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Chapter 3

Implication of Regional Activation of Toll-Like Receptor 3/Interferon-β Signaling in Human Mesangial Cells — Possible Involvement in the Pathogenesis of Lupus Nephritis

Hiroshi Tanaka, Kazushi Tsuruga and
Tadaatsu Imaizumi

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1. Introduction

It has been reported that toll-like receptors (TLRs) play a central role in the response of both the innate and adaptive immune systems to microbial ligands [1]. The activation of transcriptional factors, such as interferon regulatory factors (IRF) and nuclear factor kappa B (NF-κB) is induced by intracellular signaling cascades after recognition of presumptive antigenic ligands by TLRs. These signaling pathways result in the release of proinflammatory cytokines and chemokines which play a pivotal role in the innate and adaptive immune responses [1]. Both innate and adaptive immune systems reportedly play important roles in the pathogenesis of systemic lupus erythematosus (SLE) and lupus nephritis (LN) [2-4]. Given the pivotal roles for type I interferons (IFNs) in the pathogenesis of SLE and LN [2-5], the involvement of renal TLRs and their signaling pathways have recently been studied [4, 6, 7]. Since activation of TLRs and their downstream signaling pathways can be induced by non-infectious stimuli, endogenous ligands, this mechanism may be possibly involved in the pathogenesis of autoimmune renal diseases [1-6]. Indeed, recent studies have revealed the expressions of TLRs in resident renal cells, suggesting the involvement of the activations of TLRs and their downstream signaling pathway in the pathogenesis of glomerular diseases [4, 6].

It has been reported that glomerular mesangial cells (MCs) produce a wide variety of proinflammatory molecules that play an important role in both immune and inflammatory reactions in the kidney [7]. Thus, MCs themselves also have a pivotal role in the pathogenesis of renal diseases [8]. Given the implication of "pseudoviral" immunity in the pathogenesis of

LN, we examined the TLR3 signaling cascades triggered by polyinosinic-polycytidylic acid (poly IC), a synthetic analogue of viral dsRNA, that mimics "pseudoviral" infection in cultured human MCs, and found that activation of mesangial TLR3 signaling resulted in increased expressions of functional molecules acting as monocyte/macrophage and lymphocyte chemoattractants: CC chemokine ligand (CCL) 2 [monocyte chemoattractant protein-1 (MCP-1)], CCL5 [regulated on activation, normal T-cell expression and secretion (RANTES)], C-X-C motif ligand 10 (CXCL10) [interferon (IFN)-γ-induced protein 10 (IP-10)], and CX3CL1/fractalkine, in cultured human MCs [5, 6, 9-13]. And we found that poly IC-induced signaling in MCs via TLR3 results in induction of IFN-β, but not IFN-α, in the experimental setting we employed [5, 6, 9, 10, 13], and that newly synthesized IFN-β induces the expression of proinflammatory chemokines and cytokines [6, 9, 10, 13]. With respect to glomerular expression of TLRs, TLR 3, TLR 4, TLR 7 and TLR 9 may play roles in the modulation of inflammatory processes in glomerulonephritis, including LN and IgA nephropathy (IgAN) [2, 3, 6, 14-16]. Interestingly, TLR 7 and TLR 9 recognize mammalian nucleic acids as well as bacterial DNA or viral RNA. Thus, the generation of some autoantibodies may be attributable to possible roles of TLR 7 and TLR 9 in selected patients with LN [3, 6]. However, in this paper, we do not discuss the in-depth roles of TLR4, TLR 7 and TLR 9 in mesangial inflammation. Other general reviews of TLRs should be referred to regarding these issues. In the present paper, we summarize mesangial expressions of proinflammatory chemokines via TLR3/IFN-β signaling pathways [5, 9-13].

2. Expressions of retinoic acid-inducible gene-I (RIG-I) and melanoma differentiation-associated gene-5 (MDA5), and TLR3/IFN-β signaling in MCs

During hepatitis C virus (HCV) infection, the activation of mesangial TLR3-mediated proinflammatory chemokine/cytokine releases are reportedly involved in the pathogenesis of HCV glomerulonephritis [18]. In an experimental setting also, it has been reported that the expressions of matrix alteration-associated functional molecules, such as matrix metalloproteinase 9, plasminogen activator inhibitor type 1, and tissue plasminogen activator in human MCs induced by mesangial TLR3 activation [19, 20]. These findings suggest that viral RNA can influence subsequent glomerulosclerosis through the generation and degradation of the extracelluar matrix in the MCs except for direct viral stimulation [19, 20]. Viral double-stranded RNA (dsRNA) can activate not only TLR3 located in intracellular endosomes, but also retinoic acid-inducible gene-I (RIG-I)-like helicases receptors located in the cytosol, such as RIG-I and melanoma differentiation-associated gene-5 (MDA5) [21, 22]. Therefore, RIG-I and MDA5 may also be involved in the pathogenesis of LN [6, 7, 9, 11]. It has previously been reported that RIG-I, and not TLR3, mediated the secretion of type I IFN in poly IC/cationic lipid complex-treated glomerular endothelial cells [23]. In an experiment study using TLR3 signaling-deficient mice, it has been reported that MDA5, but not RIG-I, was required for signaling induced by poly IC/cationic lipid complex in murine MCs [7]. The cells transfected with poly IC/cationic lipid complex is thought to be a model of entry of RNA virus into the cytoplasm.

However, the precise role of RIG-I and the interaction between TLR3, MDA5 and RIG-I in mesangial inflammation remains to be elucidated.

We previously found significant expression of RIG-I in the glomeruli of biopsy specimens from patients with proliferative LN, and the level of expression correlated with the severity of the acute inflammatory lesions (Figure 1.) [24].

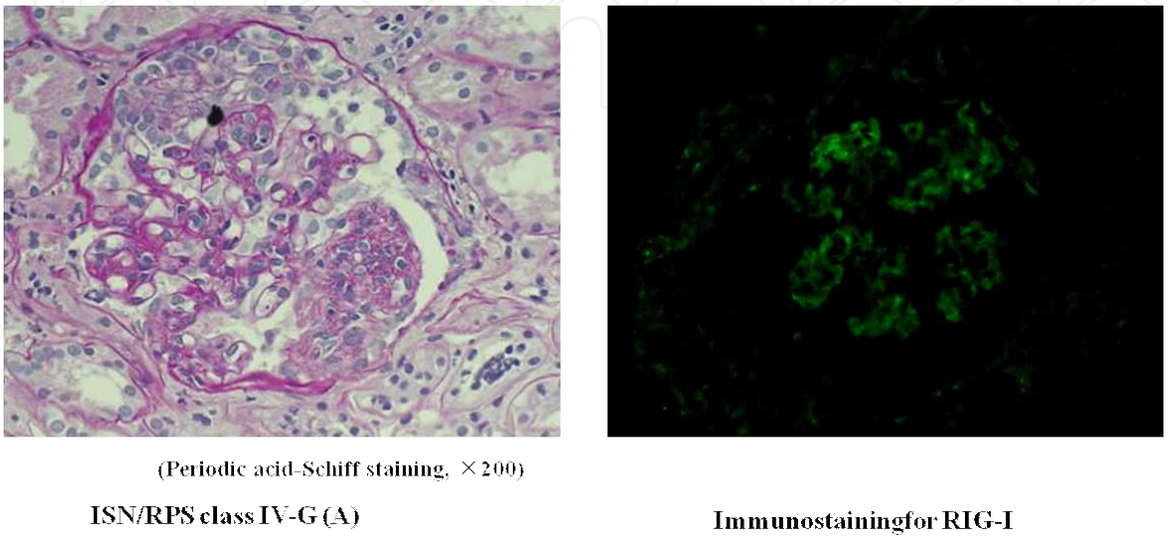

Figure 1. Glomerular immunoreactivity for RIG-I in patients with proliferative LN. The histological picture by light microscopy was classified as class IV according to the ISN/RPS criteria (left), and significant increase in the immunostaining intensity for RIG-I was observed (right) (quoted and modified from Ref. no. 24).

In addition, we found that the levels of RIG-I mRNA in the urinary sediment of patients with LN were higher than those in patients with IgAN and controls [25]. Further, repeated measurements of the mRNA expression of RIG-I in the urinary sediment of lupus patients revealed a reduction in the expression following immunosuppressive treatment [25]. These findings suggest that RIG-I may be involved in the acute inflammatory process in human LN. To examine the effect of TLR3 activation on the expression of RIG-I, human MCs were simply treated with poly IC. Treatment with poly IC is a model of cells exposed to viral dsRNA released from dying cells. Stimulation with poly IC resulted in an increase in the expression of both RIG-I mRNA and protein in a concentration- and time-dependent manner, and this was accompanied with CCL5 expression [9]. Also, we found that poly IC-induced signaling in MCs via TLR3 results in induction of IFN-β, but not IFN-α, in the experimental setting we employed (the results of our recent papers, Ref no. 9, 10, 13, should be referred to regarding this issue). Furthermore, knockdown of RIG-I expression by small interfering RNA (siRNA) significantly lowered poly IC-induced CCL5 expression. In contrast, the poly IC-induced expression of CCL2 mRNA was not affected by RIG-I siRNA. Interestingly, the poly IC-induced RIG-I expression was suppressed in response to treatment with siRNA against TLR3. Furthermore, TLR3 siRNA decreased the poly IC-induced expressions of TLR3 and IFN-β. On the other hand, RIG-I siRNA did not affect the expression of either TLR3 or IFN-β. To confirm

the role of IFN-β acting as a potential mediator of poly IC-induced RIG-I expression, IFN-β siRNA results in markedly decreases in the expressions of poly IC-induced IFN-β and RIG-I. Pretreatment of the cells with an anti-type I IFN receptor antibody also reduced the poly IC-induced expression of RIG-I. Moreover, pretreatment of the cells with dexamethasone reduced the poly IC-induced expression of both RIG-I and IFN-β, but this treatment had no effect on IFN-β-induced RIG-I expression [9]. Our recent study showed that siRNA-mediated knockdown of TLR3 inhibited the poly IC-induced expression of both IFN-β and RIG-I, whereas RIG-I knockdown had no effect on poly IC-induced IFN-β expression. Thus, RIG-I may function downstream to TLR3 in the signaling cascade activated by poly IC-induced expression of CCL5 in MCs [9]. In this signaling pathway in MCs, TLR3 and newly synthesized IFN-β are involved in poly IC-induced CCL5 expression (TLR3/IFN-β/RIG-I/CCL5 pathway).

It has been reported a pivotal role of IFN-α, rather than IFN-β, in the pathogenesis of LN [2]. In an interesting experiment using murine lupus model, early IFN receptor blockade with anti-IFN-α receptor antibody attenuated the development of glomerular inflammation [26]. However, apart from its physiological antiviral activity, IFN-β has also been reported to play a pivotal role in the inflammatory reactions in GN [2]. With respect to this issue, we think that *de novo* synthesized IFN-β from MCs acts, at least in part, as a "autocrine" mediator in residual renal cells in our experimental setting employing "human" MCs, whereas IFN-α, generally, may be released from infiltrating proinflammatory cells and acts as a "paracrine" mediator in selected clinical and experimental settings, although this theory remains speculative. Recently, it has been reported an interesting case of so-called IFN-β nephropathy which developed after long-term IFN-β treatment for relapsing multiple sclerosis [27]. Thus, regional role of IFN-β, especially in case of sustained activation, in human MCs remains to be examined in the future.

Since implications for the expression of MDA5 in human MCs have not been clarified, we next examined the role of MDA5 in CXCL10 expression in cultured human MCs [11]. Poly IC, either simply applied to the cells or transfected as a complex with a cationic lipid, induced MDA5 expression in concentration- and time-dependent manners. Transfection of the cells with siRNA against TLR3 suppressed the poly IC-induced expression of MDA5 mRNA and protein, while siRNA against TLR3 did not suppress the poly IC/cationic lipid complex-induced expression of MDA5. On the other hand, siRNA against RIG-I significantly inhibited the MDA5 expression induced by poly IC/cationic lipid complex, whereas knockdown of MDA5 had no effects on the expression of RIG-I induced by poly IC or poly IC/cationic lipid complex, suggesting that MDA5 may be located in the downstream of RIG-I in this signaling pathway in MCs [11]. These results are inconsistent with a previous report dealing with MDA5 expression in murine MCs [7]. The molecular mechanisms of pathogen recognition may vary between species, although this remains to be determined in future studies. In this experiment also, TLR3 knockdown suppressed IFN-β induction in the poly IC-treated cells, while RIG-I knockdown suppressed the induction in the cells transfected with poly IC/cationic lipid. Transfection of the cells with IFN-β siRNA markedly inhibited production of MDA5 and CXCL10 induced by poly IC treatment or poly IC/cationic lipid transfection. On the other hand, MDA5 was markedly induced by the transfection with an IFN-β expression plasmid. Thus, it is considered that newly synthesized IFN-β mediates poly IC-induced MDA5 expression. In our previous studies, poly IC treatment of MCs induced the expression of IFN-β and *de novo* synthesized IFN-β mediated the expressions of RIG-I and IFN stimulated gene (ISG) 20 [9,

10]. In the present study, we observed that IFN-β is induced either by poly IC or a poly IC/cationic lipid complex, and *de novo* synthesized IFN-β may mediate the expression of MDA5 [11]. RIG-I is involved in IFN-β expression induced by poly IC/cationic lipid complex, but not in the MDA expression by IFN-β. Taking together, we concluded that the TLR3/IFN-β/MDA5/CXCL10 pathway activates by poly IC treatment, while RIG-I/IFN-β/MDA5/CXCL10 pathway activates by poly IC/cationic lipid complex treatment in anti-viral and inflammatory reactions in MCs [11]. Furthermore, we observed mesangial MDA5 immunoreactivity in biopsy specimens from patients with both severe LN and proteinuric IgAN but no MDA5 expression in patients with non-inflammatory renal diseases. Interestingly, there was no mesangial expression of RIG-I in the specimens from patients with IgAN despite positive MDA5 staining. These observations suggested that the expression of MDA5 in severe LN is associated with signaling pathway activation via RIG-I [6, 11], whereas MDA5 expression in IgAN may be RIG-I-independent. The differential roles of MDA5 and RIG-I in severe LN and proteinuric IgAN may predict the specific molecular mechanisms of these glomerulonephritis forms [6].

3. Expression of myxovirus resistance protein 1 (Mx1) and TLR3/IFN-β signaling in MCs

It has been reported that human myxovirus resistance protein 1 (Mx1), a type I IFN-dependent transcript, which belongs to the class of dynamin-like large guanosine triphosphatases, play a role against a wide range of RNA viruses by interfering with viral replication [28]. Although its precise role in the pathogenesis of SLE remains speculative, *Mx1* gene expression in peripheral blood cells has been reported as a possible biomarker for LN therapy [29]. However, the regional implication of Mx1 for innate immune response in MCs remains to be elucidated [30].

We recently examined the expression of Mx1 in response to poly IC in cultured human MCs. Both poly IC alone and poly IC/cationic acid complex-induced Mx1 expressions in MCs are shown both time- and dose-dependently, and siRNA against IFN-β inhibited both poly IC treatment and transfection with a poly IC/cationic lipid complex-induced Mx1 expression [4]. Further, intense glomerular Mx1 expression was observed in biopsy specimens from patients with LN, whereas negative staining occurred in specimens from patients with IgAN or purpura nephritis (PN), even though both showed moderately to severe mesangial proliferation (Figure 2.).

Based on our experimental and clinical observations, both TLR3/IFN-β and RIG-I/IFN-β signaling pathways are responsible for poly IC-induced Mx1 expression in MCs. Regarding the detailed function of Mx1, we previously found that neither cell viability nor the expression of various IFN-stimulated genes was altered by Mx1 knockdown [31]. Thus, mesangial expression of Mx1 in LN patients may be a sequel of marked regional innate immune system activation [4]. We previously reported significant expression of both RIG-I and MDA5 in the glomeruli of biopsy specimens from patients with proliferative LN [11, 24]. Taking together, glomerular expressions of Mx1 as well as RIG-I and MDA5 in biopsy specimens from patients

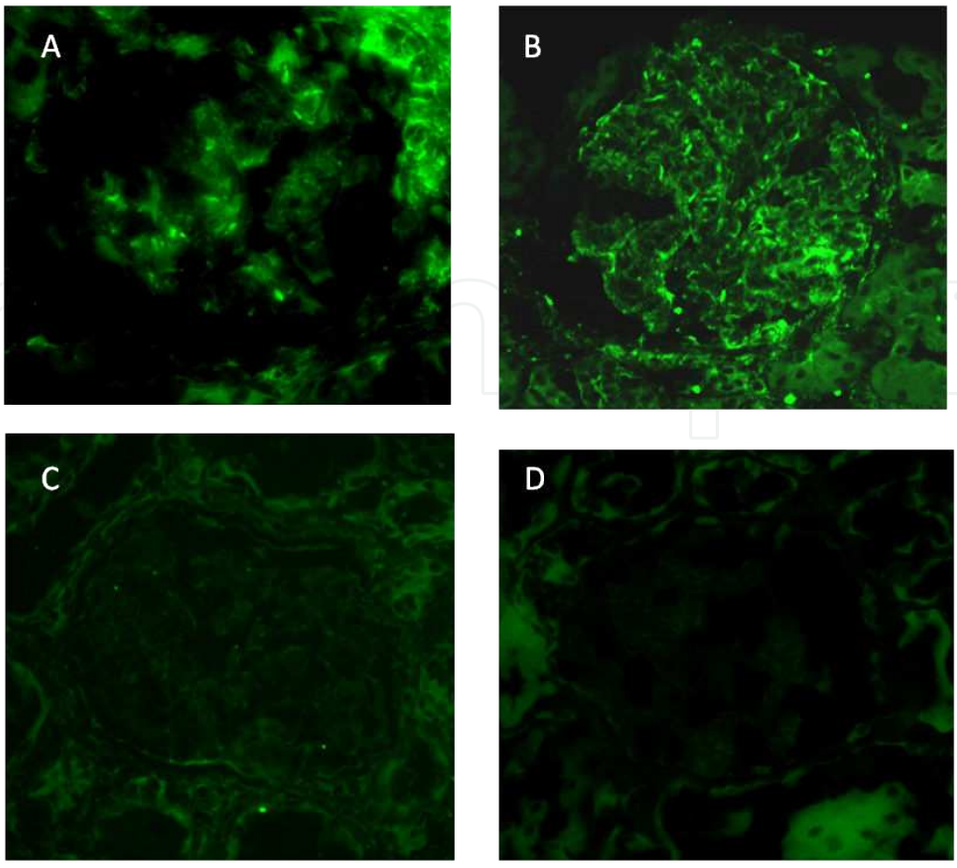

Figure 2. Immunofluorescence staining of Mx1 in renal biopsy specimens obtained from patients with proliferative LN (A, Class IV-G (A), and B, Class III (A) LN), proteinuric IgAN (C, diffuse proliferative mesangial proliferation6), and orthostatic proteinuria (D, served as a non-inflammatory control), respectively. A significant increase in Mx1 immunoreactivity was observed LN specimens (A and B), whereas immunoreactivity was negligible in the other specimens (C and D) (quoted and modified from Ref. no. 4).

with proliferative LN may further support the theory of innate immunity activation in the pathogenesis of LN [4].

4. Local activation of tumor necrosis factor (TNF)-α and TLR3/IFN-β signaling in MCs

It has been reported that patients with active SLE have local as well as systemic activation of proinflammatory cytokines [32, 33]. Among the increased serum proinflammatory cytokines in SLE, Koenig et al. recently reported that only serum soluble receptor of tumor necrosis factor (TNF)-α is actually and significantly increased, thereby possible local activation of TNF-α exists in active lupus patients [32]. However, mainly based on the observation murine LN models, it has been reported that TNF-α have both protective and deleterious effects in the pathogenesis of LN [33]. Therefore, precise role of regional TNF-α activation of in the pathogenesis of human LN remains to be determined.

Pretreatment of cultured normal human MCs with 1 ng/ml TNF-α markedly enhanced the poly IC-induced expression of CCL5 mRNA and protein, in a concentration-dependent manner. TNF-α pretreatment also enhanced the expression of protein and mRNA for IFN-β and RIG-I induced by poly IC, whereas treatment of MCs with 1 ng/ml TNF-α alone did not induce the expression of IFN-β. Transfection of siRNA against IFN-β partially but significantly inhibited the expression of CCL5 and RIG-I mRNA and protein induced by TNF-α followed by poly IC [13]. We found that the combination of pretreatment of cells with TNF-α, even at low dose (?) and subsequent treatment with poly IC resulted in the synergistic induction of CCL5 expression in MCs. Therefore, this experimental observation suggests that over production of CCL5 due to pre-existing regional activation of TNF-α may be involved in the development of LN in patients with active SLE. Increased IFN-β due to pre-existing regional activation of TNF-α may be a key mediator of CCL5 expression in MCs in this experimental setting. In a clinical setting, long-term beneficial effect of early induction regimen including TNF-α blockade has been reported in some patients with refractory LN [34], suggesting potential deleterious effects of regional TNF-α activation. Both pre-existing TNF-α activation and IFN-β/RIG-I/CCL5 axis may be involved in the pathogenesis of LN in patients with active SLE [13].

5. Expression of fractalkine/CX3CL1 and TLR3 signaling in MCs

Fractalkine/CX3CL1 (Fkn) is a chemokine that induces the chemotaxis and activation of inflammatory cells expressing its receptor, CX3CR1, and primarily regulated by proinflammatory cytokines such as TNF-α and IL-1 [35]. Fkn expression in mesangial lesions has been reported to be significantly correlated with histopathological disease activity in a rat model of human and mouse models of LN [36]. Moreover, mesangial Fkn expression may play an important role in the development of prolonged glomerular inflammation [37], and an antagonist of Fkn ameliorates the progression of this condition in a mouse model of LN [38]. However, the role of Fkn in innate immunity in human MCs remains to be elucidated.

We previously found that poly IC treatment of MCs induced both Fkn mRNA and protein expressions in a time-dependent manner. In contrast, induction of Fkn mRNA expression by poly IC/cationic lipid complex treatment was minimal, while RIG-I mRNA and protein were significantly induced. Poly IC-induced Fkn mRNA and protein expression was suppressed in response to treatment with siRNA against TLR3, while siRNAs against RIG-I and MDA5 did not affect poly IC-induced Fkn mRNA expression [12]. Transfection of MCs with siRNA against IRF3 suppressed the expression of Fkn mRNA and protein, whereas siRNA against NF-κB p65 did not affect Fkn protein expression. Interestingly, pre-treatment of cells using a blocking antibody against type I IFN receptor did not affect poly IC-induced Fkn mRNA expression, although this treatment clearly suppressed mRNA expression of poly IC-induced ISG 15. These results suggest that poly IC-induced expression of Fkn in MCs does not depend on cytosolic RNA recognition sensors RIG-I but may depend on the extracellular sensor TLR3. We then observed that knockdown of IRF3, but not NF-κB p65, inhibited poly IC-induced Fkn expression in MCs, and retreatment of cells using a blocking antibody against type I IFN

receptor did not affect poly IC-induced mesangial Fkn expression, although it clearly inhibited poly IC-induced ISG15 expression, suggesting that poly IC-induced Fkn expression in MCs primarily depends on the TLR3/IRF3 signaling pathway, but not TLR3/IFN-β signaling [12]. Recently, it has been reported that Fkn is not a target of IRF3-dependent direct response genes in "embryo" fibroblast from virally-infected mice [39]. This discrepancy may attributable to cell maturity, types, or species. Future detailed studies focused on this issue using Fkn-deficient mice are needed.

6. Conclusions

We believe that involvement of the novel TLR3/IFN-β signaling pathways, those are TLR3/IFN-β/RIG-I/CCL5 and TLR3/IFN-β/MDA5/CXCL10 pathways, and type I IFNs-independent TLR3/IRF3/Fkn pathway in MCs may contribute to mesangial inflammation (Figure 3). Cross-talk of between these signaling pathways may be involved in the pathogenesis of human LN. Since the inhibitory effect of dexamethasone may depend on the suppression of IFN-β production and not on IFN-β induced RIG-I and MDA5 expressions [9, 10], effective treatment strategies for the intervening in these signaling pathways are needed. We believe that intervention within these signaling pathways may lead to the development of future therapeutic strategies for LN.

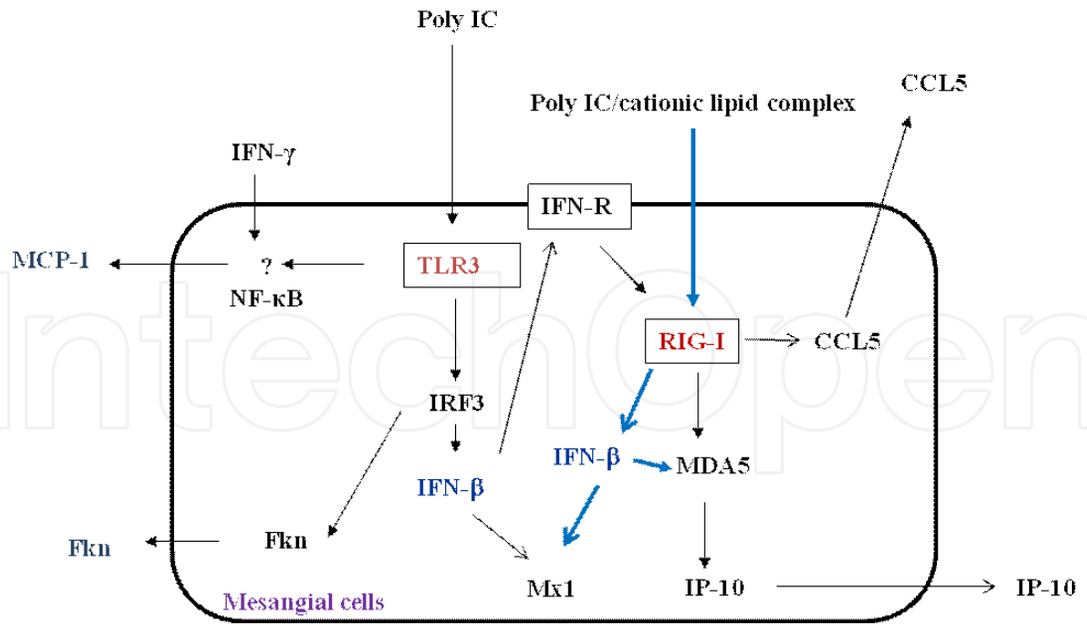

Figure 3. Proposed inflammatory signaling pathways via TLR3 induced by poly IC (black arrows) and RIG-I induced by poly IC/cationic lipid complex (blue arrows) in human mesangial cells (MCP-1, monocyte chemoattractant protein-1; Fkn, fractalkine; IFN, interferon; NF-κB, nuclear factor kappa B; TLR, toll-like receptor; IRF3, interferon regulatory factor 3; Mx1, human myxovirus resistance protein 1; RIG-I, retinoic acid-inducible gene-1; MDA5, melanoma differentiation-associated gene-5; IP-10, interferon (IFN)-γ-induced protein 10; CCL5, CC chemokine ligand 5).

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Author details

Hiroshi Tanaka[1,2], Kazushi Tsuruga[2] and Tadaatsu Imaizumi[3]

1 Department of School Health Science, Faculty of Education, Hirosaki University, Japan

2 Department of Pediatrics, Hirosaki University Hospital, Japan

3 Department of Vascular Biology, Hirosaki University Graduate School of Medicine, Hirosaki, Japan

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