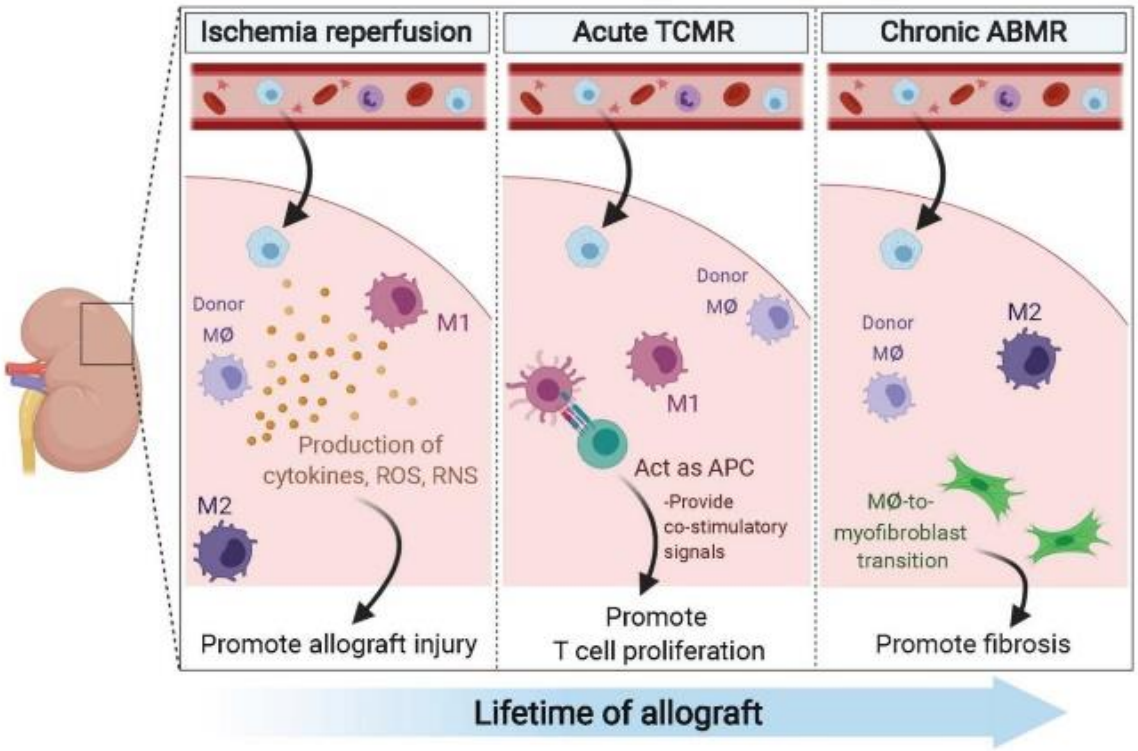

Figure 3: Role of macrophages in various forms of injury throughout the lifetime of renal grafts [4].

The polarization of this macrophage subset is induced by IL-4/IL-13. These cytokines activate the JAK/STAT6 pathway, driving the transcription of M2-associated genes, such as Arg1, Mrc1 and Chil3. High expression of numerous growth factors, including platelet-derived growth factor (PDGF), insulin-like growth factor-1 (IGF-1), and vascular endothelial growth factor (VEGF-α), is one of the distinct characteristics of M2 macrophages [37].

1.7. Macrophages and T-cell mediated rejection

Analysis of the various inflammatory cells present in the renal allograft during acute TCMR demonstrated an abundance of macrophage-associated transcripts [39], and a predominance of macrophages, comprising 32–60% of inflammatory cells [32]. Also, biopsies of patients with acute TCMR demonstrated increased transcript levels of granulocyte monocyte colony stimulating factor (GM-CSF), which increase in monocyte surface expression of major histocompatibility complex (MHC) class II (HLA-DR) and the costimulatory molecules CD40 and CD80 [40]. In acute TCMR, Intrarenal macrophages display a proinflammatory phenotype and secrete various cytokines, including IFNγ, IL-1β, IL-12, IL-18, and TNFα, which can activate endothelial cells and promote cytotoxic T-cell generation [41]. Additionally, activated inflammatory macrophages can produce reactive oxygen species (ROS) that can aggravate allograft injury. Taken together, renal tubular epithelial cell injury promotes monocyte chemotaxis and upregulates costimulatory molecules on infiltrating monocytes during acute TCMR, which can facilitate T-cell activation and amplify TCMR [32].

1.8. Macrophages and ABMR

In active AMR, a clinical study of protocol biopsies performed one year after transplant, intrarenal macrophages correlated with interstitial fibrosis and renal dysfunction at one year and three years. The vast majority (92%) of tissue macrophages were identified as having an M2 phenotype in this study [42]. Also, a clinical study with protocol biopsies performed at one, five, and ten years, demonstrated that increased intrarenal M2 macrophages corresponded to increased interstitial fibrosis and worsened renal function. [43]. In addition, in CAABMR, molecular analysis demonstrated that macrophage-associated transcripts are among the most abundant transcripts [44], and the presence of glomerular M2 polarized macrophages corresponded to elevated production of IL-1β, IL-6, and TNFα, higher TG levels and worse renal function at the time of biopsy and at three months following biopsy [45].

2. Conclusions

Cellular analysis of inflammatory infiltrates during different types of renal allograft rejection is considered a recent method for detecting graft outcomes. Many studies have focused on the role of macrophages for both types of renal allograft rejection. PSMP is a newly discovered chemoattractant for monocytes that acts in a CCL2-CCR2 dependent manner and could be used as a marker for detecting allograft outcome and patient survival. Further studies should be carried out to understand its function and therapeutic potential to improve graft survival.

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