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REGENERATIV TIBBIYOTDA MEZENXIMAL O‘ZAK HUJAYRALARNING BIOLOGIK FAOL MODDALARINI QO‘LLANILISHI

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Annotatsiya. *Aholining global qarishi va surunkali kasalliklar (masalan, yurak-qon tomir kasalliklari, osteoartrit, asab tizimining degenerativ buzilishlari) tarqalishining ortishi sharoitida regenerativ tibbiyot shikastlangan to‘qimalar va a’zolarni tiklash usullarini ishlab chiqishning asosiy yo‘nalishiga aylanmoqda. Biroq, a’zolarni ko‘chirib o‘tkazish kabi an’anaviy yondashuvlar cheklovlarga duch kelmoqda: donor materialining yetishmasligi, rad etilish xavfi va axloqiy muammolar. Shu nuqtai nazardan, mezenximal o‘zak hujayralar (MSC) o‘zining ko‘p qirrali imkoniyatlari, oson topilishi (suyak ko‘migi, yog‘ to‘qimasi, kindik qoni) va immunitet tizimini boshqarish xususiyatlari bilan e’tiborni tortmoqda. Ammo MSClardan foydalanish xavf tug‘dirishi mumkin: potensial xavfli o‘sma hosil bo‘lishi, ko‘chirib o‘tkazilgandan so‘ng yashash darajasining pastligi va standartlashtirishning murakkabligi. Bu ularning sekretomasiga - hujayralarning qayta tiklanish ta’sirini ta’minlaydigan biologik faol molekulalar (ekzosomalar, sitokinlar, o‘sish omillari) majmuasiga qiziqish uyg‘otmoqda.*

Kalit so‘zlar: *mezenximal o‘zak hujayralar, ekzosomalar, sitokinlar, o‘sish omillari, regenerativ tibbiyot, hujayra terapiyasi, immunomodulyatsiya.*

ИСПОЛЬЗОВАНИЕ БИОЛОГИЧЕСКИ АКТИВНЫХ ВЕЩЕСТВ МЕЗЕНХИМАЛЬНЫХ СТВОЛОВЫХ КЛЕТОК В РЕГЕНЕРАТИВНОЙ МЕДИЦИНЕ

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Аннотация. *Старение населения и рост хронических заболеваний (сердечно-сосудистые патологии, остеоартрит, нейродегенеративные расстройства) повышают спрос на методы регенерации тканей. Традиционная трансплантация органов ограничена дефицитом донорского материала, рисками отторжения и этическими барьерами. Мезенхимальные стволовые клетки (МСК) долгое время рассматривались как решение благодаря их способности дифференцироваться в разные типы клеток, доступности и иммуномодулирующим свойствам. Однако их применение связано с рисками: малигнизация, низкая выживаемость после трансплантации и сложности стандартизации. Это стимулирует переход к изучению секретома МСК - комплекса биомолекул (экзосомы, цитокины, факторы роста), которые опосредуют регенерацию без использования живых клеток.*

Ключевые слова: *мезенхимальные стволовые клетки, экзосомы, цитокины, ростовые факторы, регенеративная медицина, клеточная терапия, иммуномодуляция.*

USE OF BIOLOGICALLY ACTIVE SUBSTANCES OF MESENCHYMAL STEM CELLS IN REGENERATIVE MEDICINE

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Annotation. *The ageing population and the growth of chronic diseases (cardiovascular pathologies, osteoarthritis, neurodegenerative disorders) increase the demand for tissue regeneration methods. Traditional organ transplantation is limited by scarcity of donor material, risks of rejection and ethical barriers. Mesenchymal stem cells (MSCs) have long been considered as a solution due to their ability to differentiate into different cell types, availability and immunomodulatory properties. However, their use is associated with risks: malignisation, low survival after transplantation and difficulties in standardisation. This stimulates the transition to the study of the MSC secretome, a complex of biomolecules (exosomes, cytokines, growth factors) that mediate regeneration without the use of living cells.*

Key words: *mesenchymal stem cells, exosomes, cytokines, growth factors, regenerative medicine, cell therapy, immunomodulation.*

Kirish.

Aleksandr Fridenshteyn mezenximal o‘zak hujayralarni kashf qilganidan buyon yarim asr o‘tdi. U birinchi bo‘lib mezenximal o‘zak hujayralarni (MSCs) fibroblastlarga o‘xshash morfologiyaga ega, boshqa mezodermal hujayralarga tabaqalanish qobiliyatiga ega bo‘lgan va koloniya hosil qiladigan hujayralar sifatida tavsiflagan edi [27]. Dastlab, MSClar ko‘chirib o‘tkazilgandan so‘ng shikastlangan hududlarga ko‘chib o‘tadi, o‘rnashadi va to‘qimalarni tiklab, yetuk funksional hujayralarga aylanadi deb taxmin qilingan [25, 67]. Biroq, hayvonlar ustida o‘tkazilgan tajribalar va klinik sinovlar bu nazariyani shubha ostiga qo‘ydi. Turli kasalliklarda MSClarning davolash samaradorligi isbotlangan bo‘lsa-da [57], ularning o‘rnashish tezligi va davomiyligi kuchli regenerativ ta’sirlarni tushuntirish uchun yetarli emasligi ma’lum bo‘ldi. Burilish nuqtasi suyak iligidan olingan mezenximal o‘zak hujayralarni (BM-MSC), gemapoetik o‘zak hujayralari (HSCs) bilan o‘sish omillarini qo‘shmasdan, birgalikda o‘stirish sharoitida ularning hayotchanligini qo‘llab-quvvatlash qobiliyati aniqlanishi bo‘ldi [20, 51].

Bu MSClar funksiyalari haqidagi tasavvurlarni kengaytirdi: differensiatsiyadan tashqari, ular rezident hujayralarni faollashtirish orqali regeneratsiyani rag‘batlantiruvchi trofik omillar manbai sifatida qaraladigan bo‘ldi [12, 42, 46]. To‘qima shikastlanganda endogen MSClar perivaskulyar bo‘shliqlardan ko‘chib, biofaol molekulalar ajratishi va immunitet javobini boshqarishi natijasida regenerativ mikromuhitni shakllantirishi taxmin qilingan [7, 13].

Bugungi kundagi klinik amaliyotlar shuni tasdiqlaydiki, MSClarning asosiy ta’sir mexanizmi mikromuhit sharoitlariga moslashadigan parakrin ta’sirdan iborat [49]. Ushbu kashfiyot tadqiqotchilar e’tiborini bugungi kunda hujayra terapiyasining istiqbolli muqobili sifatida qaralayotgan MSClarning sekretomasini o‘rganishga qaratdi. Masalan, klinik sinovlarda allaqachon osteoartrit [41], ishemik insult [18, 38, 72], neyrodegenerativ kasalliklar (Altsgeymer kasalligi) [65], nafas olish tizimi patologiyalari [1, 2, 11], shu jumladan COVID-19ning og‘ir shakllarini davolash uchun MSClar sekretomasidan foydalanish sinovdan o‘tkazilmoqda [15, 28, 45].

Ushbu adabiyotlar sharhida respirator, jigar va nevrologik kasalliklarni MSClar sekretomasi yordamida davolash strategiyalarini optimallashtirish tahlil qilinadi, bu esa regenerativ tibbiyot uchun yangi imkoniyatlarni ochadi.

Mezenximal o‘zak hujayra sekretomalari.

Mezenximal o‘zak hujayralar, shuningdek mezenximal stromal hujayralar yoki terapevtik salohiyatga ega signal hujayralari deb ham ataladigan, turli xil hujayra turlariga differensiatsiyalanish qobiliyatiga ega bo‘lgan multipotent hujayralardir. Xalqaro hujayra terapiyasi jamiyati (ISCT) mezonlariga ko‘ra, MSClar $CD105^+$, $CD73^+$ va $CD90^+$ markerlarini ifodalashi, ammo $CD45^-$, $CD34^-$, $CD14^-$, $CD11b^-$, $CD79a^-$, $CD19^-$ markerlarini va MHC II sinfini ifodalamasligi kerak [21]. Olinish manbasiga ko‘ra ular quyidagicha tasniflanadi: neonatal (yo‘ldosh, kindik qoni, Varton jelesi) va katta yoshdagilar (suyak ko‘migi va yog‘ to‘qimasi) [76].

ISCT umumiy mezonlariga mos kelishiga qaramay, turli manbalardan olingan MSClar proliferativ faolligi, differensiatsiyalanish potensiali va immunomodulyator xususiyatlari bo‘yicha farqlanadi. Ularning sekretomasi tarkibi ham o‘zgaruvchan bo‘lib, hujayralarning kelib chiqishi, o‘stirish sharoitlari va mikromuhitga bog‘liq. Bu esa aniq ta’sir mexanizmlarini aniqlashni murakkablashtiradi [39, 46, 63].

Sekretoma tarkibiga quyidagilar kiradi: eriydigan omillar (sitokinlar, xemokinlar va gormonlar) va hujayradan tashqari vezikulalar (EV). EVlar o‘lchamiga ko‘ra tasniflanadi: kichik EVlar (<200 nm), ularga ekzosomalar kiradi va o‘rta/yirik EVlar (>200 nm) [21]. MSC-EVlar ta’siri ularning yuklamasi bilan, ya’ni oqsillar, mRNK, miRNK va lipidlar bilan bog‘liq [64, 70].

Masalan, miRNKlar genlar ekspressiyasining 70%gacha qismini boshqaradi [26]. Ayrim miRNKlar vazifasi regeneratsiya jarayonlari bilan bog‘liq:

miR-199a - kardiomiotsitlar ko‘payishi;

miR-23-a-p, miR-130-a-3p - qon tomir hosil bo‘lishi;

miR-126-3p, miR-223-3p - immunitet tizimini moslashuvi;

miR-133b, miR-26a, miR-124 - asab tizimini himoyalash [58].

Garchi MSClardagi EVlar tiklanish xususiyatlarining asosiy vositachilari sifatida qaralsa-da [9], ma’lumotlar ziddiyatli: ba’zi tadqiqotlarda to‘liq sekretom yoki uning vezikulasiz qismi immunitet tizimini moslashtirishda EVlardan ustunroq [55]. Shunga qaramay, EVlarga bo‘lgan qiziqish ularning barqarorligi, organizm uchun havfsizligi va klinik qo‘llashning qulayligi tufayli ortib bormoqda [23]. Hujayra terapiyasiga nisbatan afzalliklari, ta’sirlarning takrorlanuvchanligi va oldindan ma’lumligi hisoblanadi [19], biroq ularning biologik membranalardan o‘tish mexanizmlari hali munozarali [56]. MSClar sekretomasining asosiy davolash ta’sirlari 1-jadvalda batafsil ko‘rsatilagan.

1 jadval.

MCSlar biologik faol moddalarini yurak-qon tomir, suyak, buyrak va oshqozon-ichak kasalliklarida ta’siri

Qo‘llanilishi	Asosiy ta’siri	Manba
Yurak qon-tomir kasalliklarri	• Ishemiyaga uchragan kardiomiotsitlarga VEGF, HGF, FGF, IGF-1 va TB4 sekretsiyasi hisobiga sitoprotektiv va regenerativ ta’siri. • Yurak fibroblastlarida I va III turdagi kollagen ekspressiyasini ingibitorlash hisobiga antifibrotik ta’sir • AKT va MAPK/ERK1/2 yo‘li orqali VEGF faollashuvi hisobiga reendoteli-zatsiyani tezlashtirish. • Hujayra ichidagi kalsiy miqdorini va ishqoriy fosfataza faolligini ka-maytirish orqali tomirlarning kalsifikatsiyasini yengillashtirish.	[4] [30] [32] [52]
Suyak to‘qimasi kasalliklari	• Kosacha sohasidagi suyak nuqsonlarida suyak to‘qimasining regener-atsiyasi VEGF va IGF-1 sekretsiyasi hisobiga bo‘lishi mumkin. • VEGF yordamida kalamush kalvar suyagi nuqsoni modelida angiogenez, suyak to‘qimasi regeneratsiyasi va endogen MSClarni mobilizatsiya qilish im-koniyati. • MCP-1/-3 va IL-3/-6 yordamida endogen MSClarni jalb qilish, osteoblastlar differensiatsiyasi, angiogenez, hujayralar proliferatsiyasi, yallig‘lanish va apoptozni ingibitorlash orqali distraksion osteogenez sharoitida qadoqning shakllanishini tezlashtirish.	[3] [35] [54]
Buyrak kasalli-klari	• bFGF, IL-10, TGF-a va Bcl-2 ekspressiyasining kuchayishi, proliferativ in-deksning oshishi va apoptotik indeksning pasayishi, buyrak funksiyasining yaxshilanishiga olib keladi.	[66] [68]
Oshqozon-ichak kasalliklari	• MSClar ta’sirida IL-6 sekretsiyasi orqali Arg-1 ekspressiyasining oshishi bilan yallig‘lanishga qarshi M2 fenotipiga makrofaglarning qutblanishi. • IL-1b, IL-6, TNF-a va TLR4 kabi yallig‘lanishni kuchaytiruvchi markerlarni kodlovchi genlar faolligining pasayishi va yallig‘lanishga qarshi IL-10 darajasi-ning ko‘tarilishi hisobiga yallig‘lanishni susayishi.	[36] [77]

Respirator kasalliklarda mezenximal o‘zak hujayra sekretomalarining ahamiyati.

O‘pka fibrozini va o‘pka to‘qimasining o‘tkir shikastlanishini davolashda MSClarning terapevtik salohiyatini tasdiqlovchi ko‘plab tadqiqotlar mavjud [17]. O‘pka fibrozi patogenezi havo alveolalarining stroma hujayralari, asosan miofibroblastlar bilan almashinuviga bog‘liq. Bular hujayra tashqi matriks oqsillarini, jumladan, noto‘g‘ri shakllanigan kollagenni sintezlaydi, bu esa fibrozning zo‘rayishiga va nafas olish funksiyasining izdan chiqishiga olib keladi [50]. Ushbu holat infeksiyalar, autoimmun patologiyalar, surunkali yallig‘lanish yoki noma’lum sabablar tufayli rivojlanishi mumkin [8].

O‘tkir respirator distress sindromi va uning yengilroq shakli - o‘pkaning o‘tkir shikastlanishi alohida e’tiborga loyiq. Bu holatlar alveolo-kapillyar to‘siqning buzilishiga olib keladigan kuchli yallig‘lanish javobi bilan tavsiflanadi O‘tkazuvchanlikning buzilishi oqsil ekssudatining to‘planishi, shish va fibrogenez bilan kuzatiladi. Alveolyar suyuqlik klirensining pasayishi esa gaz almashinuvini yomonlashtirib, gipoksemiya va giperkapniyani keltirib chiqaradi. O‘tkir respirator distres sindromi bilan og‘rigan bemorlarning aksariyatida poliorgan yetishmovchilik kuzatiladi, bunda sepsis (o‘pka va o‘pkadan tashqari kelib chiqadigan) asosiy etiologik omil hisoblanadi. O‘tkir respirator distres sindromini samarali davolash usullari mavjud bo‘lmagan sharoitda, MSCs sekretomalarini qo‘llash istiqbolli davolash strategiyasi sifatida e’tiborga olinmoqda [48]. SARS-CoV-2 bilan bog‘liq virusdan keyingi o‘pka fibrozining kutilayotgan ko‘payishi alohida dolzarblik kasb etmoqda [8].

Nafas yo‘llarida interleykin-1β (IL-1β) darajasining ko‘tarilishi o‘pka to‘qimasida neytrofillarning to‘planishi bilan bog‘liqdir. Shu sababli, IL-1

retseptori antagonisti IL-1RAni qo‘llash o‘pkaning o‘tkir shikastlanishini davolashning istiqbolli usuli hisoblanadi. Tajribalar shuni ko‘rsatdiki, IL-1RA ishlab chiqaruvchi MSClar alveolyar makrofaglar tomonidan IL-1α, IL-1β va TNF-α sintezini to‘xtatish orqali sichqonlar o‘pkasidagi yallig‘lanishni butunlay bartaraf etadi. Bundan tashqari, IL-1RA VEGF174 faollashuvi orqali II turdagi alveolyar epiteliy hujayralarining angiogenezi va regeneratsiyasini bilvosita rag‘batlantiradi. Bu esa alveolyar epiteliyning shikastlanishdan so‘ng tiklanishi uchun juda muhimdir. IL-1RAning yana bir qo‘shimcha ta’siri TLR-4 ekspressiyasini faollashtirish bo‘lib, u bakterial patogenlarning yo‘q qilinishini kuchaytiradi [33].

Conese va hamkasblari tadqiqotlarga ko‘ra, MSClarning terapevtik samaradorligi bronxoalveolyar lavaj (BAL) suyuqligi va plazmadagi yallig‘lanishni kuchaytiruvchi mediatorlar (TNF-α, MIP-2) darajasining pasayishi, shuningdek, yallig‘lanishga qarshi sitokin — IL-10 konsentratsiyasining oshishi bilan bog‘liq [17]. Alveolyar epiteliy va endoteliyni himoya qilish, hamda suyuqlik klirensini normallashtirishga yordam beradigan keratinotsitlarning o‘sish omillari (KGF) va angiopoetin-1 (Ang-1) MSClarning muhim omillari hisoblanadi [48].

MSC-EVlar alohida qiziqish uyg‘otmoqda, chunki ularni qo‘llash o‘pka yallig‘lanishi belgilarining sezilarli darajada pasayishini ko‘rsatdi, jumladan:

– bakterial yuklanishning kamayishi [47];

– BALda oqsil ekstravazatsiyasining pasayishi [47];

– neytrofillar giperaktivatsiyasining susayishi [40];

– yallig‘lanishni kuchaytiruvchi mediatorlar (HIMF/FIZZ-1, IL-6, MCP-1, MIP-2, TNF-α) darajasining pasayishi [40].

Nataliya va hamkasblari tadqiqotlarga ko‘ra, hayvonlarda bleomitsin orqali hosil qilingan o‘pka fibrozi modelida yog‘ to‘qimasi mezenximal o‘zak hujayralarining hujayra tashqi vezikulalari (AD-MSCs-EVs) fibrotik o‘zgarishlarni sezilarli darajada kamaytirgan, sekretomaning eriydigan qismi esa bunday ta’sirni ko‘rsatmagan [50].

Jigar kasalliklarida mezenximal o‘zak hujayra sekretomalarining ahamiyati.

Jigar patologiyalari dunyoda o‘limning yetakchi sabablaridan biri bo‘lib qolmoqda. Metabolik buzilishlar (II tip qandli diabet, jigar noalkogol yog‘ kasalligi), virusli infeksiyalar (gepatit B), toksik zaharlanish yoki o‘sma jarayonlari natijasida kelib chiqqan jigarning o‘tkir yoki surunkali shikastlanishi uning gomeostazni tiklashga qaratilgan noyob regenerativ qobiliyatini faollashtiradi [60]. Biroq, takroriy shikastlanishlar fibrozga, surunkali yallig‘lanishga va parenximaning progressiv disfunksiyasiga olib keladi. Jigar yetishmovchiligining terminal bosqichi a’zo transplantatsiyasini talab qiladi, u katta a’zolarni transplantatsiya qilish bo‘yicha ikkinchi o‘rinda turishiga qaramay, global ehtiyojning atigi 10 foizini qoplaydi. Shu munosabat bilan, tobora ko‘proq tadqiqotlar jigar regeneratsiyasini rag‘batlantirish uchun MSClardan foydalanishga qaratilgan [69].

Yallig‘lanish jigar noalkogol yog‘ kasalligi va boshqa shikastlanishlar patogenezining asosiy komponenti sifatida fibrozni va funksional yetishmovchilikni kuchaytiradi. Bu jarayonda MSClarning immunomodulyator xususiyatlari hal qiluvchi ahamiyatga ega. Masalan, BM-MSClarning konditsiyalangan muhiti (BM-MSC-CM) IL-1β, IL-6, MCP-1, MIP-2 va TNF-α darajalarini pasaytirib, neytrofillar infiltratsiyasini va Kupfer hujayralarining faollashishini to‘xtatadi [22]. MSClar tomonidan ajratib chiqariladigan boshqa sitokinlar (TGF-β, HGF, IL-10) va fermentlar T-limfotsitlar va antigen taqdim etuvchi hujayralar (APCs) proliferatsiyasini boshqaradi, shu bilan haddan tashqari yallig‘lanish javobini cheklaydi [14, 24, 61].

Zagoura va hamkasblari tadqiqotlarga ko‘ra, sichqonlarda CCl4 yordamida keltirib chiqarilgan shikastlanish modelida amniotik MSClar sekretomida mavjud bo‘lgan anneksin-A1 (ANXA1) yallig‘lanishni kamaytirish bilan bir vaqtda gepatoprogenitor hujayralarning ko‘payishi va tabaqalanishini rag‘batlantirdi [76].

Virusli infeksiyalar, alkogol yoki metabolik buzilishlar bilan bog‘liq jigar fibrozi jigarning yulduzsimon hujayralarining (HSC) faollashuvi orqali rivojlanadi. Odatda, Disse bo‘shlig‘ida joylashgan tinch holatdagi HSClar A vitaminini saqlaydi, ammo shikastlanganda I turdagi kollagen ishlab chiqaruvchi miofibroblastlarga o‘zgaradi [59]. Davolashning muhim jihati bu jarayonni to‘xtatishdir. MSClar tomonidan ishlab chiqariladigan IL-10, IL-1RA, HGF va TNF-α kollagen sintezini kamaytirishi va HSC apoptozini keltirib chiqarishi aniqlangan [38, 43].

MSClarning trofik omillari gepatotsitlarning ko‘payishi va migratsiyasini rag‘batlantiradi, shu bilan birga ularning apoptozini to‘xtatadi. Xagorari va hamkasblari tadqiqotlarga ko‘ra, BM-MSClari tomonidan ishlab chiqariladigan IL-6, CCl4 bilan shikastlangan sichqonlarning gepatotsitlarida FGL1 ekspressiyasini keltirib chiqaradi va hujayraga himoyalovchi ta’sir ko‘rsatadi [74]. Boshqa eruvchan omillar (SDF-1, IGF-1, Nrf-2, HIF, HO-1, VEGF) apoptotik belgilarni boshqaradi, proapoptotik omil bo‘lgan Bax darajasini pasaytirib va antiapoptotik Bcl-2 ifodasini oshirib, shu bilan bir vaqtda antioksidant tizimlar faolligini kuchaytiradi [29].

Zheng va hamkasblari tadqiqotlarga ko‘ra jigar ishemiyasi/reperfuziyasi modelida kindik MSClarining kondetsiyalangan muhiti (UC-MSC-CM) PINK1-ga bog‘liq mitofagiyani faollashtirish orqali gepatotsitlar apoptozini bostirib, mitoxondrial gomeostazni yaxshilash qobiliyatini namoyon etdi [78].

MSClarning angiopoetinlar (ANGPTs), HGF, IGF-1, VEGF-A va uning retseptorlari (VEGF-R1,

VEGF-R2) ajratilishi orqali amalga oshiriladigan angiogen salohiyatini alohida ta'kidlash lozim. Ushbu omillar endotelial hujayralar ko'payishini va yangi qon tomirlar hosil bo'lishini rag'batlantiradi, natijada shikastlangan to'qimalar qon bilan ta'minlanishini yaxshilaydi [53].

Shunday qilib, MSClar sekreti polivalent ta'sirga ega bo'lib, u immunomodulyatsiya, antiapoptotik, antifibrotik va angiogen faollikni o'z ichiga oladi. Ushbu mexanizmlarning uyg'unligi gepatotsitlarning funksional faolligini va ko'payishini rag'batlantiradi, shu orqali jigar shikastlanishining kamayishini ta'minlaydi.

Neyrologik kasalliklarida mezenximal o'zak hujayra sekretomalarining ahamiyati.

Yaqin vaqtgacha markaziy asab tizimi o'zgarmas va tiklanishga qodir emas deb hisoblanar edi. Ammo hozirda neyroplastiklik inson umri davomida saqlanib qolishi aniq ma'lum [10]. Bu jarayon turli mexanizmlar orqali amalga oshadi, jumladan yetuk neyronlarda sinaptogenezning boshqarilishi hamda mikrogliya kabi qo'llab-quvvatlovchi glial hujayralar faoliyati orqali ham. Qiziq tomoni shundaki, neyroplastiklik katta yoshdagi odam bosh miyasining maxsus bo'shliqlarida neyral o'zak hujayralari (NSCs) va neyronal progenitor hujayralar (NPCs) mavjudligi bilan ham ta'minlanadi [73]. Bu hujayralar normal hujayraviy yangilanish sharoitida ham, miya shikastlanishidan keyin ham yo'qolgan hujayralarni almashtirish uchun zaxira vazifasini bajaradi [34].

MSClar tomonidan ishlab chiqriladigan biologik faol moddalar immunomodulyator va neyroregulyator xususiyatlarga ega bo'lgani sababli, uning neyron hujayralariga, shu jumladan NSClarga ta'siri ularning ko'payishi va tabaqalanishini rag'batlantirish uchun istiqbolli usul bo'lishi mumkin. Bu, o'z navbatida, NSClarning kamayishi bilan bog'liq keng ko'lamli nevrologik va ruhiy kasalliklarni rivojlanishini oldini olish mumkin [62].

MSClar sekretomi tarkibiga kiruvchi omillar orasida BDNF, FGF-2, GDNF, IGF, NGF va neyrotrofin-3 kabi neyronlar va glial hujayralar populyatsiyasini saqlab turishda muhim rol o'ynaydigan neyrotrofinlar alohida ajralib turadi [6, 16, 31].

Ma'lumotlar hali dastlabki bo'lsa-da Walker va hamkasblari tadqiqotlarga ko'ra yog' to'qimasidan olingan konditsiyalangan mezenximal o'zak hujayralar (AT-MSC-CM) yon amiotrofik sklerozga chalingan sichqonlar modelida qo'llanilishi ijobiy ta'sir ko'rsatgani ma'lum bo'ldi. AT-MSC-CMni yon amiotrofik skleroz kasalligining kechki bosqichlarida tizimli qo'llash uning rivojlanishini sekinlashtirdi va yon amiotrofik sklerozi kasalligi dastlabki bosqichlarida nerv-mushak birikmalari denervatsiyasining oldini oldi [71].

Ishemik insult paytida neyronal shikastlanish immun tizimining faollashuvi va yallig'lanishga sabab bo'luvchi mediatorlar darajasining ko'tarilishi bilan kechadi, bu esa keyinchalik markaziy asab tizimiga immun hujayralarning kirib kelishiga olib keladi. Ko'plab tadqiqotlar shuni ko'rsatadiki, MSClarni yuborish VEGF proangiogen omili ekspressiyasini oshiradi va shu orqali TNF-α va NF-κB darajalarini pasaytirishi mumkin. NF-κBning kamayishi MSC larning yallig'lanishga qarshi va apoptozni oldini oluvchi ta'siri bilan bog'liq. Xususan, BM-MSClar miya parenximasi hujayralarini neyrotrofinlar, jumladan BDNF va FGF ajratib chiqarishga undaydi. Wang va hamkasblari tadqiqotlarga ko'ra, BM-MSClarni vena orqali yuborish, shuningdek, BDNF, FGF-2, HGF, IGF-1, NAP-2 va VEGF kabi o'sish omillarining ajralishini rag'batlantiradi, bu esa insultdan so'ng neyronlarning o'sishi va yangi qon tomirlarning hosil bo'lishini tezlashtiradi [72].

MSClar tomonidan ishlab chiqariladigan gepatotsitlarning o'sish omili (HGF) c-Met retseptori bilan o'zaro ta'sir qilib autoimmun kasalliklarda tiklanish, qayta miyelinlanish va asab hujayralarining rivojlanishida, jumladan tarqoq skleroz kasalligida muhim rol o'ynashi aniqlandi [37]. Bai va hamkasblarining tadqiqoti shuni ko'rsatdiki, MCSlar tomonidan yo'lga qo'yiladiagn HGF/c-Met yo'li qayta miyelinlanishda hal qiluvchi ahamiyatga ega. MSClar sekretomi va HGF birgalikda yuborilganda yallig'lanishni qo'zg'atuvchi sitokinlar (IL-2, IL-17, IFN-γ, TNF-α, IL-12p70) darajasi pasayib, yallig'lanishga qarshi sitokinlar (IL-4, IL-10) miqdori oshadi [5].

Mendes-Pinheiro va hamkasblarining tadqiqotida, Parkinson kasalligida 6-gidroksidofamin (6-OHDA) toksini qo'llanilgan hayvon modellarida o'tkazilgan tajribalar shuni ko'rsatdiki, inson BM-MSCdan olingan sekretomni yuborish qora modda va striatumda dofaminergik neyronlar yo'qolishini sezilarli darajada kamaytiradi. Qizig'i shundaki, BM-MSClarning o'zini ko'chirib o'tkazish bunday yaqqol natija bermadi, bu esa ularning sekretomining yuqoriroq samaradorligini ko'rsatadi [44].

Bundan tashqari, UC-MSC-EVlar qon-miya to'sig'idan o'tib, o'rta miyaning qora moddasiga yetib borish qobiliyatiga ega. Chen va hamkasblarinig tadqiqotlariga ko'ra, BM-MSC-EVlar dofaminergik neyronlar yo'qolishini kamaytirgan va Parkinson kasalligi modeli bo'lgan kalamushlarda xulq-atvor ko'rsatkichlarini yaxshilagan [14].

XULOSA. Zamonaviy ma'lumotlar tahlili mezenximal o'zak hujayralar sekretomasining keng ko'lamli ijtimoiy ahamiyatga ega kasalliklarni davolashdagi sezilarli terapevtik salohiyatini ishonchli tarzda ko'rsatmoqda. Tadqiqotlar izchil ravishda shuni tasdiqlayaptiki, MCSlarning asosiy davolash ta'siri to'g'ridan-to'g'ri hujayra almashinuvi orqali emas, balki ularning sekretomi vositasida amalga oshiriladi. Bunda hujayradan tashqari vezikulalar, sekretomning asosiy fraksiyasi sifatida, butun hujayralarga nisbatan sezilarli afzalliklarga ega. Bu afzalliklar qatoriga xavflarni (o'sma paydo bo'lishi, to'qima rad etilishi, emboliya) kamaytirishga asoslangan yuqori xavfsizlik darajasi, biologik to'siqlarni yengib

o‘tish imkonini beruvchi noyob bioyo‘nalish, hamda dori vositalarini yaxshiroq standartlashtirish imkoniyati kiradi. Muhimi shundaki, klinikadan oldingi tajribalarda MCS-EVlari ko‘pincha o‘pka va jigar fibrozi, neyrodegenerativ kasalliklar va ishemik shikastlanish kabi patologiyalarda qiyosiy yoki hatto ustun samaradorlikni namoyon etmoqda.

Shunday qilib, MCS sekreti, ayniqsa uning vezikulyar fraksiyasi, regenerativ tibbiyotda an’anaviy hujayra terapiyasining istiqbolli va xavfsiz muqobili hisoblanadi. Uning samaradorligi nafas olish, jigar va asab tizimi kasalliklari modellarida isbotlangan. Bu ko‘p qirrali ta’sirga ega bo‘lgan kuchli vositaning muvaffaqiyatli klinik qo‘llanilishi uchun quyidagi sa’y-harakatlar zarur: MCS-EVlarni ajratish va tavsiflashning qat’iy standartlashtirish protokollarini ishlab chiqish, yetkazib berish usullarini takomillashtirish va biotarqalishini o‘rganish, molekulyar ta’sir mexanizmlari haqidagi bilimlarni chuqurlashtirish va nihoyat, keng ko‘lamli tasodifiy nazorat qilinadigan klinik sinovlarni o‘tkazish. Ushbu sohadagi yutuqlar yallig‘lanish, fibroz, apoptoz va regeneratsiya buzilishi bilan xarakterlanadigan kasalliklarni davolashda sezilarli rivojlanish va o‘zgarishlarni va’da qilmoqda.

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