classification criteria for SS; AECG) (2002年)、アメリカリウマチ学会分類基準 (American College of Rheumatology classification criteria for SS; ACR) (2012年)) が、日常臨床や臨床研究において用いられている。このような複雑な患者背景から、本邦における近年の正確なSS患者数や臨床的特徴、治療の実態は明らかになっていない。

したがって、本研究では本邦におけるSSの頻度、病型、診断および分類基準の満足度、治療の現状を明らかにすることを目的とした。

B. 研究方法

1. 一次調査

本研究班拡大SS分科会において、2011年度にSSに関する全国疫学調査 (一次調査、二次調査) を実施した。一次調査では、全国の医療機関の14095診療科(内科7999、眼科2391、耳鼻咽喉科2011、膠原病内科936、口腔外科758)より、病床数毎(100床未満:5%、100-199床:10%、200-299床:20%、300-399床:40%、400-499床:80%、500床以上:100%)、大学病院:100%、膠原病内科:100%の抽出率により無作為に調査対象診療科を合計4729診療科抽出した (表1)。これらの調査対象診療科に往復はがきを送付し、2010年1年間に受診したSS患者数および二次調査への協力の可否について調査した。

2. 二次調査

一次調査において二次調査への協力の同意が得られた214診療科 (内科56、眼科33、耳鼻咽喉科25、膠原病内科51、口腔外科49) に、二次調査票を送付した。調査票を用いて、SS患者症例毎の年齢、性別、病型 (一次性、二次性)、腺外病変、厚生省改訂診断基準 (JPN) (1999年)、アメリカ・ヨーロッパ改訂分類基準 (AECG) (2002年)、アメリカリウマチ学会分類基準 (ACR) (2012年) の満足度、治療内容に関して情報を収集した。

C. 研究結果

1. 一次調査

一次調査では、1084診療科 (回答率23%、1084/4729診療科) から回答を得た。各診療科からの報告SS患者数をもとに、本邦におけるSS患者数は68,483人と算出された(表2)。

2. 二次調査

二次調査では98診療科から2195例のSS患者の調査票を回収した。平均年齢は60.8±15.2歳、男性/女性の比率は1/17.4、病型は一次性/二次性SSが58.5%/39.2%、一次性SSのうち腺型/腺外型は69.1%/24.7% (不明6.2%) であった (図1)。二次性SSに合併する膠原病では、関節リウマチ (rheumatoid arthritis; RA) が38.7%と最多であり、全身性エリテマトーデス (systemic lupus erythematosus; SLE) が22.2%で続いていた (図1)。

JPN基準の満足度は53.8%(1182/2195例)、AECG基準は47.7% (1046/2195例)、ACR基準は49.6% (1089/2195例) であった。一方で、いずれの基準も満たさなかった症例は36.4% (798/2195例) であった (図2)。

治療内容に関して、ステロイドは34.3% (752/2195例)、免疫抑制薬は16.3% (358/2195例)、生物学的製剤は3.1% (68/2195例)、唾液分泌刺激薬は31.7% (695/2195例) で投与されていた (図3)。

D. 考察

一次調査では、2010年1年間に全国の医療機関を受診したSS患者数は68,483人と算出された。2011年10月1日当時の本邦の全人口は127,799,000人と報告されており、SSの有病率は0.05%と推定された。ただし、本研究では、全国の医療機関を受診したSS患者を対象としており、SSの診断は主治医の診断に基づいている。したがって、本研究では医療機関を受診していない症例は含まれておらず、sub-clinicalなSSも算定されていない可能性が考えられる。

二次調査で明らかになった本邦におけるSSの臨床像は、既報と類似していた。二次調査で収集した主治医の診断に基づくSS患者2195例における、診断・分類基準の満足度は50%程度であった。各基準の満足度の一致率に関しては、JPN基準とACR基準は高く (κ係数:0.77-0.80)、AECGと他の2つの基準は中等度(κ係数:0.50-0.56)であった。腺型一次性SS886例中、126例 (14.2%) が

ステロイド投与を受けていた。一方で、一次性SSにおいて免疫抑制薬は主に腺外病変に対して投与されていた。生物学的製剤は3%のみで投与され、主に二次性SSに合併したRAに対して用いられていた。

E. 結論

SSに関する全国疫学調査（一次調査、二次調査）により、本邦におけるSSの頻度、病型、腺外病変、診断および分類基準の満足度、治療の現状が明らかとなった。これらの結果は、今後のSSの重症度分類や診療ガイドラインの策定において、有用な情報になると考えられる。

F. 健康危険情報

なし

G. 研究発表

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H. 知的財産権の出願・登録状況

1. 特許取得

なし

2. 実用新案登録

なし

3. その他

なし

表1　一次調査の対象診療科の抽出

層別	内科		眼科		耳鼻咽喉科		アレルギー・膠原病内科		口腔外科	
	対象科数 / 調査科数	抽出率	対象科数 / 調査科数	抽出率	対象科数 / 調査科数	抽出率	対象科数 / 調査科数	抽出率	対象科数 / 調査科数	抽出率
一般	3095	5.1%	405	4.7%	228	4.8%	306	100.0%	69	4.3%
99床以下	158		19		11		306		3	
一般	2367	10.0%	582	10.1%	446	9.9%	270	100.0%	126	10.3%
100-199床	236		59		44		270		13	
一般	1023	19.9%	391	19.9%	355	20.0%	130	100.0%	101	19.8%
200-299床	204		78		71		130		20	
一般	662	40.0%	387	39.5%	369	40.1%	67	100.0%	125	40.0%
300-399床	265		153		148		67		50	
一般	321	79.8%	211	80.1%	204	78.4%	48	100.0%	87	81.6%
400-499床	256		169		160		48		71	
一般	384	100.0%	286	100.0%	282	100.0%	67	100.0%	167	100.0%
500床以上	384		286		282		67		167	
大学病院	147	100.0%	129	100.0%	127	100.0%	48	100.0%	83	100.0%
	147		129		127		48		83	
総対象科数	7999		2391		2011		936		758	14095
総調査科数	1650		893		843		936		407	4729

(Tsuboi H, et al. Mod Rheumatol, 2013 [Epub ahead of print])

表2　一次調査
全国のシェーグレン症候群患者数の算出

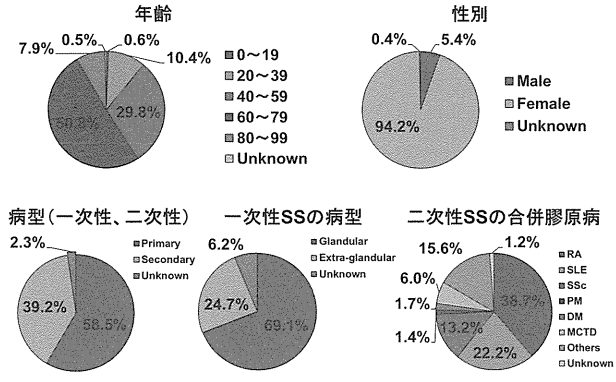
	一次調査送付診療科数	返信数	返信率(%)	報告患者数	対象科数	全国患者数
総計	4729	1084	23%	12401	14095	68483

＜全国患者数の算出方法＞

Σ［各層別毎の（報告患者数 / 返信数）×対象診療科数］

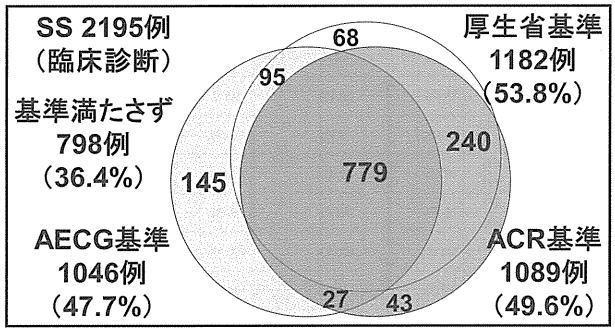
(Tsuboi H, et al. Mod Rheumatol, 2013 [Epub ahead of print])

図1　二次調査（N=2195）年齢、性別、病型



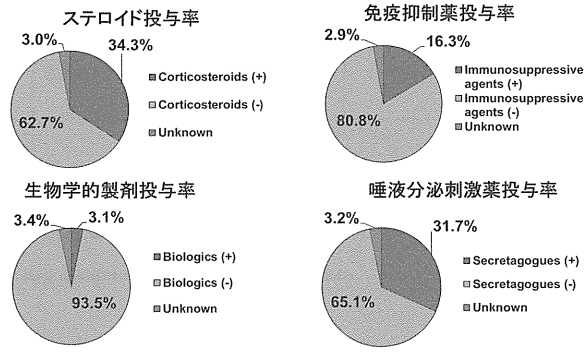
(Tsuboi H, et al. Mod Rheumatol, 2013 [Epub ahead of print])

図2　二次調査（N=2195）
3つの診断・分類基準の満足度の比較



(Tsuboi H, et al. Mod Rheumatol, 2013 [Epub ahead of print])

図3　二次調査（N=2195）
ステロイド、免疫抑制薬、生物学的製剤、唾液分泌刺激薬の投与率



(Tsuboi H, et al. Mod Rheumatol, 2013 [Epub ahead of print])

IV　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25年度）

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研究成果の刊行に関する一覧表（平成25年度）

書籍

著者氏名	論文タイトル名	書籍全体の編集者名 書籍名	出版社名 出版地	出版年 ページ
住田孝之	これからの治療の展望	住田孝之、川上純 シェーグレン症候群の診断と治療マニュアル 改訂第2版	診断と治療社 東京	2014 242-246
三村俊英, 秋山雄次, 舟久保ゆう, 佐藤浩二郎, 中嶋京一, 梶山浩, 横田和浩, 吉田佳弘	自己抗体,リウマチ性疾患・アレルギー性疾患・免疫不全症	黒川清／春日雅人／北村聖 臨床検査データブック	医学書院 東京	2013 430-451, 889-899
三村俊英	免疫・アレルギー疾患	北村聖 臨床病態学2巻	ヌーヴェルヒロカワ 東京	2013 522-528
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細野　祐司、中嶋　蘭、　三森　経世	抗MDA5抗体と皮膚筋炎	矢田　純一、羅　智靖 臨床免疫・アレルギー科	科学評論社 東京都	2013 110-114
中嶋　蘭、　藤井　隆夫、三森　経世	自己免疫疾患の新規自己抗体:新しい筋炎特異的抗体	高久　史麿、尾前　照雄 Pharma Medica	メジカルビュー社 東京都	2013 31-35
室　慶直	顔面の馬蹄形～環状浸潤性紅斑から疑うSjögren症候群	総編集　古江増隆、専門編集　土田哲也 皮膚科臨床アセット20 日常診療において忘れてはならない皮膚科症候群	中山書店 東京	2013 41-45
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谷口紗織, 小川 葉子, 坪田一男	「7. コアメカニズムの考え方と治療　眼鏡による治療」	横井則彦 専門医のための眼科診療クオリファイ　19　ドライアイスペシャリストへの道	中山書店 東京	2013 256-257
小川 葉子	ドライアイ　外来で診る　眼科疾患	坪田一男、根岸一乃 慶應義塾大学薬学部	應義塾大学薬学部 東京	2013 51-70
坪井洋人、浅島弘充、住田孝之	自己抗体	住田孝之、川上純 シェーグレン症候群の診断と治療マニュアル 改訂第2版	診断と治療社 東京	2014 94-103

Ⅴ　平成25年度班会議プログラム

プログラム

9:00- 9:30　班全体およびSS分科会統括　住田孝之

9:30- 9:50　SLE/ AOSD分科会統括　山本一彦(代:山田亮)

9:50-10:10　PM/DM分科会統括　上阪　等

10:10-11:40　SS分科会研究報告　座長　住田孝之

1　10:10-10:20　M3Rを分子標的とした自己免疫性唾液腺炎に関する研究3

筑波大学医学医療系(膠原病・リウマチ・アレルギー)　住田孝之

2　10:20-10:30　エストロゲンによるEBウイルス再活性化の制御に関する研究

鶴見大学歯学部　斎藤一郎

3　10:30-10:40　シェーグレン症候群の病態進展における IL-33に関する研究

九州大学大学院歯学研究院 口腔顎顔面病態学講座 顎顔面腫瘍制御学分野　中村誠司

4　10:40-10:50　シェーグレン症候群唾液腺組織および培養唾液腺上皮細胞におけるToll-like receptor3による細胞死下流分子発現に関する研究

長崎大学大学院医歯薬学総合研究科医療科学専攻展開医療科学講座(第一内科)　川上　純

5　10:50-11:00　シェーグレン症候群における口腔内病変と唾液中EGFの関係に関する研究(3)
～3年間の変化の評価～

兵庫医科大学リウマチ・膠原病科　佐野　統

6　11:00-11:10　シェーグレン症候群培養唾液腺上皮細胞におけるケモカイン、サイトカイン発現解析

金沢医科大学血液免疫内科学　梅原久範

7　11:10-11:20　シェーグレン症候群類似のドライアイと加齢的解析に関する研究

慶應義塾大学医学部　眼科　坪田一男

8　11:20-11:30　シェーグレン症候群の診断におけるドライアイ検査の診断精度の検討

東京女子医科大学医学部医学科眼科　高村悦子

9　11:30-11:40　シェーグレン症候群患者に関する全国疫学調査(一次調査、二次調査)

筑波大学医学医療系内科(膠原病・リウマチ・アレルギー)　坪井洋人

11:40-12:20　昼食

12:20–14:00　　SLE/AOSD分科会研究報告　　座長　山本一彦

1　12:20–12:30　全身性自己免疫疾患を抑制する転写因子Egr2の誘導機構に関する研究

東京大学医学部アレルギー・リウマチ内科　山本一彦

2　12:30–12:40　SLE/ASODの遺伝因子解析に関する研究

京都大学大学院医学研究科　山田　亮

3　12:40–12:50　FcγレセプターIIB欠損マウスを用いたRAとSLEの特異性を決める遺伝的要因についての研究

順天堂大学　膠原病内科　天野浩文

4　12:50–13:00　細胞特異的FcγRIIB 欠損マウスを用いたループス腎炎発症機序の解析

順天堂大学大学院医学研究科分子病理病態学　広瀬幸子

5　13:00–13:10　全身性エリテマトーデスにおけるMAIT細胞の解析

順天堂大学免疫学講座　三宅幸子

6　13:10–13:20　全身性エリテマトーデス難治性病態の治療標的分子探索に関する研究

慶應義塾大学医学部リウマチ内科　竹内　勤

7　13:20–13:30　全身性エリテマトーデスにおける尿中ポドサイトマーカーに関する研究

埼玉医科大学リウマチ膠原病科　三村俊英

8　13:30–13:40　抗リン脂質抗体陽性全身性エリテマトーデスの血栓形成機序解析に関する研究

北海道大学大学院医学研究科免疫・代謝内科学分野　渥美達也

9　13:40–13:50　Still病の治療法、およびSLEを含む膠原病患者の抗ACE2抗体に関する研究

国立国際医療研究センター　三森明夫

10　13:50–14:00　B 細胞を標的とした全身性エリテマトーデスの治療の開発に関する研究

産業医科大学医学部第一内科学講座　田中良哉

14:00–14:20　　コーヒーブレイク

14:20–15:50　　PM/DM分科会研究報告　　座長　上阪　等

1　14:20–14:30　細胞傷害性T細胞阻害による自己免疫性筋炎治療に関する研究

東京医科歯科大学大学院　膠原病・リウマチ内科学　上阪　等

2　14:30–14:40　皮膚筋炎におけるmicroRNA解析

熊本大学大学院生命科学研究部皮膚病態治療再建学分野　神人正寿

3　14:40–14:50　マウス多発筋炎モデルにおけるL-selectinの役割に関する研究

筑波大学医学医療系皮膚科学　藤本　学

4　14:50–15:00　抗MDA5抗体陽性皮膚筋炎における抗体価の推移と生命予後の関連性に関する研究

京都大学大学院医学研究科内科学講座臨床免疫学　三森経世

5　15:00–15:10　自施設膠原病患者における抗EJ抗体の臨床的意義

名古屋大学大学院医学系研究科　皮膚結合組織病態学　室　慶直

6　15:10–15:20　筋炎の病理所見と自己抗体との関連の検討

東京大学医学系研究科神経内科　清水　潤

7　15:20–15:30　皮膚筋炎患者血清が微小血管構成細胞に与える影響に関する検討

山口大学大学院医学系研究科神経内科学　神田　隆

8　15:30–15:40　Myositis Disease Activity Core Setを用いた評価により明らかとなった外来における多発性筋炎/皮膚筋炎患者の疾患活動性と身体機能の現状把握に関する研究

東京女子医科大学リウマチ科　川口鎮司

9　15:40–15:50　多発性筋炎/皮膚筋炎患者の有所見割合－臨床調査個人票の解析－

埼玉医科大学医学部公衆衛生学　太田晶子

10　15:50–16:00　多発(性)筋炎/皮膚筋炎(PM/DM)の診断基準の妥当性に関する疫学調査の進捗状況について

東京医科歯科大学大学院脳神経病態学　石原正一郎

16:00–16:10　　閉会の辞(事務連絡)

VI　研究成果刊行物・別刷

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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$^{-/-}$xIFNγ$^{-/-}$ 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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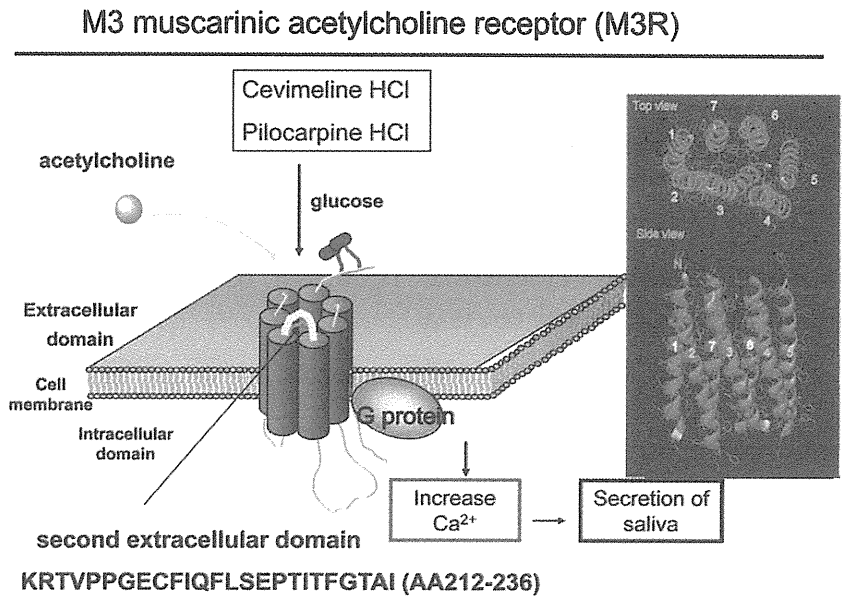

Fig. 1. Structure of M3R molecule and individual domains. The N-terminal domain comprises amino acids 1–68, the first extracellular domain is AA125-144, the second extracellular domain is AA213-237, and the third extracellular domain is AA 511-530. (reference [25]).

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.

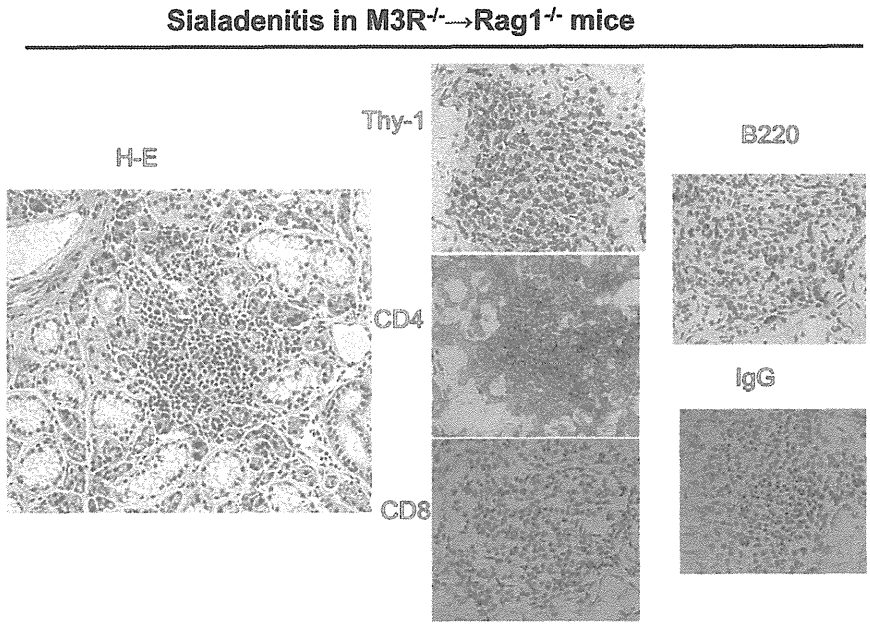

Fig. 2. Histological and immunohistochemical analyses of salivary glands in MIS mice. The moderate ~ severe mononuclear cell infiltration was observed in salivary glands from M3R−/− → Rag1−/− mice. The majority of infiltrating cells was Thy-1+ CD4+ T cells, although CD8+ T cells, B cells, and IgG deposition 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-$\gamma^{-/-}$	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 $Rag1^{-/-}$ ($M3R^{-/-} \rightarrow Rag1^{-/-}$) mice [40]. High serum levels of anti-M3R Abs and low saliva volume were detected in $M3R^{-/-} \rightarrow Rag1^{-/-}$ 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 $M3R^{-/-} \rightarrow Rag1^{-/-}$ 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-$\gamma^{-/-} \rightarrow Rag1^{-/-}$ 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-$17^{-/-} \rightarrow Rag1^{-/-}$ 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 $M3R^{-/-} \rightarrow Rag2^{-/-}$ 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

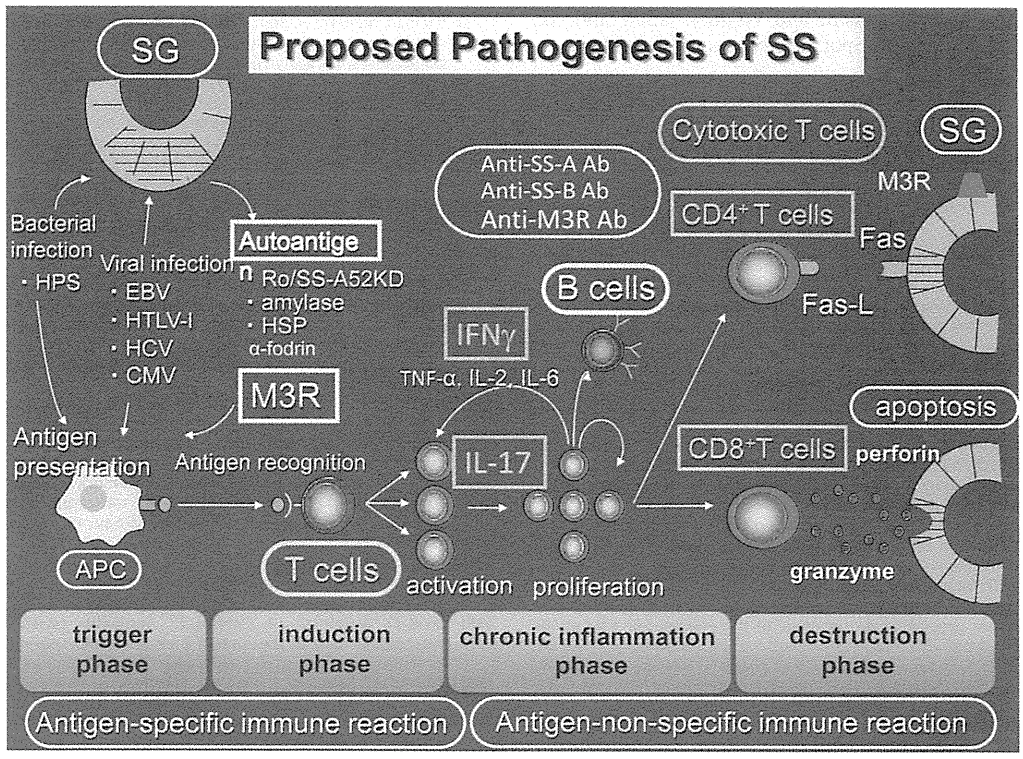

Fig. 3. Proposed pathogenesis of SS. SG: salivary glands, EBV: Epstein Barr virus, HTLV-1: human T-cell lymphotropic virus type I, HCV: hepatitis C virus, CMV: cytomegalovirus, APC: antigen presenting cells, HSP: heat shock protein, M3R: M3 muscarinic acetylcholine receptor, Ab: antibodies, IL: interleukin,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

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