総論

1. **分類基準**：2010 厚労省, 2013 ACR/EULAR, Guideline : 2016 BCR , Review: 2017 Lancet
2. **病態生理**：2019 NRR 線維化メカニズムと治療標的 /TGF-β , 2017 Nature SatM, 2020 JCI $CD4^{+}$CTL, $CD8^{+}$CTL

各論 Recommendation: 2016 JDA, 2016 BCR, 2017 EULAR, 2018 Algorithmは臓器ごとに示す

SSc-ILD：Recommendation, SLS1 (poCY), SLS2 (poCY vs MMF), SLS3 (MMF vs MMF+Pirfenidon), focuSSced (TCZ), HSCT

SSc-PAH：Recommendation, BREATHE (Bosentan), ARIES (Ambrisentan), SUPER (Sildenafil), AMBITION (Ambrisentan +Tadalafil), GRIPHON (Selexipag), PATENT (Riociguat)

SSc-皮膚：Recommendation, mRSS

SSc-血管：Recommendation, RAPIDS (Bosentan), DUAL (Macitentan), SEDUCE (Sildenafil)

SSc-SRC：Recommendation, Guideline 2016 UKSSG, 2016 Nat Rev Nephrology

SSc-腸管：Recommendation

SSc-関節炎, 皮膚石灰化：Recommendation

総論　1. 分類基準

- Criteria：2010 厚労省, 2013 ACR/EULAR
- Guideline : 2016 BCR
- Review: 2017 Lancet

全身性強皮症の診断基準（厚生労働省2010年）

2010 Criteria
厚労省

大基準

両側性の手指を越える皮膚硬化

小基準

①手指に限局する皮膚硬化＊1
②爪郭部毛細血管異常＊2
③手指尖端の陥凹性瘢痕，あるいは指尖潰瘍＊3
④両側下肺野の間質性陰影
⑤抗 Scl-70（トポイソメラーゼ I）抗体，抗セントロメア抗体，抗 RNA ポリメラーゼ III 抗体のいずれかが陽性

除外基準

以下の疾患を除外すること
腎性全身性線維症，汎発型限局性強皮症，好酸球性筋膜炎，糖尿病性浮腫性硬化症，硬化性粘液水腫，ポルフィリン症，硬化性萎縮性苔癬，移植片対宿主病，糖尿病性手関節症，Crow-Fukase 症候群，Werner 症候群

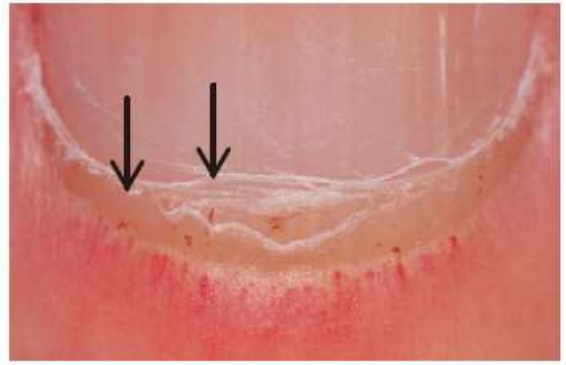
診断の判定

大基準，あるいは小基準①及び②～⑤のうち 1 項目以上を満たせば全身性強皮症と診断する．

注釈

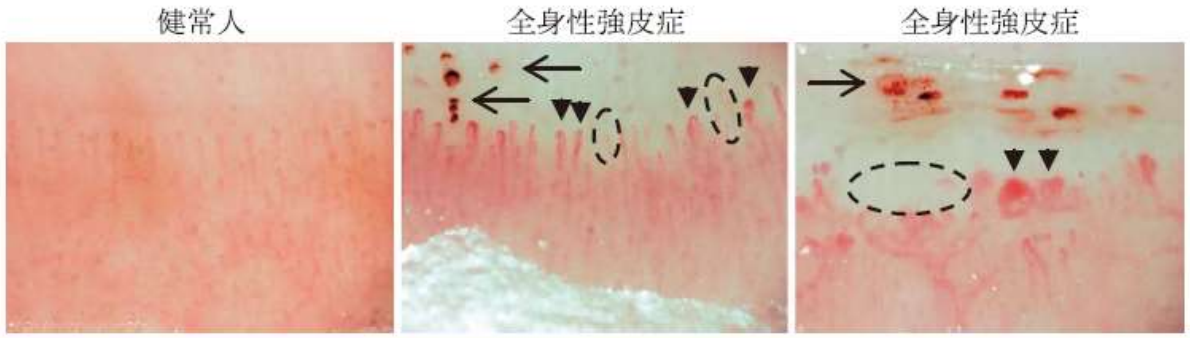
＊1　MCP 関節よりも遠位にとどまり，かつ PIP 関節よりも近位に及ぶものに限る
＊2　肉眼的に爪上皮出血点が 2 本以上の指に認められる#，または capillaroscopy あるいは dermoscopy で全身性強皮症に特徴的な所見が認められる##
＊3　手指の循環障害によるもので，外傷などによるものを除く
#爪上皮出血点（図 1）は出現・消退を繰り返すため，経過中に 2 本以上の指に認められた場合に陽性と判断する
##図 2 に示すような，毛細血管の拡張（矢頭），消失（点線内），出血（矢印）など

図 1　爪上皮出血点



[日本皮膚科学会ガイドライン(2016)]

図 2　capillaroscopy 像



2013 Classification Criteria for Systemic Sclerosis

An American College of Rheumatology/European League Against Rheumatism Collaborative Initiative

[Arthritis Rheum. 2013 Nov;65(11):2737-47.]

Table 1. The American College of Rheumatology/European League Against Rheumatism criteria for the classification of systemic sclerosis (SSc)*

Item	Sub-item(s)	Weight/score†
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints *(sufficient criterion)*	–	9
Skin thickening of the fingers *(only count the higher score)*	Puffy fingers	2
	Sclerodactyly of the fingers (distal to the metacarpophalangeal joints but proximal to the proximal interphalangeal joints)	4
Fingertip lesions *(only count the higher score)*	Digital tip ulcers	2
	Fingertip pitting scars	3
Telangiectasia	–	2
Abnormal nailfold capillaries	–	2
Pulmonary arterial hypertension and/or interstitial lung disease *(maximum score is 2)*	Pulmonary arterial hypertension	2
	Interstitial lung disease	2
Raynaud's phenomenon	–	3
SSc-related autoantibodies (anticentromere, anti–topoisomerase I [anti–Scl-70], anti–RNA polymerase III) *(maximum score is 3)*	Anticentromere	3
	Anti–topoisomerase I	
	Anti–RNA polymerase III	

* These criteria are applicable to any patient considered for inclusion in an SSc study. The criteria are not applicable to patients with skin thickening sparing the fingers or to patients who have a scleroderma-like disorder that better explains their manifestations (e.g., nephrogenic sclerosing fibrosis, generalized morphea, eosinophilic fasciitis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft-versus-host disease, diabetic cheiroarthropathy).
† The total score is determined by adding the maximum weight (score) in each category. Patients with a total score of ≥9 are classified as having definite SSc.

2013 Criteria ACR/EULAR

- 感度 91%, 特異度 92%
  (1980 ACR criteriaはSen 75%, Spe 72%)
- スコアリング
  1. 両手指のMCPより近位の皮膚硬化: 9 [Sufficient criterion]
  2. 手指の硬化[Score高い方]: Puffy fingers 2, or MCPより遠位だがPIPより近位の硬化 4
  3. 指尖部病変[Score高い方]: 指尖部潰瘍 2, or 指尖部陥凹瘢痕(pitting scar) 3
  4. Telangiectasia: 2
  5. Abnormal nailfold capillaries: 2
  6. PAH and/or ILD: PAH 2, or ILD 2
  7. Raynaud's phenomenon: 3
  8. SSc関連自己抗体: ACA or Anti-topoisomerase I or anti-RNA pol3 のいずれか陽性で3
- 合計9以上でSScと分類.
- 指をspareする皮膚硬化患者には適応できない
- 他疾患で説明可能な患者も除外
  (Nephrogenic sclerosing fibrosis[腎性全身性線維症: Gd造影剤], generalized morphea[汎発型限局性強皮症], eosinophilic fasciitis[好酸球性筋膜炎], scleroderma diabeticorum[糖尿病性浮腫性硬化症], scleromyxedema, erythromyalgia[肢端紅痛症], porphyria, lichen sclerosis[苔癬硬化症], GVHD, diabetic cheiroarthropathy[糖尿病性手関節症])

2013 Classification Criteria for Systemic Sclerosis

An American College of Rheumatology/European League Against Rheumatism Collaborative Initiative

[Arthritis Rheum. 2013 Nov;65(11):2737-47.]

Table 2. Definitions of items/sub-items in the American College of Rheumatology/European League Against Rheumatism criteria for the classification of systemic sclerosis (SSc)

Item	Definition
Skin thickening	Skin thickening or hardening not due to scarring after injury, trauma, etc.
Puffy fingers	Swollen digits—a diffuse, usually nonpitting increase in soft tissue mass of the digits extending beyond the normal confines of the joint capsule. Normal digits are tapered distally with the tissues following the contours of the digital bone and joint structures. Swelling of the digits obliterates these contours. Not due to other causes such as inflammatory dactylitis.
Fingertip ulcers or pitting scars	Ulcers or scars distal to or at the proximal interphalangeal joint not thought to be due to trauma. Digital pitting scars are depressed areas at digital tips as a result of ischemia, rather than trauma or exogenous causes.
Telangiectasia	Telangiectasiae are visible macular dilated superficial blood vessels, which collapse upon pressure and fill slowly when pressure is released. Telangiectasiae in a scleroderma-like pattern are round and well demarcated and found on hands, lips, inside of the mouth, and/or are large mat-like telangiectasiae. Distinguishable from rapidly filling spider angiomas with central arteriole and from dilated superficial vessels.
Abnormal nailfold capillary pattern consistent with systemic sclerosis	Enlarged capillaries and/or capillary loss with or without pericapillary hemorrhages at the nailfold. May also be seen on the cuticle.
Pulmonary arterial hypertension	Pulmonary arterial hypertension diagnosed by right-sided heart catheterization according to standard definitions.
Interstitial lung disease	Pulmonary fibrosis seen on high-resolution computed tomography or chest radiography, most pronounced in the basilar portions of the lungs, or occurrence of "Velcro" crackles on auscultation, not due to another cause such as congestive heart failure.
Raynaud's phenomenon	Self-reported or reported by a physician, with at least a 2-phase color change in finger(s) and often toe(s) consisting of pallor, cyanosis, and/or reactive hyperemia in response to cold exposure or emotion; usually one phase is pallor.
SSc-related autoantibodies	Anticentromere antibody or centromere pattern seen on antinuclear antibody testing, anti–topoisomerase I antibody (also known as anti–Scl-70 antibody), or anti–RNA polymerase III antibody. Positive according to local laboratory standards.

用語の定義

- Puffy fingers: 指骨や関節の輪郭を曖昧にする腫脹
- Telangiectasia: 圧迫で消失, 解除で復元
- 爪郭部毛細血管異常 (SSc pattern): Capillaryの拡張, 消失±点状出血. Cuticle (甘皮)に見られることもある.
- Raynaud's phenomenon: 二相性以上の色調変化, pallor→ cyanosis→充血

1980 ACR Criteriaの限界: lcSScが分類不能

1980 ACR Scleroderma Classification Criteria

- **Major criterion:** proximal cutaneous sclerosis/skin thickening (non-pitting) proximal to the MCPs (metacarpophalangeal joints), affecting other parts of the body
  - usually bilateral, symmetrical, and almost always including sclerodactyly
  - **The major criterion is sufficient.**
- **Minor criteria: 2 or 3 are needed if no major criterion:**
  - sclerodactyly
  - digital pitting scars of fingertips or loss of substance of the distal finger pad
  - bibasalar pulmonary fibrosis

1 major criterion or ≥ 2 minor criteria were found in 97% of definite SSc cases (sensitivity 97%) but in only 2% of the comparison patients (specificity 98%)

Subcommittee for Scleroderma Criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. *Arthritis Rheum* 1980; 23:581-90.

American College of Rheumatology

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What are the limitations of the 1980 ACR classification criteria for SSc?

1. They don't classify some of those with limited cutaneous SSc
2. They don't always classify early SSc
3. They don't include antibodies that are common in SSc such as anti-centromere
4. They don't include nailfold changes that could help differentiate SSc from primary Raynaud's Phenomenon (RP)

Subcommittee for Scleroderma Criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. *Arthritis Rheum* 1980; 23:581-90

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2013 ACR CriteriaはSen .95, Spe .93

Limitations of the 1980 ACR Scleroderma classification

- Pittsburgh cohort of 639 patients with SSc[1]
  - 20% of limited SSc patients did not *meet ACR criteria*
- French Canadian cohort of 259 patients with SSc[2]
  - 66% of limited SSc patients did not meet *ACR criteria*

- 10 to 20% of limited SSc patients do not meet criteria for SSc[3]
- Many SSc patients diagnosed by expert clinicians would be excluded based on ACR criteria

1. Subcommittee for Scleroderma Criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. *Arthritis Rheum* 1980; 23:581-90 2. Lonzetti LS, *et al. Arthritis Rheum* 2001; 44:735-6. 3. J Walker, J Pope Clinical Rheumatol 2007

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Sensitivity and Specificity on ACR-EULAR Classification Criteria for SSc

	Derivation sample (N=200)		Validation sample (N=405)	
	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
1980 ARA SSc Criteria	.80 (.72-.87)	.77 (.68-.84)	.75 (.70-.80)	.72 (.64-.79)
2001 LeRoy and Medsger criteria	.76 (.68-.84)	.69 (.68-.84)	.75 (.70-.80)	.78 (.70-.85)
2013 SSc Criteria	.95 (.90-.98)	.93 (.86-.97)	.91 (.87-.94)	.92 (.86-.96)

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2016
BCR/BHPR

BSR and BHPR guideline for the treatment of systemic sclerosis (2016)

[Rheumatology 2016;55:1906-10.]

Part A: general approach to SSc management

Importance of early diffuse SSc: current priorities and approach

Recommendations in management of early SSc

(i) Early recognition and diagnosis of dcSSc is a priority, with referral to a specialist SSc centre (III, C).

(ii) Patients with early dcSSc should be offered an immunosuppressive agent: MTX, MMF or i.v. CYC (II/C), although the evidence base is weak. Some patients might later be candidates for autologous haematopoietic stem cell transplant (ASCT; see below).

(iii) D-Pen is not recommended (IIa/C) [6].

(iv) ASCT may be considered in some cases, particularly where there is risk of severe organ involvement, balancing concerns about treatment toxicity (IIa/C) [7].

(v) Skin involvement may be treated with either MTX (II, B) or MMF (III, C). Other options include CYC (III, C), oral steroid therapy (in as low a dose as possible to suppress symptoms, and with close monitoring of renal function; III, C) and, possibly, rituximab (III, C) [8].

(vi) AZA or MMF should be considered after CYC to maintain improvement in skin sclerosis and/or lung function (III, C).

- Early dcSSc(発症<3年)が重要（治療機会はそこだけに限られる）

i. 発症早期のdcSScを診断することが最優先事項

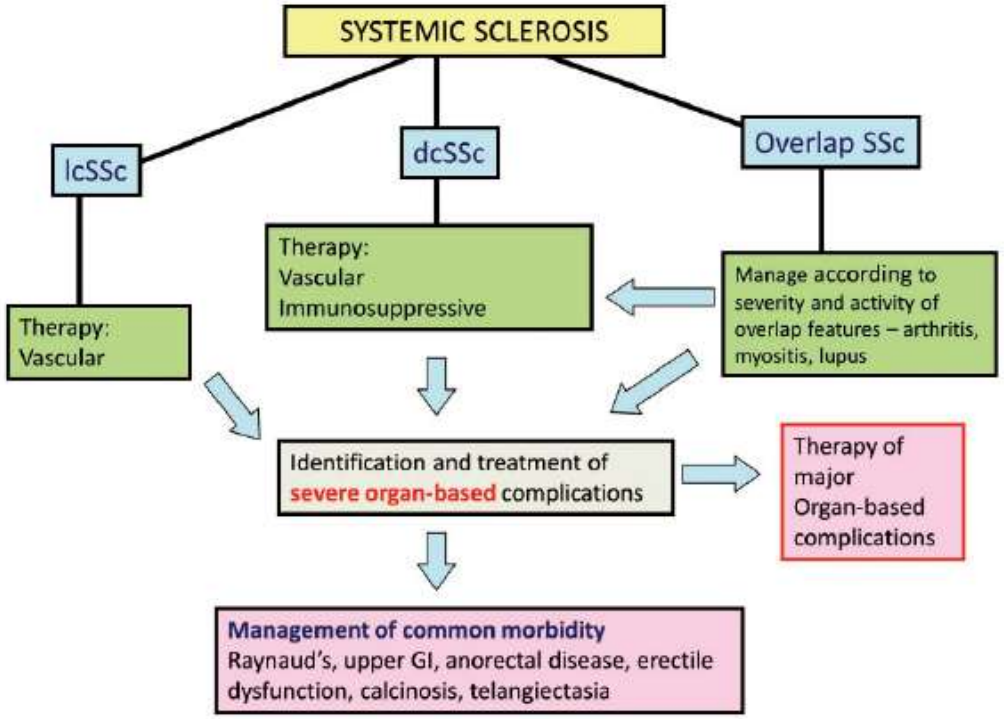
ii. 早期dcSScには免疫抑制剤が検討されるべき：MTX, MMF, IVCY(evidence弱くとも）. 一部患者はASCT(幹細胞移植)検討.

iii. D-ﾍﾟﾆｼﾗﾐﾝは推奨しない

iv. ASCTは重症の臓器障害リスクが高い症例に有益性評価のうえ検討されるかもしれない.

v. 皮膚病変はMTXかMMFで加療. 他の選択肢はCYかPSL(できるだけ少量, 腎機能モニターする) or RTX.

vi. AZAかMMFは皮膚か肺へのCY後の維持療法として検討すべき.



Systemic sclerosis

Lancet 2017; 390: 1685–99

Panel 2: **Typical features of the major subsets of systemic sclerosis**

Limited cutaneous systemic sclerosis

- Distal skin sclerosis
- Long history of Raynaud's phenomenon
- Late-stage complications frequent
- Pulmonary arterial hypertension and severe gut disease frequent and serious

Diffuse cutaneous systemic sclerosis

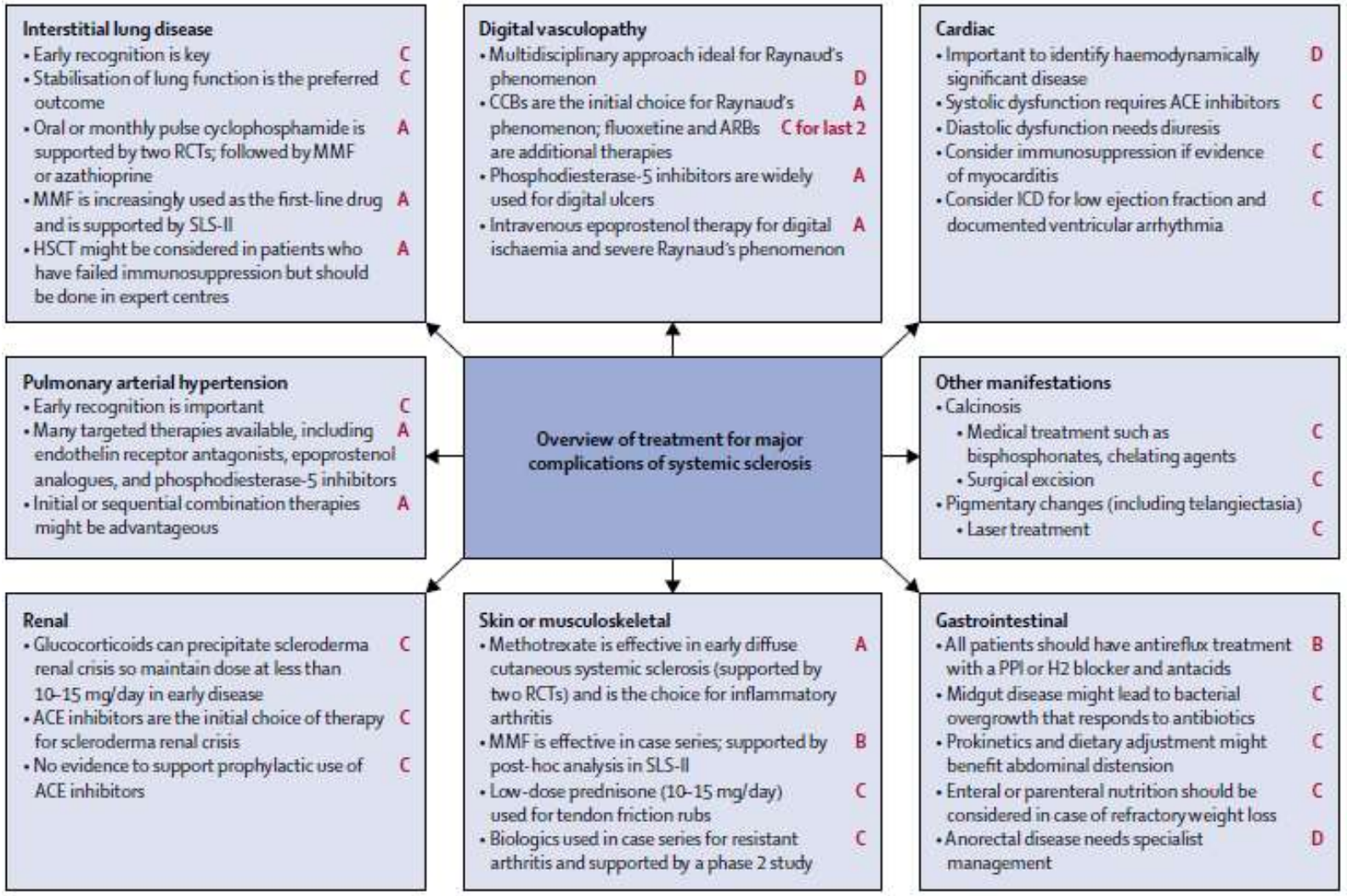
- Proximal limb or trunk involvement, with skin sclerosis
- Short history of Raynaud's phenomenon
- Increased risk of renal crisis and cardiac involvement
- High frequency of severe lung fibrosis

Sine scleroderma

- Raynaud's phenomenon
- Typical systemic sclerosis serology or capillaroscopic features
- No skin thickening
- Organ-based or other vascular manifestations

Systemic sclerosis overlap syndrome

- One of the three subsets together with clinical and investigational features of another autoimmune rheumatic disease



総論　2. 病態生理

- 2019 Nat Rev Rheumatol_線維化メカニズムと治療標的/TGF-β
- 2017 Nature_SatM
- 2020 JCI_$CD4^+$CTL_$CD8^+$CTL

Emerging targets of disease-modifying therapy for systemic sclerosis [Nat Rev Rheumatol. 2019;15(4):208-24.]

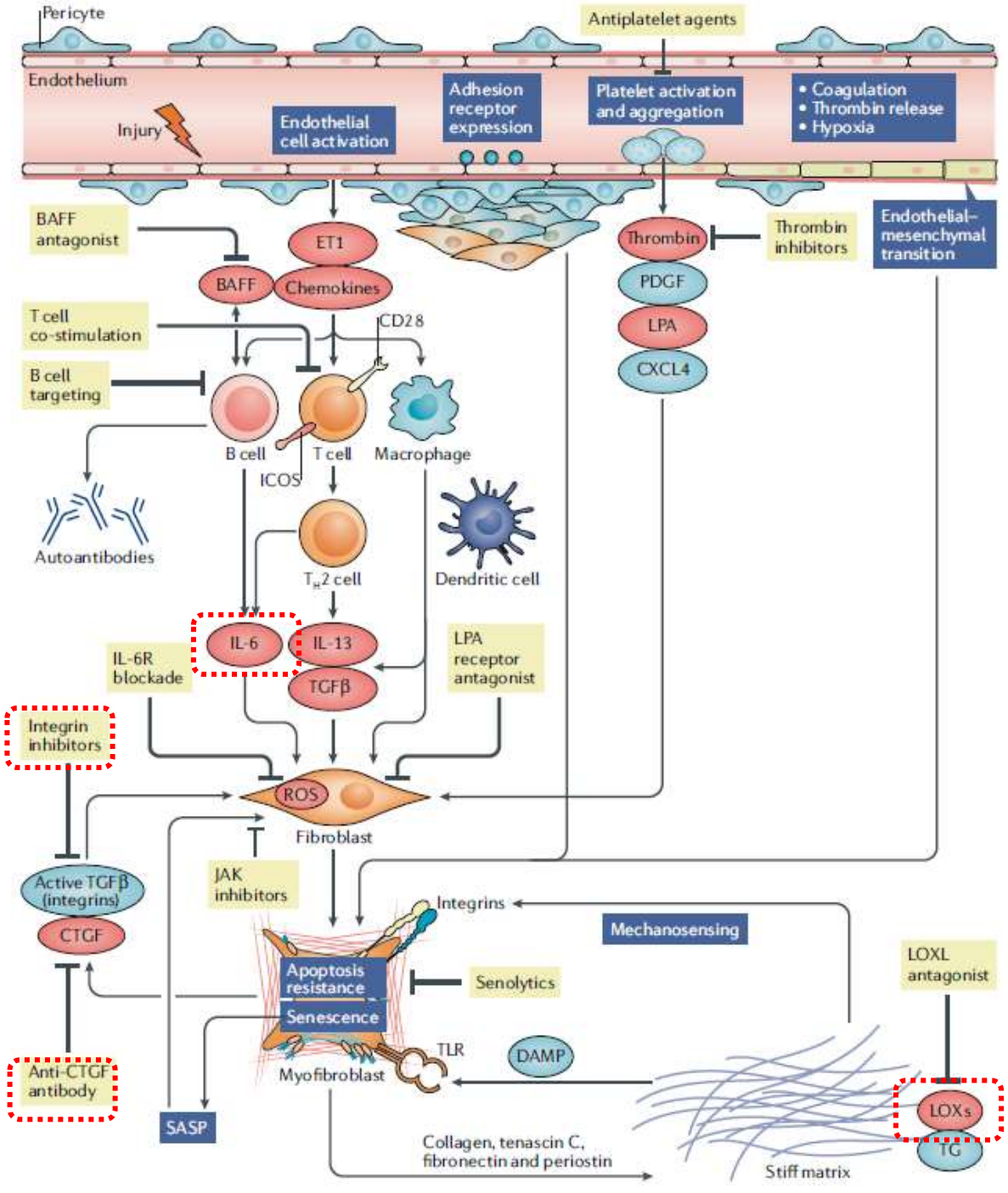
- EULAR recommendation 2017: RP/DUに血管拡張薬[CCB, PDE5i, ERA, Prostanoid]. ILDに免疫抑制剤[MTX, CY]とHSCT. MMFはgraded recommendationがなかったがSLSIIでCYと同等でより安全.
- ACR expert consensus guideline 2018: MMF 1st lineの点が違い. 炎症性関節炎[MTX→PSL/HCQ/TCZ/RTX]
- SScの治療では基本的に血管(RPとPAH)とILDが対象. どの治療もcurableでなく, survivalを大きく改善しない.

Fibrosisについて

- FibrosisはECM(extracellular matrix)の沈着による. 創傷治癒では適切に管理されているが過剰になると組織を無血管の硬い組織と置換し機能障害する.
- 線維化の要素 1)metabolically activated/ apoptosis-resistant myofibloblastの存在(fibroblast/pericyte/内皮細胞由来) 2)ECMをcrosslinkする物質(LOXsが触媒) 3)ECM turnoverの障害.
- 線維化の中心= activated myofibroblast →ECM産生
- TGF-β=線維化を惹起する最重要物質

TGF-βを標的にする

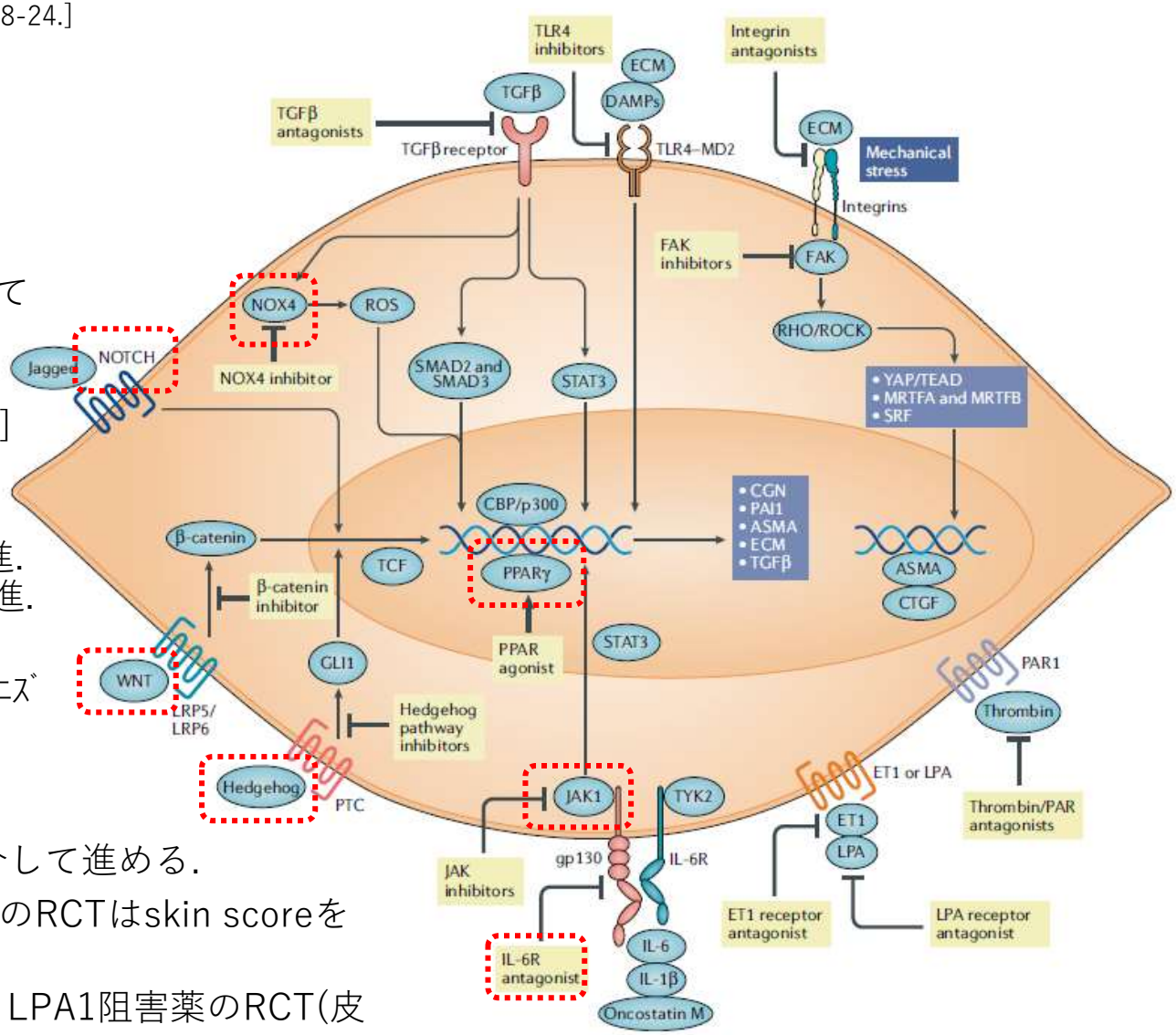
- TGF-β：①上皮・内皮・mesenchymal cellにECM産生させる②上皮/内皮cellのmesenchymal cellへの分化誘導③NOX4刺激しROS産生
- TGF-βはlatent formでECM中に分泌. 活性化(integrin)が治療上重要step.
- Metformin：直接TGF-βに結合して阻害する.
- Fresolimumab：humanized anti-TGF-β Ab(全isoform阻害)小規模SScの皮膚硬化下げたがcontrolなし. 免疫・腫瘍への理論上の懸念あり. 全阻害ではなくαVβ6ｲﾝﾃｸﾞﾘﾝは傷害組織にのみでるのでその阻害のIPFへの治験進行中.
- ﾁﾛｼﾝｷﾅｰｾﾞはTGF-β シグナルを阻害する：imatinib (ABL-1阻害)はSSc効果乏しかった. VEGFとPDGF阻害薬のnintedanibの治験は有用だった(SENSCIS).



Emerging targets of disease-modifying therapy for systemic sclerosis [Nat Rev Rheumatol. 2019;15(4):208-24.]

その他の線維化メカニズム

- IL-6, Oncostatin M, Anti-CTGF Ab
- PPARγ：核受容体TF, この活性化でfibrosis減らす. LanifivranorはRRARγ活性化薬でRCT2施行中. PPARGがSScのSNP.
- Thrombin: fibrinogenをfibrinに変更する. Fibroblastを直接刺激して増殖させSSc患者で多い. Dabigatran (thrombin阻害薬)のRCT1.
- NOX4: TGFbのtargetでSScで発現↑しROS産生. TGF b とWNTのautocrineとして増幅. NOX4阻害薬(GKT137831)SSc抑. [orphan drug]



Developmental pathwayを標的

- WNT: β-cateninとAXIN2を介しfibrosisを促進. 皮膚omicsでも亢進. WNT阻害外用薬(C82). Hedgehog: PTCと結合しGLI1↑. SScで亢進. NOTCHも同様.
- Pirfenidone: myofibroblast分化, TGFb-STAT3ｼｸﾞﾅﾙ抑制するがﾒｶﾆｽﾞﾑ不明. Hedgehog経路は抑制されているらしい.

Inflammation-driven fibrosisを標的

- IL-6: BM由来免疫細胞はIL-6産生して線維化反応をJAK-STATも介して進める.
- SSc患者でIL6高い, IL6KOmouseはBLM誘発線維化に抵抗性. TCZのRCTはskin scoreを改善させた.
- LPA: LPA1はfibroblastに発現, 遊走・ECM産生・生存に関与する. LPA1阻害薬のRCT(皮膚score不変)

Cannabinoid receptorを標的

- Cannabinoid: 植物由来のアラキドン酸→Gﾀﾝﾊﾟｸ結合ﾚｾﾌﾟﾀｰを活性化.CB1はニューロン, CB2は間質細胞. IL6産生抑制する.

Emerging targets of disease-modifying therapy for systemic sclerosis [Nat Rev Rheumatol. 2019;15

炎症システム：自然免疫

- **TLR:** DAMPsを認識. TLR4は皮膚や肺に発現しTGFβへの感受性を亢進させる. TLR4-KO mouse はfibrosis↓でIL6低い. TLR4阻害薬は有用.
- Type 1 IFNが亢進しているのでTLR9がSSc皮膚・肺で亢進, CD3T/CD19Bでも亢進. TLR7/TLR9 antagonistがDM, PsVの治療で開発中.
- **DC:** Detect receptorがある(C-type lectin R, RIG-I R, NOD R). TLR7/TLR9亢進(type1 IFN関連). pDCがSScの臓器浸潤する.
- **Macrophage:** M2 MΦだけがTGF-β, IL-6など産生する. ECMﾘﾓﾃﾞﾘﾝｸﾞなど促進. PentraxinなどSAP(serum amyloid P-component)がMΦの活性化阻害する→IPDについてtrial中.
- **Chemokine:** Monocyte由来 CCL2, CCL7. CCL2-KOはBLM線維化抵抗性. pDCはCXCL4産生. CCL3, CXCL18
- **JAK-STAT:** IFNα/IFNβはtype1 IFN→JAK1活性化. TOFA(JAK1/3), Bari(JAK1/2)がSScに効くかは検討中でTOFAのSScがphase1/2. SScの皮膚でJAK2亢進.

Table 2 | **Potential targets for antifibrotic therapy in SSc**

Mediator	Cellular source	Fibrotic effect	Therapy	Refs
TGFβ family	Leukocytes, fibroblasts and platelets; sequestered in latent form in the ECM; activated in a tissue-specific manner by αV integrins	Stimulates fibroblast proliferation, survival, ECM production and collagen cross linking; associated with myofibroblast transdifferentiation and EMT	• Fresolimumab (monoclonal antibody that targets all three TGFβ isoforms) • Humanized monoclonal antibody to αVβ6 integrin (phase II trial) • Small-molecule inhibitor of αVβ1 integrin	21
IL-6	Fibroblasts, B cells and macrophages	Activated fibroblasts via gp130 and JAK–STAT pathways	Tocilizumab	55,56
Oncostatin M (IL-6 family)	Various	Fibroblast activation via IL-6 receptor and JAK–STAT pathways	GSK233308	31
Thrombin	Generated via the coagulation cascade	PAR1 activation, myofibroblast transdifferentiation and ECM production	Dabigatran	39
LPA	Generated at sites of injury via ENPP2	Fibroblast migration and ECM production	LPA receptor 1 antagonists	59
BAFF	B cells	Promotes B effector cell activation and survival	BAFF antagonists	130
ICOS	T cell co-stimulatory receptor	Promotes T follicular helper cell activation	ICOS inhibitor	194

BAFF, B cell activating factor; ECM, extracellular matrix; EMT, epithelial–mesenchymal transition; ENPP2, ectonucleotide pyrophosphatase/phosphodiesterase family member 2; gp130, IL-6 receptor subunit-β; ICOS, inducible T cell co-stimulator; JAK, Janus kinase; LPA, lysophosphatidic acid; PAR1, protease-activated receptor 1; SSc, systemic sclerosis; STAT, signal transducer and activator of transcription; TGFβ, transforming growth factor-β.

Table 3 | **Inflammatory targets for SSc therapy**

Mediator	Inflammatory effect	Therapies	Refs (ongoing trials)
JAK–STAT signalling	Cytokine receptor-mediated signal transduction via activation downstream of STAT	Tofacitinib: partial and reversible inhibitor of JAK1, JAK2 and JAK3; prevents phosphorylation of STATs	109
B cell activation	Antibody production and IL-6 production; profibrotic cytokines	Rituximab: binds to CD20 on B lymphocytes; recruits antibodies and activates complement, thereby mediating cell lysis	195–197
T cell activation	Profibrotic cytokine production	Abatacept: inhibits T cell activation by binding to CD80 and CD86, thereby blocking their interaction with CD28	198

JAK, Janus kinase; SSc, systemic sclerosis; STAT, signal transducer and activator of transcription.

Emerging targets of disease-modifying therapy for systemic sclerosis [Nat Rev Rheumatol. 2019;15(4):208-24.]

炎症システム：獲得免疫

- **B:** 特異的自己抗体産生がある, SSc皮膚で浸潤多いのでSScとの関連は考えられる. BAFF, APRILが亢進している.
- RTX: 皮膚・肺はopen labelで改善, RCTは3つongoing. BLMは有意差が皮膚になかった.
- **T:** T細胞除外治療は, ABTがRCTが早期dcSScでRCTしたが皮膚で有意差なし.

血管

- **Selexipag(ｳﾌﾟﾄﾗﾋﾞ):** prostacyclin receptor agonist. 1つのRCTで有意差なし[Arthritis Rheumatol. 69, 2370–2379 (2017)], もう1つで有意差あり[Eur. Respir. J. 50, 1602493 (2017)].
- **Macitentan(ｵﾌﾟｽﾐｯﾄ):** Dual ERA. 742人PAHは予後改善[N. Engl. J. Med. 369, 809–818 (2013)], 2RCTで指改善なし[JAMA 315, 1975–1988(2016).].

Table 4 | **Current SSc therapeutics in clinical trials**

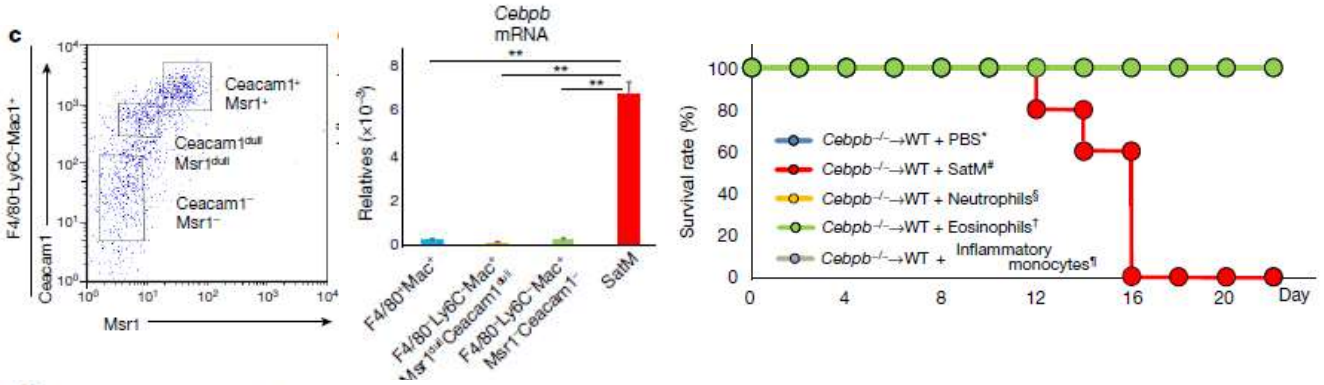
Phase I	Phase II	Phase III	Phase IV
No results available			
• Dimethyl fumarate, NCT02961062 • Human anti-TGFβ1 monoclonal antibody, NCT00043706 • Rilonacept, NCT01538719 • MEDI-551, NCT00946699	• Tofacitinib, NCT03274076 • Sirolimus, NCT03365869 • SAR156597, NCT02921971 • Brentuximab vedotin, NCT03222492 and NCT03198689 • Campath, NCT01639573 • GSK2330811, NCT03041025 • Atorvastatin, NCT02370784 • Fibrogammin P (coagulation factor XIII concentrate), NCT02551042 • Ifetroban, NCT02662511 • Pirfenidone and mycophenolate mofetil versus pirfenidone, NCT03221257 • Bortezomib, NCT02370693 • Crisaborole, NCT03351114 • Abatacept, NCT02161406 • SAR100842, NCT01651143 • IVA337, NCT02503644 • Selexipag, NCT02260557 • JBT-101, NCT02465437 • Riociguat, NCT02283762 and NCT02915835 • Zibotentan, NCT02047708	• Tocilizumab, NCT01532869 and NCT02453256 • Lenabasum, NCT03398837 • Nintedanib, NCT02597933 and NCT03313180 • Rituximab, NCT01862926 • Rosuvastatin, NCT00984932 • Relaxin, NCT00704665	• Polydeoxyribonucleotides, NCT03388255 • Bosentan, NCT01395732
Positive findings			
Fresolimumab, NCT01284322	• Nilotinib, NCT01166139 • Belimumab, NCT01670565 • Pomalidomide, NCT01559129 • Mycophenolate mofetil, NCT00883129	Autologous HSCT, NCT00114530 and NCT01895244	None
Negative findings			
None	Imatinib mesylate, NCT00555581, NCT00613171, NCT00512902, NCT00506831 and NCT00479934	None	None

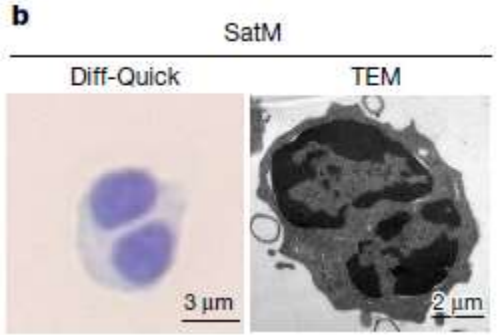
The table shows active and completed interventional trials for systemic sclerosis (SSc) identified in a search of the ClinicalTrials.gov database conducted on 17 July 2018. HSCT, haematopoietic stem cell transplantation; TGFβ1, transforming growth factor-β1.

Identification of an atypical monocyte and committed progenitor involved in fibrosis

Takashi Satoh[1,2*], Katsuhiro Nakagawa[1,2*], Fuminori Sugihara[3], Ryusuke Kuwahara[4], Motooki Ashihara[5], Fumihiro Yamane[1,2], Yosuke Minowa[5], Kiyoharu Fukushima[1,2], Isao Ebina[1,2,5], Yoshichika Yoshioka[3], Atsushi Kumanogoh[6,7] & Shizuo Akira[1,2]

[Nature. 2017;541(7635):96-101.]

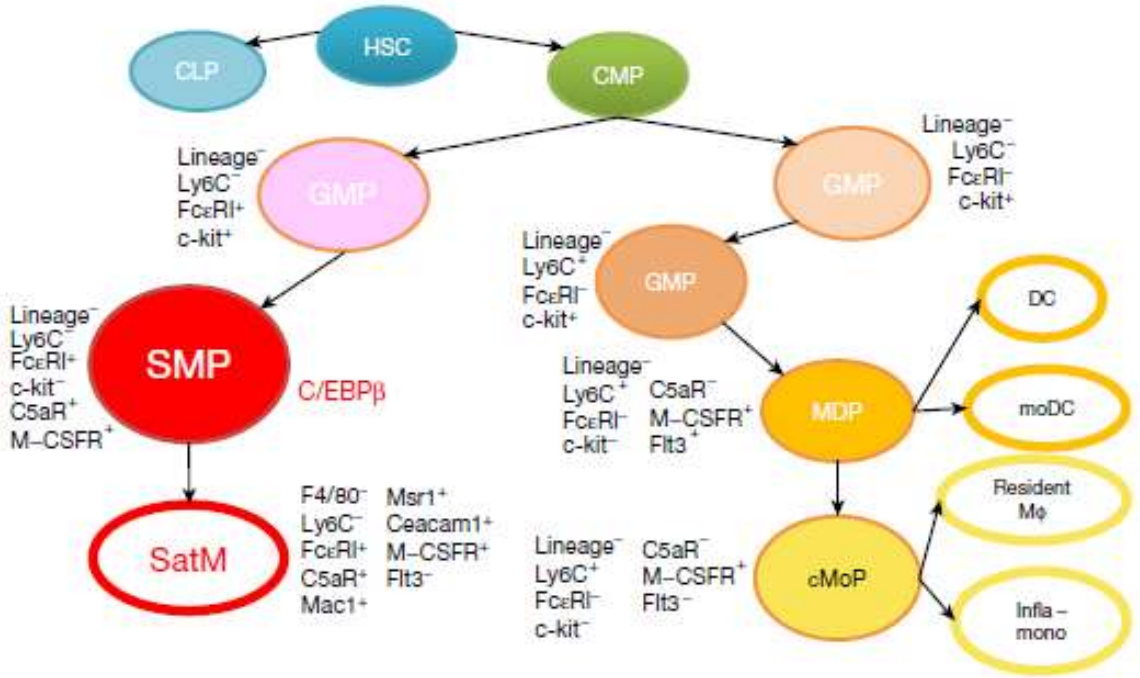




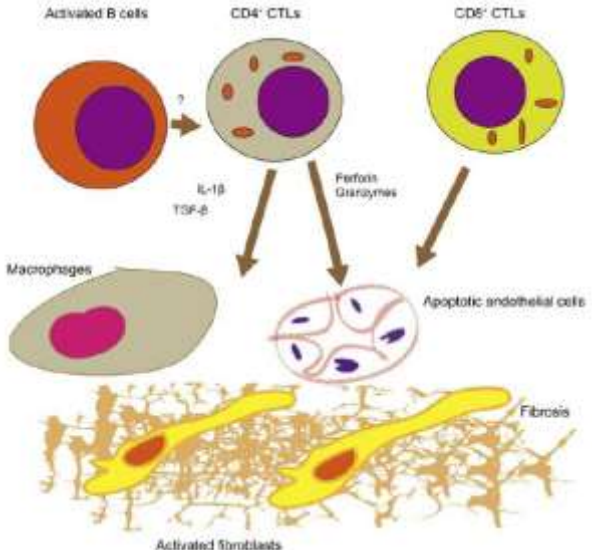
SatM: 核が分葉しGranulocyteとMonocyte両方の特徴があり命名

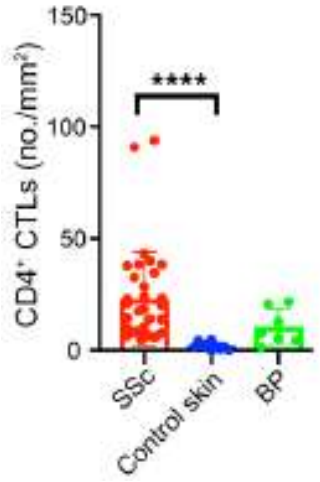
- SatMはTGFβを産生しない.
- SatMと共培養したFibroblastは線維化の因子Spp1発現亢進する.
- SatMはTNF-αを産生する.
- SatMはGranulocyteとMonocyteの両方の遺伝子を発現する.

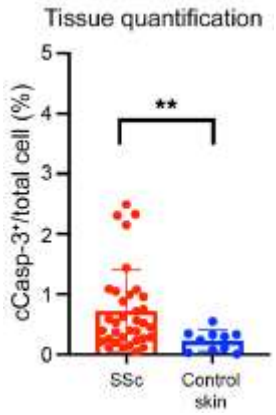
- FibrosisにはMonocyteとMacrophageが関連する.
- Ceacam1⁺Msr1⁺Ly6C⁻F4/80⁻Mac1⁺ monocytes [segregated-nucleus-containing atypical monocytes (SatM)]が線維化にcriticalと発見. 線維化モデルでこれだけ増加している.
- SatMはCCAAT/enhancer binding protein β (C/EBPβ)で規定されている.
- *Cebpb* KOはSatMがなくBLM誘発線維化おこらず, SatM移入で線維化する.
- SatMはLy6C⁻FcεRI⁺ granulocyte/macrophage progenitors 由来で, macrophage/dendritic-cell progenitors 由来ではない.

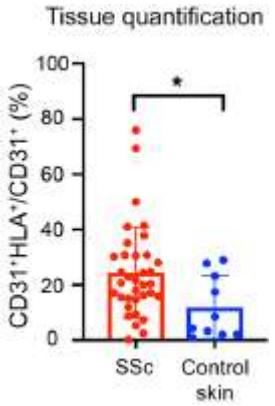


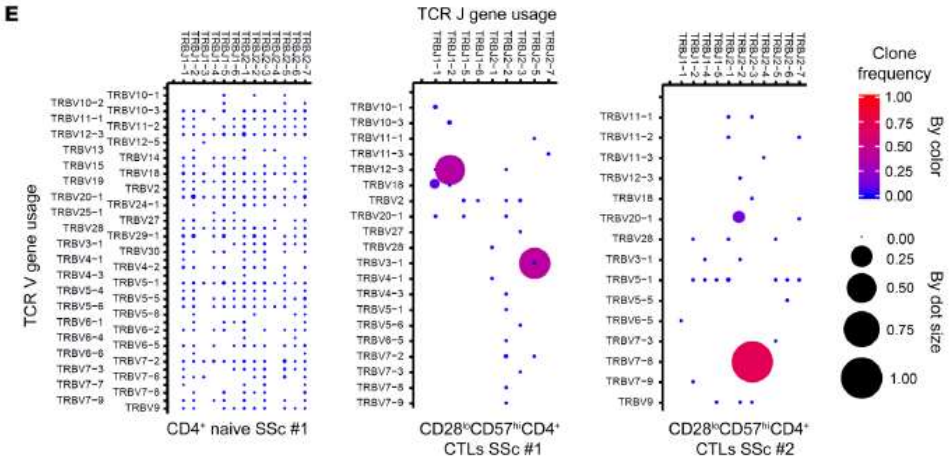
Cytotoxic CD4⁺ T lymphocytes may induce endothelial cell apoptosis in systemic sclerosis [J Clin Invest. 2020;130(5):2451-2464.]

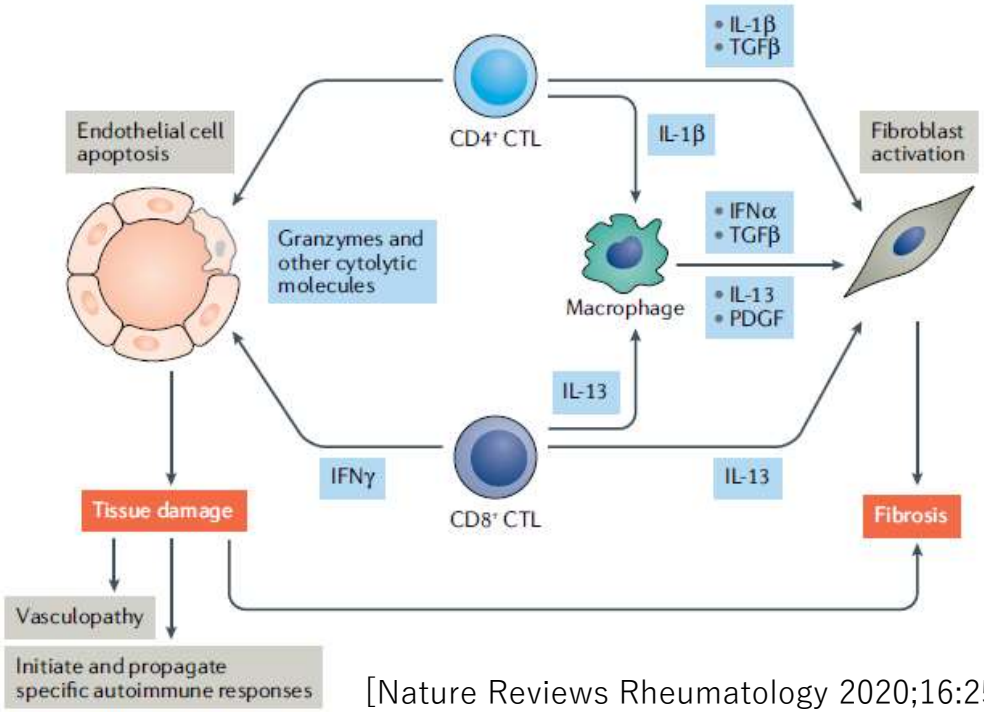












[Nature Reviews Rheumatology 2020;16:253–54.]

- 35人未治療early dcSSc皮膚の解析.
- CD4⁺CTLとCD8⁺CTLが組織に多い.
- SSc皮膚にはapoptotic cellが蓄積しremodelingと線維化,
- HLA-DR⁺ 内皮細胞がSSc apoptosisの標的.でvasculopathyと合致する.
- 血中CD4⁺CTLは代謝活性signatureが高く, clonalに増殖している.
- 強皮症＝CTLが内皮細胞等のapoptosis誘導し, 過剰な組織修復が線維化を起こす疾患, と解釈される.