EURASIAN JOURNAL OF MEDICAL AND NATURAL SCIENCES
Innovative Academy Research Support Center
IF = 9.2 www.in-academy.uz/index.php/ejmns

THE ROLE OF GROWTH FACTOR-B1 IN SYSTEMIC SCLEROSIS

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https://doi.org/10.5281/zenodo.17151636

ARTICLE INFO

Received: 11th September 2025
Accepted: 17th September 2025
Online: 18th September 2025

KEYWORDS

Systemic sclerosis, transformative growth factor-B, mechanism.

ABSTRACT

Systemic sclerosis (SSc) is a complex, multi-organ autoimmune disease of unknown etiology. The manifestation of the disease is caused by the interaction of three main pathological features, including antigen-specific immune system and abnormal immune system, resulting in autoantibody production, vascular endothelial activation of small blood vessels, and tissue fibrosis as a result of fibroblast dysfunction. Given the heterogeneity of the clinical picture of the disease, the lack of universal models prevented adequate testing of potential treatments for SSc. In any case, recent studies have identified the role of various molecular mechanisms that contribute to the clinical picture of the disease. Transformative growth factor B (TGF-b) has been identified as a regulator of pathological fibrogenesis in SSC. Various processes such as cell growth, apoptosis, cell differentiation, and extracellular matrix synthesis are controlled by TGF-b, a type of cytokine secreted by macrophages and many other cells. Understanding the important role of TGF-B pathways in systemic sclerosis Pathology provides a potential pathway for treatment and a better understanding of this severe disease.

РОЛЬ ФАКТОРА РОСТА В1 ПРИ СИСТЕМНОМ СКЛЕРОЗЕ

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https://doi.org/10.5281/zenodo.17151636

ARTICLE INFO

Received: 11th September 2025
Accepted: 17th September 2025
Online: 18th September 2025

KEYWORDS

ABSTRACT

Системный склероз (SSC) - сложное полиорганное аутоиммунное заболевание неизвестной этиологии. Проявления

Системный склероз, трансформирующий фактор роста-В, механизм.

заболевания вызваны взаимодействием трех основных патологических признаков, включая антиген-специфическую иммунную систему и неспецифическую иммунную систему, что приводит к выработке аутоантител, активации эндотелия сосудов мелких кровеносных сосудов и фиброзу тканей в результате дисфункции фибробластов. Учитывая неоднородность клинической картины заболевания, отсутствие универсальных моделей не позволило адекватно протестировать потенциальные методы лечения SSc. В любом случае, недавние исследования выявили роль различных молекулярных механизмов, способствующих клинической картине заболевания. Трансформирующий фактор роста В (TGF-B) был идентифицирован как регулятор патологического фиброгенеза в SSC. Различные процессы, такие как рост клеток, апоптоз, дифференцировка клеток и синтез внеклеточного матрикса, контролируются типом цитокинов TGF-B, секретируемых макрофагами и многими другими клетками. Понимание важной роли путей TGF-B в патологии системного склероза позволяет лучше понять потенциальный путь лечения и это серьезное заболевание.

TIZIMLI SKLEROZDA O‘SISH OMILI-B1NING O‘RNI

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ARTICLE INFO

Received: 11th September 2025
Accepted: 17th September 2025
Online: 18th September 2025

KEYWORDS

Tizimli skleroz, transformatsion o'sish omili-b, mexanizm.

ABSTRACT

Tizimli skleroz (SSc) noma'lum etiologiyali murakkab, ko'p organli autoimmun kasallikdir. Kasallikning namoyon bo'lishi uchta asosiy patologik xususiyatning o'zaro ta'siridan kelib chiqadi, shu jumladan antigenga xos immunitet tizimi va o'ziga xos bo'lmagan immunitet tizimining nosog'lomligi, natijada otoantikor ishlab chiqarish, mayda qon

tomirlarining tomir endotelial faollashuvi va fibroblast disfunktsiyasi natijasida to'qima fibrozi. Kasallikning klinik ko'rinishining geterogenligini hisobga olgan holda, universal modellarning etishmasligi SSc uchun potentsial davolash usullarini etarli darajada sinovdan o'tkazishga to'sqinlik qildi. Qanday bo'lmasin, yaqinda o'tkazilgan tadqiqotlar kasallikning klinik ko'rinishiga hissa qo'shadigan turli xil molekulyar mexanizmlarning rolini aniqladi. Transformatsiya qiluvchi o'sish omili b (TGF-b) SScda patologik fibrogenezning regulyatori sifatida aniqlangan. Hujayra o'sishi, apoptoz, hujayra differentsiatsiyasi va hujayradan tashqari matritsa sintezi kabi turli jarayonlar makrofaglar va boshqa ko'plab hujayralar tomonidan chiqariladigan sitokin turi TGF-b tomonidan boshqariladi. Tizimli skleroz patologiyasida TGF-b yo'llarining muhim rolini tushunish davolash uchun potentsial yo'l va ushbu og'ir kasallikni yaxshiroq tushunish imkonini beradi.

Tizimli skleroz (SSc) nisbatan kam uchraydigan kasallik bo'lib, tarqalishi taxminiy hisob-kitoblarga ko'ra 1 million kattalarga 30 dan 443 gacha [1]. SSc birinchi navbatda o'rta yoshli ayollarga ta'sir qiladi, balki barcha yoshdagi bolalar va erkaklarga ham ta'sir qiladi [2]. Kamdan kam bo'lsa-da, SSc og'ir kasallik bo'lib, unda tashxis qo'yilgan bemorlarning yarmidan ko'pi ichki organlarning shikastlanishi tufayli vafot etadi[3]. Kasallikning xususiyatlari yaxshi hujjatlashtirilgan bo'lsa ham, SSc patogenezi asosan noma'lumligicha qolmoqda. Kollagen to'planishi tufayli terining fibrozi kasallikning tez-tez uchraydigan topilmasi bo'lib, terining ta'sirlanish darajasi SScni tasniflashning bir usuli hisoblanadi [4]. Ikki asosiy kichik to'plamlar cheklangan teri pastki to'plami (lcSSc) va diffuz teri pastki to'plami (dcSSc) kasallikning teriga ta'sir qilish darajasiga asoslangan [2]. Cheklangan teri osti to'plamida terining qalinlashishi ekstremitalarning distal qismida cheklangan va tizimli ishtiroki minimaldir; holbuki, diffuz teri osti to'plamida tizimli shikastlanish sezilarli bo'lib, terining qalinlashishi keng tarqalgan[5]. Amerika revmatologiya kolleji (ACR) va revmatizmga qarshi Yevropa ligasi (EULAR) kasallikni ertaroq, aniqroq tashxislash imkonini berish uchun SSc uchun yangi tasniflash mezonlarini ishlab chiqdi [6-7]. Yangi standartlarga ko'ra, metakarpofalangeal bo'g'imlarga proksimalga cho'zilgan barmoqlarning terining qalinlashishi SSc bilan kasallangan bemorni tasniflash uchun etarli.

Tizimli skleroz patogenezi Tizimli skleroz autoimmun revmatik kasallik sifatida tavsiflanadi[9]. Kasallikning aniq etiologiyasi noma'lum bo'lib qolsa-da, immunologik faollashuv, vaskulopatiya va kollagen to'planishi SSc ning uchta asosiy xususiyati bo'lib, ular hali to'liq tushunilmagan tarzda o'zaro bog'liq ko'rinadi [10]. Qon tomir endotelial faollashuvi va proliferativ vaskulopatiya otoantikorlarni ishlab chiqarish bilan bog'liq

immunoinflamatuar anomaliyalar bilan bog'liq [11]. Immunologik nosimmetrikliklar kasallikning markaziy xususiyati bo'lib, SSc bilan kasallangan bemorlarning 90% dan ko'prog'ida antinuklear antikorlar aniqlanganda, otoantikorlarning erta ishlab chiqarilishidan dalolat beradi [12]. Shuningdek, B hujayralari kasallikning rivojlanishida bir nechta funktsiyalarga ega ekanligi, shu jumladan otoimmun faollashuvi [12-14] aniqlangan. SSc [13-14] bilan og'rigan bemorlarning sodda va xotira B hujayralarida B hujayralari faollashuvining muhim regulyatori bo'lgan CD19 ning haddan tashqari ko'payishi kuzatiladi. Transgen sichqonlarda CD19 ni haddan tashqari oshirib yuboradigan turli autoantikorlar darajasining ko'tarilish belgisi ham mavjud [14]. Ushbu topilma shuni ko'rsatadiki, CD19 ifodasining o'sishi SSc [13-16] bo'lgan odamlarda otoantikor ishlab chiqarishni keltirib chiqarishi mumkin. Shuning uchun, sitokin ishlab chiqarishni va natijada to'qimalarning fibrozini oshiradigan anormal B hujayralari faollashuvi immunoin yallig'lanish anomaliyalarini SSc ga xos bo'lgan fibroz bilan bog'lashi mumkin [13,15]. Immun faollashuvi va SSc ga xos bo'lgan fibroz o'rtasidagi boshqa potentsial bog'liqlik tug'ma immun javobda topilishi mumkin. Makrofaglar kabi filtratlarda yallig'lanishni keltirib chiqaradigan moddalarning to'planishi kasallikning dastlabki bosqichlarida tez-tez uchraydi va ma'lum sitokinlarning ko'payishi makrofaglarni M1 yoki M2 fenotipiga qarab faollashtiradi [17]. M 1 makrofaglari yallig'lanish reaktsiyasini rag'batlantiradi va odatda interferon-gamma (IFNg) tomonidan faollashadi [15-16]. Boshqa tomondan, yallig'lanishga qarshi M2 makrofaglari yarani tiklash va tomirlarni tiklash uchun muhimdir va interleykin 4 (IL-4) yoki IL-13 [15-16,18] tomonidan faollashtiriladi. To'lovga o'xshash retseptorlar (TLR) immun faollashuvini SSc ga xos fibroz bilan bog'lashda muhim rol o'ynaydi. TLRlar makrofaglar, fibroblastlar va boshqa turli xil hujayralar membranalarida ifodalangan naqshni aniqlash retseptorlari (PRR) sinfidir [19-20]. TLR signalizatsiyasi IL-1 retseptorlari bilan bog'langan kinaz-4 (IRAK4) ni qabul qiluvchi MyD88 domenini o'z ichiga olgan sitoplazmik Toll/IL-1 retseptorlari (TIR) adapteri orqali amalga oshiriladi. Keyin IRAK4 orqali fosforillanish faollashadi va TNF retseptorlari bilan bog'liq bo'lgan omil-6 bilan bog'lanadi. Bu I kB kinaz kompleksi, MAP kinazlari (JNK, p38 MAPK) va yadro omil-kB [21-22] faollashishiga olib keladi. TLR'lar invaziv qismlardan saqlangan patogen bilan bog'liq molekulyar naqshlarni (PAMPs) aniqlash uchun ishlaydi [19-20]. PAMPlarga qo'shimcha ravishda zarar bilan bog'liq molekulyar naqshlar (DAMPs) deb nomlanuvchi endogen ligandlar ham TLR signalini uzatish yo'llarini faollashtiradi. DAMPlar to'qimalarning shikastlanishi natijasida chiqariladi va ularning TLR yo'llarining faollashishi sitokinlar va yallig'lanish mediatorlarini ishlab chiqarishga olib keladi [19,23-25]. Misol uchun, SScda TLR2 ning yuqori regulyatsiyasi kasallik bilan og'rigan bemorlarda yallig'lanish belgisi bo'lgan endogen ligand amiloid A ga javob sifatida yallig'lanishga qarshi sitokin IL-6 sekretsiyasining oshishiga olib keladi [26-27]. TLR4 uchun endogen ligandlar hujayra shikastlanishi, oksidlovchi stress va hujayradan tashqari matritsaning (ECM) qayta tuzilishiga javoban chiqariladi, bu ham SScda patologik fibrozga yordam beradi [21]. Aslida, SSc bilan og'rigan bemorlarning teri va o'pka fibroblastlarida TLR4 ning konstitutsiyaviy ifodasi kollagen sintezining haddan tashqari faollashishiga, shuningdek, TGF-b1 stimulyatsiyasiga sezgirlikning oshishiga olib kelishi mumkin [19,21,24].

Ularning muhim roli tufayli TLR signalizatsiya yo'llarining vositachilarini yaxshiroq tushunish mumkin bo'lgan terapevtik ta'sirni tushuntirishga yordam beradi.

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