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G. 知的財産権の出願・登録状況 (予定を含む)

1. 特許取得

出願

2012年2月6日　日本国特許出願　特発性炎症性筋疾患の予防または治療剤　(出願番号：特願2012-023521)　(上阪)

2012年3月21日　日本国特許出願　特発性炎症性筋疾患の予防又は治療剤　(出願番号：特願2012-063595)　(上阪)

2. 実用新案登録

なし

3. その他

なし

III　研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表（平成23-25年度）

雑誌

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Review

The role of M3 muscarinic acetylcholine receptor reactive T cells in Sjögren's syndrome: A critical review

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ABSTRACT

CD4+ T cells constitute the majority of infiltrating cells in salivary glands and lachrymal glands of patients with Sjögren's syndrome (SS). The pathophysiology of SS involves T cell recognition of antigens through the T cell antigen receptor, which triggers cytokine production and chronic inflammation. The M3 muscarinic acetylcholine receptor (M3R) molecule is expressed in exocrine glands, such as salivary glands and lachrymal glands, and plays an important role in exocrine secretion. Previous studies indicated the presence of M3R reactive T cells in peripheral blood of 40% of patients with SS and autoantibodies against M3R in sera of 9–100% of the same patients. Thus, M3R is considered a candidate receptor for autoantigen recognition by T and B cells. The relationship between B cell epitopes and the function of anti-M3R antibodies has been reported, suggesting the pathogenic role of anti-M3R antibodies in xerostomia commonly seen in SS patients. We generated new experimental mouse model, M3R-induced sialadenitis (MIS), using $Rag1^{-/-}$ mice inoculated with splenocytes from $M3R^{-/-}$ mice immunized with M3R synthetic peptides. Mice with MIS developed severe SS-like sialadenitis. Cell transfer experiments using $M3R^{-/-}$xIFN$\gamma^{-/-}$ mice and $M3R^{-/-}$xIL-$17^{-/-}$ mice showed that IFNγ and IL-17 are key cytokines in the pathogenesis of sialadenitis. These findings indicate the crucial roles of M3R-reactive Th1 and Th17 cells in autoimmune sialadenitis, and suggest that these cells, in addition to anti-M3R antibodies, are potential targets in new treatments for SS.

1. Introduction

Sjögren's syndrome (SS) is an autoimmune disease characterized by lymphocytic infiltration in the lachrymal and salivary glands, leading to dry eyes and mouth. Similar infiltration is also found in the kidneys, lungs, thyroid, and liver. Immunohistochemical studies have shown that most infiltrating lymphocytes in the labial salivary/lachrymal glands and kidneys are CD4+ T cell receptor (TCR)αβ T cells. The antigen specificity of T cells is governed by the expression of T cell receptor (TCR) on T cells. The usage of TCR α and TCR β genes of T cells in some organs have been examined by immunological and molecular biological methods. Autoantigens recognized by T cells infiltrating the salivary glands have been analyzed and several candidate autoantigens have been clarified.

In this review, we focus on M3 muscarinic acetylcholine receptor (M3R) in patients with SS as a salivary glands-specific autoantigen (Fig. 1). To date, five subtypes of muscarinic acetylcholine receptors (M1R-M5R) have been identified, and M3R is expressed in exocrine glands and plays crucial roles in exocrine secretion. Acetylcholine binds to and activates M3R on salivary gland cells, causing a rise in intracellular Ca^{2+} concentration via inositol 1, 4, 5-triphosphate (IP3) and IP3 receptors. Consequently, the rise in intracellular Ca^{2+} concentration activates apical membrane Cl^- channels and induces salivary secretion [1]. Activation of M3R also induces trafficking of aquaporin 5 (AQP5) to the apical membrane from the cytoplasm, which causes rapid transport of water across the cell membrane [2]. M3R has four extracellular domains; the N-terminal region, the first, second, and third extracellular loops. Among these domains, the second extracellular loop is critical for receptor activation by agonists [3]. We review B cell epitopes and T cell epitopes on M3R molecule and their functions of anti-M3R antibodies (Abs) and M3R reactive T cells. Furthermore, we describe in this review mice with experimentally-induced SS. These mice were generated to determine the pathogenic role of M3R reactive T cells in autoimmune sialoadenitis. Using this model, we discuss the role of M3R reactive T cells (Th1 and Th17 cells) in the pathogenesis of SS.

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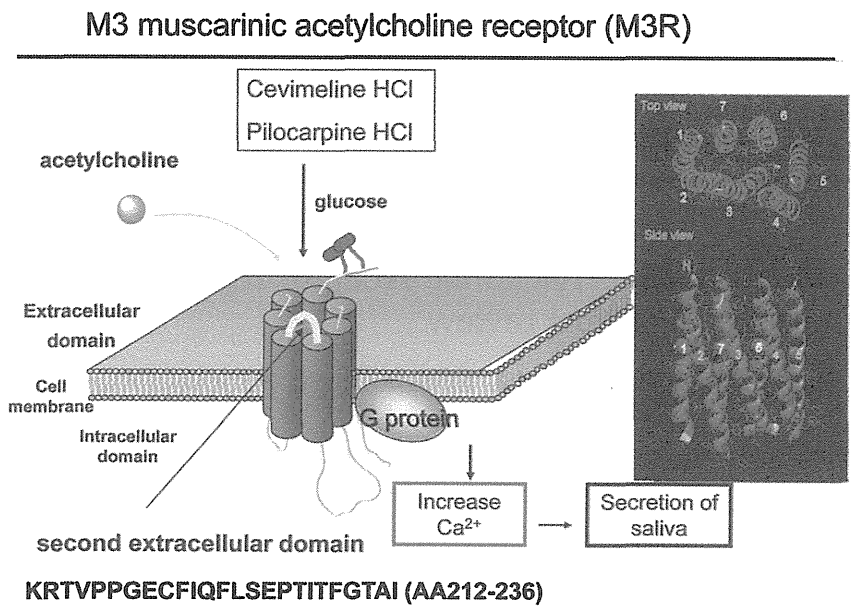

Fig. 1. Structure of M3R molecule and individual domains. The N-terminal domain comprises amino acids 1–68, the first extracellular domain is AA125-144, the second extracellular domain is AA213-237, and the third extracellular domain is AA 511-530. (reference [25]).

2. T cells and autoantigens in various organs of patients with SS

SS is an autoimmune disease characterized by infiltration of lymphocytes into the lachrymal and salivary glands, leading to dry eyes and mouth. Infiltration of the same cells is also found in the kidneys, lungs, thyroid, and liver. Immunohistochemical studies have shown that most infiltrating lymphocytes are CD4+αβ T cells. The antigen specificity of T cells is governed by the TCR expressed on T cells. Thus, the use of TCR α and TCR β genes has been examined by immunological and molecular biological methods. Employing polymerase chain reaction (PCR), T cell lines, immunofluorescence staining, and flowcytometry, several studies have demonstrated the presence of TCR Vβ and Vα genes on T cells present in the salivary glands, lachrymal glands, kidneys and peripheral blood of patients with SS, suggesting a preferential selection of TCR genes. Moreover, sequence analysis of the CDR3 region has indicated the presence of certain conserved amino acid motifs. These observations support the notion that infiltrating T cells recognize relatively few epitopes on the autoantigen [4–19] as shown in Table 1.

3. M3R reactive T cells in peripheral blood of patients with SS

Autoantigens recognized by T cells that have infiltrated the salivary glands have been analyzed. Several studies [20–23] have identified various potential autoantigen candidates, such as Ro/SSA 52 kDa, α-amylase, heat shock protein, and TCR V β6. In 2006, we provided evidence for the presence of M3 muscarinic acetylcholine receptor (M3R) reactive T cells in peripheral blood of about 50% of patients with SS [23]. Table 2 summarizes the types of autoantigens recognized by T cells infiltrating the salivary glands in patients with SS.

The second extracellular domain of M3R is an interesting molecule, because it plays an important role in intracellular signaling. In one study [23], the 25-mer synthetic amino acids encoding the second extracellular domain of M3R (KRTVPPGECFIQFLSEPTITFGTAI, AA213-237) were used as the antigen for T cells, and the number of INF-γ-producing T cells was counted by flowcytometry using a magnetic activated cell sorting (MACS) secretion assay. The results showed a high proportion of INF-γ-producing T cells among peripheral blood mononuclear cells (PBMC) in 40% of SS patients with HLA-DR B1*0901allele, and confirmed the presence of M3R (2nd position) reactive INF-γ-producing autoreactive T cells among PBMC of SS patients. These results suggested that M3R reactive T cells play a role in the development of SS. Interestingly, the 25 mer amino acids (KRTVPPGECFIQFLSEPTITFGTAI, AA213-237) contain anchored motifs that bind to HLA-DR B1*0901, indicating that this protein is a T cell epitope on the M3R molecule [23].

Table 1
TCR repertoire of T cells infiltrating various organs in SS patients.

TCR repertoire	Methods	Authors	Year	Reference
T cells in salivary glands				
Vβ2/Vβ13	Family PCR	Sumida et al.	1992	[5]
Restricted Jβ	Sequencing	Yonaha et al.	1992	[6]
Vβ5,6,13	Anchored PCR	Dwyer et al.	1993	[7]
Restricted Vβ	T cell lines	Legras et al.	1994	[8]
Conserved CDR3	Sequencing	Sumida et al.	1994	[9]
Limited Vα	Inversed PCR	Sumida et al.	1994	[10]
Vβ2,8	IF	Smith et al.	1997	[11]
Fas-sensitive TCR	SSCP	Sumida et al.	1997	[12]
TCR BV2/AV2	Single cell PCR	Matsumoto et al.	1999	[13]
TCR BV13S2	Quantitative PCR	Kay et al.	1999	[14]
T cells in lachrymal glands				
Heterogeneous Vβ	Family PCR	Mizushima et al.	1995	[15]
Common TCR	SSCP	Matsumoto et al.	1996	[16]
T cell in kidneys				
Vβ2	Family PCR	Murata et al.	1995	[17]
Peripheral T cells				
Decreased TCR Vβ6.7α	FC	Kay et al.	1991	[18]
TCR BV13.2	ARMS-PCR	Kay et al.	1995	[19]

(Reference [4]).
TCR, T cell receptor; PCR, polymerase chain reaction; IF, immunofluorescence; SSCP, single strand conformational polymorphism; FC, flowcytometry; ARMS, amplification refractory mutation system.

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Table 2
T cell epitopes on autoantigens recognized by T cells in SS patients.

Autoantigens	T cell epitopes	Method	Authors	Year	Reference
Ro/SS-A52kD	DEREQLRIFG	T cell lines	Sumida et al.	1996	[20]
HSP10/60	WVNMLRRGI	SSCP	Sumida et al.	1997	[21]
TCRBV6S7	WAEILRIGRV	SSCP	Sumida et al.	1997	[21]
α-amylase	EKMSYLKNWGEG NPFRPWWERYQPV	West-Western	Matsumoto et al.	1999	[22]
M3R	VPPGECFIQFLSEPT	MACS cytokine secretion assay	Naito et al.	2006	[23]

TCR, T cell receptor; PCR, polymerase chain reaction; IF, immunofluorescence; SSCP, single strand conformational polymorphism; FC, flowcytometry; ARMS, amplification refractory mutation system.

4. Presence of anti-M3R antibodies in patients with SS (Table 3)

Experimental and clinical studies suggested the presence of anti-M3R antibodies in patients with SS [24,25]. Bacman and coworkers [26] analyzed IgG in sera of patients with primary SS and focused on its interaction with M3R in rat exorbital lacrimal glands by indirect immunofluorescence (IF) and binding assay. They showed attenuated staining for SS IgG in epithelial cells and demonstrated weakening of the staining intensity by incubation of SS IgG with a synthetic peptide corresponding to the 2nd extracellular loop of M3R. Their results indicated the presence of autoantibodies against the 2nd domain of M3R in patients with SS. Waterman et al. [27] reported that the sera of 5 of 9 (55%) patients with primary SS and from 6 of 6 patients (100%) with secondary SS induced approximately 50% inhibition of carbachol-induced bladder contraction. Furthermore, Gao et al. [28] generated human M3R-expressing CHO cells. They detected anti-M3R autoantibodies in 9 of their 11 (82%) SS patients, and these autoantibodies were of the IgG1, IgG3 and IgA isotypes. Naito et al. [29] also detected autoantibodies against the 2nd extracellular domain of M3R in about 9% (11/122) of their patients with primary SS using synthetic peptides encoding M3R AA213-237. They also detected antibodies against the 2nd extracellular domain of M3R (AA213-237) in 14/102 (14%) of their patients with secondary SS. Their results were the first on the binding of anti-M3R antibodies against synthetic peptides. Marczinovits et al. [30,31] detected antibodies against the 16-mer synthetic peptide KRTVPPGECFIQFLSE(KRSE 213-228) and recombinant glutathione S-transferase (GST)-KRSE fusion protein. The sensitivities of the assays used in their study were 77.5–90% for KRSE and 97% for GST-KRSE, and immunological recognition with the recombinant fusion antigen was significantly better than that for the free peptide. Nakamura et al. [32] showed high prevalence (52.8%, 20/38) of autoantibodies to synthetic peptides encoding the 2nd extracellular domain of M3R in patients with juvenile-onset SS, suggesting that anti-M3R Abs could be useful as a diagnostic marker for juvenile-onset SS.

Tsuboi et al. [33] examined the prevalence of autoantibodies against each of the four synthetic peptides of M3R in patients with SS. They found antibodies to the N-terminal, 1st, 2nd and 3rd domains of SS in 42.9% (18 of 42), 47.6% (20 of 42), 54.8% (23 of 42), and 45.2% (19 of 42), compared with 4.8%, 7.1%, 2.4%, and 2.4% of healthy subjects. These findings confirm the presence of autoantibodies against not only the 2nd extracellular domain of M3R but also the N-terminal, 1st, and 3rd extracellular domains of M3R in sera of patients with SS, and suggest that the detection of these autoantibodies could be employed for the diagnosis of SS.

Recently, He et al. [34] reported the presence of antibodies against cycle 2nd extracellular domain of M3R (AA205-220) (anti-c2M3RP) in the sera of 62.2% of their patients with primary SS. The specificity of anti-c2M3RP antibodies was 95.1%, which was much higher than that for linear polypeptide (84.7%), suggesting that c2M3RP might act as an autoantigen and plays a role in the production of anti-c2M3RP antibodies.

5. B cell epitopes on M3R and functional analysis of anti-M3R antibodies (Table 4)

Functional analysis of IgG in SS patients was conducted by Bacman et al. [26] using nitric oxide synthase (NOS) activation and cGMP production in rat exorbital lacrimal glands. They demonstrated that antibodies against the 2nd extracellular domain of M3R suppressed both NOS activation and cGMP production, suggesting that long-term interaction of anti-M3R antibodies on lacrimal glands could lead to tissue damage through NO release after immunological stimulation. In another study, Waterman et al. [27] demonstrated that their IgG fraction purified from the sera of SS patients inhibited the action of carbachol-induced acetylcholine at M3R in neuronal cells, indicating anti-muscarinic receptor activity in the IgG fraction from their patients. Cavill et al. [35] purified anti-M3R antibodies using affinity column and tested their concentration-dependent inhibition of carbachol-induced colon contractions. They demonstrated that anti-M3R antibodies from SS patients inhibited colon contractions, supporting the notion that antibodies against the 2nd extracellular domain of M3R shares functional properties in patients with SS. In another study, Li et al. [2] purified IgG fraction from sera of SS patients and analyzed its inhibitory activity on pilocarpine-induced Ca influx and AQP-5 expression in rat parotid acinar cells. They showed that SS IgG inhibited Ca influx and modulated pilocarpine-induced APWP -5 trafficking to the apical membrane, suggesting that anti-M3R antibodies are involved in glandular dysfunction and impaired autonomic function in SS patients. Dawson et al. [36] examined the function and activity of IgG isolated from patients with primary SS using microfluorimetric Ca^{2+} imaging and patch clamp electrophysiological techniques in mouse and human submandibular acinar cells. They demonstrated that anti-M3R antibodies resulted in 50% suppression of carbachol-induced increase in Ca^{2+} in mouse

Table 3
Presence of anti-M3R Abs in patients with SS.

SS	B cell epitopes	Frequency	Method	Year	Reference
Primary SS IgG	2nd		IF (rat LG)	1998	[30]
Primary SS IgG	M3R on bladder	55%	functional assay	2000	[27]
Secondary SS IgG	M3R on bladder	100%	functional assay	2000	[27]
IgG1, IgG3, IgA	M3R	82%	M3R–CHO	2004	[28]
Primary SS	2nd (213–237)	9%	ELISA	2005	[29]
Secondary SS	2nd (213–237)	14%	ELISA	2005	[29]
Primary SS	2nd (213–228)	77.5–90%	ELISA	2005	[30,31]
	2nd (fusion protein)	97%	ELISA	2005	[30]
Juvenile-onset SS	2nd (213–237)	52.6%	ELISA	2008	[32]
Primary + secondary SS	N-terminal (1–68)	42.9%	ELISA	2010	[33]
	1st domain (125–144)	47.6%	ELISA	2010	[33]
	2nd domain (213–237)	54.8%	ELISA	2010	[33]
	3rd domain (511–530)	45.2%	ELISA	2010	[33]
Primary SS	cycle-2M3R (205–220)	62.2%	ELISA	2011	[34]

(Reference [24]).
TCR, T cell receptor; PCR, polymerase chain reaction; IF, immunofluorescence; SSCP, single strand conformational polymorphism; FC, flowcytometry; ARMS, amplification refractory mutation system; ELISA, enzyme-linked immunosorbent assay.

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and human acinar cells, indicating that IgG from SS patients contains autoantibodies that can reduce saliva production.

Koo et al. [37] analyzed the role of antibodies using microspectrofluorometry and surface plasmon resonance-based optical biosensor system (BIAcore system). They showed that antibodies against the 3rd extracellular domain of M3R had inhibitory activity against carbachol-induced Ca^{2+} influx in human salivary gland cell lines. They proposed that the 3rd extracellular loop of M3R represented a function epitope bound by SS IgG. In contrast, Tsuboi et al. [33] demonstrated that only autoantibodies against the 2nd extracellular domain of M3R suppressed cevimeline-HCl-induced Ca^{2+} influx in human salivary gland cell lines, whereas antibodies against the N-terminal and 1st extracellular domain of M3R enhanced Ca^{2+} influx, and anti-3rd extracellular domain of M3R had no activity. These findings were supported by two newly established murine monoclonal antibodies against the human 2nd extracellular domain of M3R(213-237) [38]. These two monoclonal antibodies significantly suppressed cevimeline-HCl-induced Ca^{2+} influx in human salivary glands. Moreover, He et al. [34] provided clinical evidence for the close association between anti-M3RP205-220 (2nd extracellular domain of M3R, AA205-220) IgG from SS patients and salivary flow rate, suggesting that these anti-M3R antibodies may be functional. Kovacs et al. [31] also reported that autoantibodies against the second extracellular domain of M3R (AA213-228) were associated with leukopenia in patients with SS. Further examination using specific monoclonal antibodies against each of the four domains is needed to clarify the importance of B cell epitope in dysfunctional salivary production.

Recently, Jin et al. [39] reported that IgG from patients with primary SS reduced the expression level of M3R in the membrane, inhibited carbachol-induced Ca^{2+} transients in human salivary gland cells, and decreased membrane clathrin expression. These results suggest that SS-IgG induces internalization of M3R partly through a clathrin-mediated pathway. Their results also provided support to the notion that anti-M3R antibodies cause salivary dysfunction in patients with SS via not only a reduction in Ca^{2+} influx but also down-regulation of M3R molecules on epithelial cells of salivary glands Tables 3 and 4.

Table 4
B cell epitopes on M3R and function of anti-M3R antibodies in patients with SS.

SS	B cell epitopes	Function	Method	Year	Reference
primary SS IgG	2nd	decreased	NOS/cGMP(rat LG)	1998	[26]
Primary + secondary SS IgG	M3R	inhibit	carbachol/Ach-stimulated bladder contractions	2000	[27]
M3R purified IgG	2nd	inhibit	carbachol-evoked colon contraction	2004	[35]
IgG	M3R	inhibit	pilocarpine-induced Ca influx/2 AQP-5 trafficking (rat PAC)	2004	[2]
Primary SS	2nd (213–228)		associated with leukopenia	2005	[31]
Primary SS IgG	M3R	reduction	Ca influx (mouse and human SAC)	2006	[36]
Primary + secondary SS IgG	3rd (514–527)	inhibit	Ca influx (HSG)	2008	[37]
Primary + secondary SS	N-terminal(1–68)	increase	Ca influx (HSG)	2010	[33]
	1st (125–144)	increase	Ca influx (HSG)	2010	[33]
	2nd (213–237)	decrease	Ca influx (HSG)	2010	[33]
	3rd (511–530)	no change	Ca influx (HSG)	2010	[33]
mouse monoclonal M3R Abs	2nd (213–237)	decrease	Ca influx (HSG)	2012	[38]
Primary SS IgG	2nd (M3RP205-220)		link to saliva flow rate	2012	[34]
Primary SS IgG	M3R		M3R internalization (HSG)	2012	[39]

(Reference [24]).
PAC, parotid acinar cells; SAC, submandibular acinar cells; HSG, human salivary glands cell lines; Ach, acetylcholine.

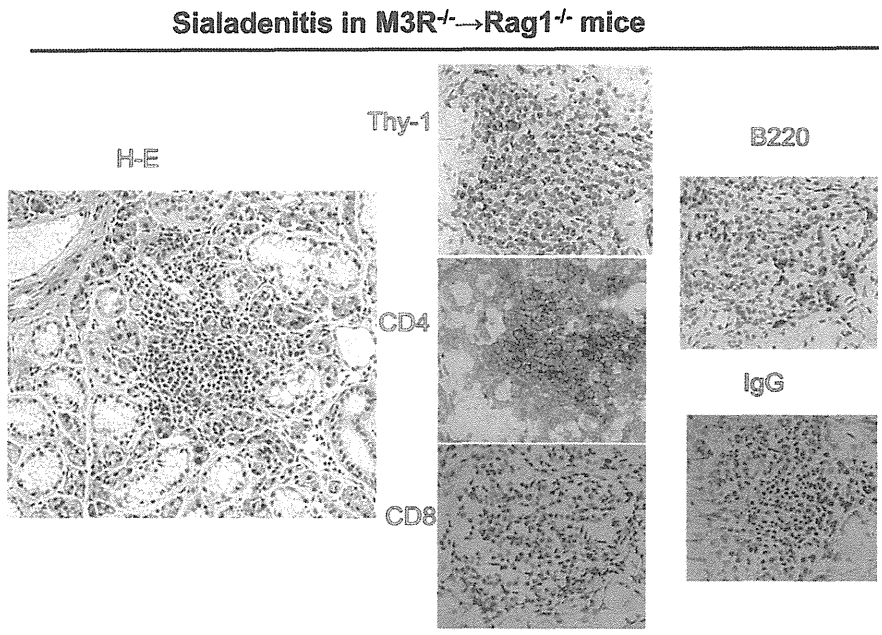

Fig. 2. Histological and immunohistochemical analyses of salivary glands in MIS mice. The moderate ~ severe mononuclear cell infiltration was observed in salivary glands from M3R−/− → Rag1−/− mice. The majority of infiltrating cells was Thy-1+ CD4+ T cells, although CD8+ T cells, B cells, and IgG deposition were present. (reference [25]).

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Table 5
Functions of M3R reactive Th1 and Th17 cells in MIS.

Recipient	Transfer			Sialadenitis
	Cells	Mice	Immunogen	
Rag1 $^{-/-}$	splenocytes	M3R$^{-/-}$	M3R	+++
Rag1 $^{-/-}$	CD3^{+}	M3R$^{-/-}$	M3R	+++
Rag1 $^{-/-}$	CD3^{-}	M3R$^{-/-}$	M3R	–
Rag1 $^{-/-}$	splenocytes	M3R$^{-/-}$ xIFN-γ $^{-/-}$	M3R	+
Rag1 $^{-/-}$	splenocytes	M3R$^{-/-}$ xIL-17$^{-/-}$	M3R	+

6. SS Mouse model: M3R-induced sialadenitis (MIS)

To clarify the role of the immune response to M3R in the pathogenesis of SS, we generated a mouse model with SS-like sialadenitis; the M3R-induced sialadenitis (MIS) model. For this purpose, M3R$^{-/-}$ mice were immunized with murine M3R peptides and their splenocytes were inoculated into Rag1$^{-/-}$ (M3R$^{-/-}$ → Rag1$^{-/-}$) mice [40]. High serum levels of anti-M3R Abs and low saliva volume were detected in M3R$^{-/-}$ → Rag1$^{-/-}$ mice. Histological examination showed marked infiltration of mononuclear cells in the salivary glands, and immunohistochemical analysis demonstrated that the majority of these cells were CD4+ T cells with a few B cells and several IFN-γ- and IL-17-producing cells (Fig. 2). Apoptotic cells were also present in the salivary glands. These histological and immunohistochemical findings in M3R$^{-/-}$ → Rag1$^{-/-}$ mice resemble those seen in the salivary glands of patients with SS.

In another series of experiments, the transfer of CD3+ T cells alone from M3R$^{-/-}$ mice immunized with M3R peptides into Rag1$^{-/-}$ mice resulted in cell infiltration and destruction of epithelial cells in the salivary glands, indicating that M3R reactive T cells are essential for sialadenitis (Table 5). The incidence of sialadenitis was significantly lower in M3R$^{-/-}$xIFN-γ$^{-/-}$ → Rag1$^{-/-}$ mice than the control, suggesting that INF-γ acts as an effector cytokine in the development of autoimmune sialadenitis [41]. In addition, sialadenitis was significantly less common in M3R$^{-/-}$xIL-17$^{-/-}$ → Rag1$^{-/-}$ mice, supporting the notion that IL-17 is also important cytokine for sialadenitis (Iizuka M, in preparation). Judging from the results using IFN-γ and IL-17 knockout mice, we concluded that M3R reactive Th1 and Th17 cells play a crucial role in the generation of sialadenitis (Fig. 3).

Our preliminary data suggested that the major T cell epitope on M3R might be the 1st domain of M3R, because T cells can recognize the 1st domain of M3R and produce both IFN-γ and IL-17. M3R$^{-/-}$ mice immunized with only the 1st domain of M3R induced sialadenitis in M3R$^{-/-}$ → Rag2$^{-/-}$ mice (Asashima et al. in preparation), suggesting that M3R reactive T cells play a pathogenic role in the development of autoimmune sialadenitis like SS. Considered together, the above results highlight the importance of the immune response to M3R in the pathogenesis of SS-like autoimmune sialadenitis.

7. Future antigen-specific therapy

M3R reactive Th1 and Th17 cells play a central role in the generation of SS, suggesting the potential usefulness of T cell target therapy. In general, T cells recognize the peptide antigen in MHC on antigen presenting cells (APC), though the TCR and CD80/86-CD28 interaction is also necessary for T cell activation. We propose the following therapeutic strategy to use analog peptide ligand (APL) of the antigen to suppress TCR recognition of the antigen by T cells.

One of the T cell epitopes in the M3R molecule is the 25 mer amino acids (KRTVPPGECFIQFLSEPTITFGTAI, AA213-237), which

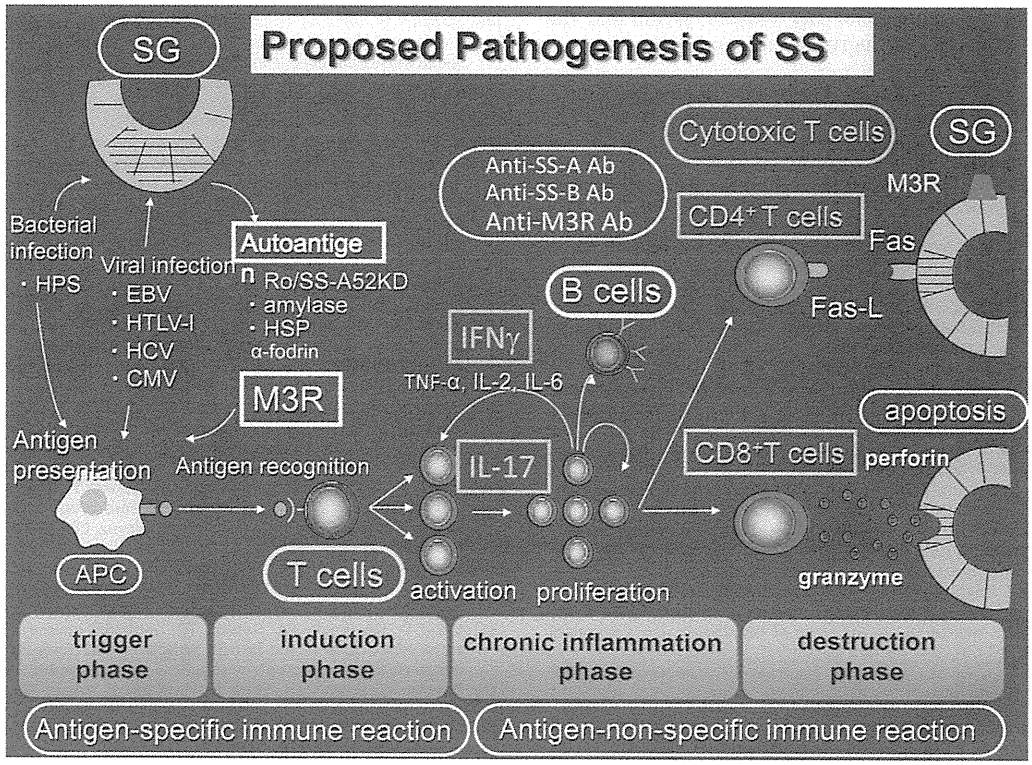

Fig. 3. Proposed pathogenesis of SS. SG: salivary glands, EBV: Epstein Barr virus, HTLV-1: human T-cell lymphotropic virus type I, HCV: hepatitis C virus, CMV: cytomegalovirus, APC: antigen presenting cells, HSP: heat shock protein, M3R: M3 muscarinic acetylcholine receptor, Ab: antibodies, IL: interleukin, IFN: interferon.

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contains anchored motifs that bind to HLA-DR B1*0901. In fact, AA213-237 reactive T cells in PBMC of 40% of SS patients produced IFN-γ [23]. We screened 24 altered peptides that are known to inhibit AA213-237 reactive T cell response, as a marker of INF-γ release *in vitro*. The results demonstrated that VPPGECKQFLSEPT (M3R 223 I → K) and VPPGECFIAFLSEPT (M3R 224 Q → A) are candidate altered peptide ligands of the second extracellular domain of M3R [23]. These encouraging results suggest that the M3R reactive T cell response can be regulated using APL, such as M3R 223I → K and/or M3R 224Q → A, representing antigen-specific therapy, in M3R-induced sialadenitis, without any side-effect (e.g., infection or malignancy).

8. Conclusion

M3R reactive T cells were detected in 40% of patients with SS, suggesting that the M3R immune response in SS might function as an autoantigen recognized by autoreactive T cells. Autoantibodies against M3R were identified in around 50% of SS patients and Abs to the 2nd loop of M3R lowered $[Ca^{2+}]_i$, suggesting that certain anti-M3R Abs act as pathogenic Abs. In MIS mice, M3R reactive Th1 and Th17 cells were essential for the development of sialadenitis, suggesting that M3R reactive T cells play a crucial role in the pathogenesis of SS-like autoimmune sialadenitis. Extrapolation of these studies to human suggests the importance of the M3R immune response in the pathogenesis of SS. Furthermore, early evidence suggests the potential of T cell target therapy as well as B cell target in SS.

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