

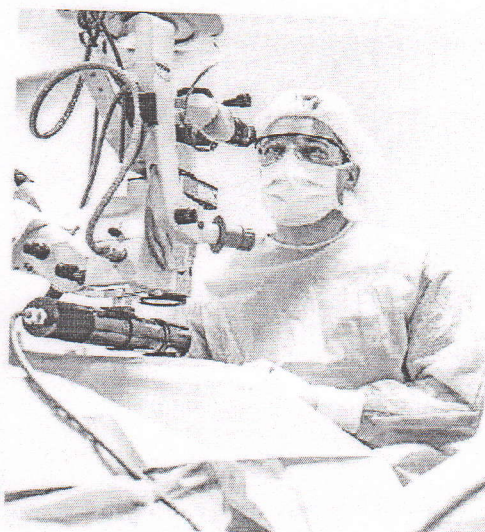
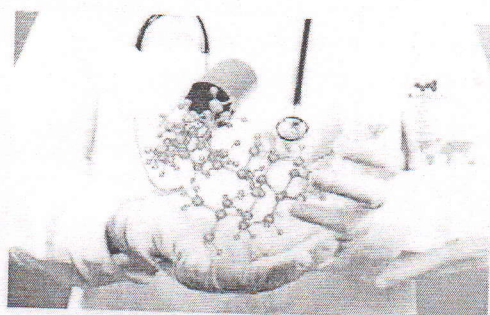


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BRUTSELLANING UZOQ MUDDATLI HUYAYRA ICHI PARAZITIZMINI MOLEKULAR O'RGANISH (adabiyotlar sharxi)

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✓ *Resume*

Makroorganizmga nisbatan spetsifik evolyutsiya brucellaga hujayra ichida turg'un saqlanishga, makroorganizmning hujayraviy immunitetini o'ziga xos boshqarib immun hujayralarda uzoq vaqt persistensiyasiga imkon beradi. Brucella evolyutsiyasi hujayra ichida saqlanishga yo'naltirilgan bo'lib asosan hujayra lizosomal fermentlariga nisbatan chidamlilikka bog'liq. Maqolada brutselloz qo'zg'atuvchisining hujayra ichida persistensiyasini ta'minlovchi molekulyar mexanizmlar ko'rsatilgan. Bakteriyaning hujayra ichida saqlanishi molekulyar mexanizmlarini tushunish bizga brucella bakteriyasi ustidan epidemiologik nazoratni oshirishga, profilaktika va davolashning yangi usullari va vositalarini ishlab chiqishga katta yordam beradi.

Kalit so'lar: Brutsellyoz, Brucella, makroorganizm, hujayra ichi parazitizmi, immunitet, sitokinlar, gen.

МОЛЕКУЛЯРНОЕ ИССЛЕДОВАНИЕ ДОЛГОВРЕМЕННОГО КЛЕТОЧНОГО ПАЗИТИЗМА БРУЦЕЛЛЫ (обзор литературы)

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Специфическая эволюция по отношению к макроорганизму позволяет бруцеллам оставаться стабильными внутри клетки, длительно сохраняться в иммунных клетках за счет регуляции клеточного иммунитета макроорганизма. Эволюция бруцелл направлена на внутриклеточном паразитировании и в основном обусловлена устойчивостью к клеточным лизосомальным ферментам. В статье показаны молекулярные механизмы, обеспечивающие внутриклеточную персистенцию возбудителя бруцеллеза. Понимание молекулярных механизмов внутриклеточного накопления бактерий в значительной степени поможет нам усилить эпидемиологический контроль над бруцеллезными бактериями и разработать новые методы и средства диагностики и лечения.

Ключевые слова: бруцеллез, бруцеллы, макроорганизм, внутриклеточный паразитизм, иммунитет, цитокины, гены.

MOLECULAR STUDY OF LONG-TERM CELL PARASITISM OF BRUCELL (review)

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✓ *Resume*

Specific evolution in relation to the macroorganism allows brucella to remain stable inside the cell, long-term persistence in immune cells by regulating the cellular immunity of the macroorganism. The evolution of Brucella is aimed at intracellular storage and is mainly due to resistance to cellular lysosomal enzymes. The article shows the molecular mechanisms that provide intracellular persistence of the brucellosis pathogen. Understanding the molecular mechanisms of intracellular storage of bacteria will greatly help us to increase epidemiological control over brucella bacteria and to develop new methods and means of prevention and treatment.

Keywords: Brucellosis, Brucella, macroorganism, intracellular parasitism, immunity, cytokines, genes.

Dolzarbliigi

Brutsellyoz – zoonoz infeksiyon kasallik bo'lib, *Brucella* oilasiga mansub bakteriyalar tomonidan chaqirilib, qishloq xo'jaligi va yovvoyi hayvonlardan odamga yuqadi va aksariyat holatlarda mehnatga layoqatli yoshdagi bemorlarda surunkali kechish va keyinchalik nogironlikka sabab bo'lishi bilan dolzarbliigi tavsiflanadi. *Brucella* oilasi bakteriyalari fakultativ hujayra ichi patogenlar bo'lib, ular immunitet hujayralarida saqlanib qolishi hisobiga uzoq yillar davomida surunkali kechishi mumkin [1]. Brutsellyoz hozirgi kunda ham butun dunyoda aholi salomatligiga xavf soluvchi dolzarb muammolardan biri hisoblanadi. Dunyoda bu kasallik bilan kasallanish ko'rsatkichlari xanuz yuqori darajada saqlanib qolmoqda. Jahon sog'liqni saqlash tashkilotining (JSST) ma'lumotlariga ko'ra, dunyoda har yili insonlarda 500.000 dan ortiq yangi tashxis qo'yilgan brutsellyoz holatlari qayd etiladi. Ammo asl xolat 1,5 million atrofida deb baxolanadi [2].

Brucella xayvonlardan odamlarga muloqot, alimantar va aerogen (havo-chang) yo'llar orqali yuqadi, hamda odam organizmida uzoq muddat xujayra ichida parazitlik qiladi. Brutsellyoz butun dunyoda sog'liqni saqlash tizimida dolzarb muammoligicha qolmoqda. Bunga sabab esa kasallikning surunkali kechishga moyilligi hamda surunkali formalarning antibiotikaterapiyaga chidamliligidir [3, 4, 5, 6, 7, 8]. Surunkali kechish oqibatida esa ishga layoqatli aholi qatlamida nogironlik yuzaga keladi. Juda kam hollarda kasallik bemorlardan sog'lomlarga yuqishi kuzatiladi [9]. Natijada kasallik nafaq tibbiy balki ijtimoiy-siyosiy ko'rinishga ega bo'ladi [7, 8].

Inson uchun nisbatan yuqori patogenlikka ega turlar sifatida *Br. melitensis* (asosiy xo'jayini kichik shoxli hayvonlar – qo'y, echki), *Br. suis* (cho'chqa, quyon, bug'u, kemiruvchilar), *Br. abortus* (yirik shoxli hayvonlar – sigir) va *Br. canis* (itlar)lar deb hisoblanadi. Kasallik o'zida qo'zg'atuvchi saqlagan xayvon maxsulotlari va chiqindilari bilan to'g'ridan to'g'ri kontakt orqali ham yuqadi [6, 10, 11]. Ba'zi adabiyotlarda bemorlardan sog'lomlarga yuqishi ham aytiladi. [9].

Brucella bakteriyasida makroorganizmining makrofaglar, dendritik hujayralari, platsentar trofoblast hujayralariga nisbatan yuqori darajada tropizmi mavjud. Bundan tashqari yana sut emizuvchilarning boshqa bir qancha hujayralariga nisbatan moyillik namoyon qiladi: endotelial hujayralar, epiteliyal hujayralar, fibroblastlar, mikroglia hujayralari [1, 7].

Ovqat hazm qilish tizimi orqali organizmga tushgan brutsella makroorganizm shilliq qavatidan o'tgach dendritik hujayralar hamda makrofaglar tomonidan fagotsitozga uchraydi, bu jarayonda ushbu hujayralar yuzasidagi aktin tolalari to'plami qatnashadi. Bakteriya bilan o'zaro tasirdan so'ng ushbu to'plamlar hujayra devorining invaginatsiyasiga sabab bo'ladi va birlamchi fagosoma hosil bo'ladi. Opsonlangan brutsellalar komplement orqali hujayra ichiga yo'nalgan bir vaqtda opsonlanmagan brutsellalar lektin va fibronektin retseptorlari bilan ta'sirlashadi. Opsionlanmagan brutsellalar hujayra ichida yashab qolishi mumkin, bundan farqli o'laroq opsonlangan yoki makrofagning IFN-gamma faollashuvi orqali hujayra ichiga tushgan brutsella makrofag ichida lizisga uchraydi [8]. Lipid tolalari makrofaglarning hujayra membranasida xolesteringa boy mikrodomenlarni o'z ichiga oladi, ushbu mikrodomenlar brutsellaning hujayra ichiga tushishida va uning hujayra ichida yo'naltirilgan harakatiga yordam beradi [7].

Brutsellani internalizatsiyasidan so'ng, brutsellani o'z ichiga olgan vakuola - BCV hosil bo'ladi. Fagotsitozlangan brutsellalarning 90% ga yaqini kislorodli erkin radikallar, azot oksidi va fagolizosomalar ichidagi fermentlarning bakteritsid ta'sirida nobud bo'ladi. Qolgan bakteriyalar ushbu bakteritsid omillarni yengib, erta va kech endosomalar bilan o'zaro ta'sirlashadi va lizosoma bilan vaqtincha qisqa muddatli qo'shilish jarayonidan so'ng lizosomal oqsillarni faol ravishda chiqarib tashlashi va BCVni endoplazmatik retikulum (ER) ga yo'naltirishi mumkin. ERda esa hujayra ichki resurslaridan foydalangan holda brutsella erkin ko'payadi [12, 13]. BCV dagi kislotalikning oshishi bakteriyalarga zarar etkazmaydi, ammo infeksiyaning dastlabki bosqichlarida hujayra ichida omon qolish uchun zarur bo'lgan bakterial genlarining ekspressiyasini yuzaga keltiradi [14, 15].

Hujayra ichidagi ko'payish davom etishi va bakteriyaning hujayra ichida saqlanib qolishi uchun *Brucella* bir qator vakuol o'zgarishlarini boshdan kechiradi. Bu o'zgarish jarayonida dastlabki endotsitar eBCV vakuola replikativ rBCV vakuolaga aylanadi, jarayon so'ngida esa avtofag aBCV vakuolasi bilan yakunlanadi. Avtofagiya bilan bog'liq bo'lgan makroorganizm oqsillari BECLIN1, PI3K, ULK1 va Atg14L BCV vakuolasining biogeneza muhim rol o'ynaydi va yakunda organizmga bakteriyalarning chiqishi bilan tugovchi brutsellaning hujayra ichi hayot siklining tugashiga tasir ko'rsatadi [16, 17]. Fagotsitozning yuqorida keltirib o'tilgan xususiyatlari brutsellaning makroorganizm hujayrasida va umuman olganda organizmning o'zida saqlanib turishiga sharoit yaratadi.

Hujayra membranalarida (TLR) yoki sitozolda (NLR) mavjud bo'lgan retseptorlar bakteriyalar uchun xos bo'lgan tuzilmalarni aniqlashga qodir: lipopolisaxaridlar, lipoproteinlar va flagellin, bu esa o'z navbatida yallig'lanishga qarshi dastlabki reaksiyaning paydo bo'lishiga olib keladi. *Brucella*, TLR va NLR retseptorlari ishtirok etadigan tanib olish jarayonidan yashirinish uchun passiv va aktiv molekulyar mexanizmlarga ega. *Brucella* lipopolisaxarid tuzilishi enterobakteriyalarning lipopolisaxaridi (C12-C16) bilan solishtirganda ko'proq yog' kislotasi qoldig'ini (C28) o'z ichiga olgan lipid A xususiyatlariga ega va bu modifikatsiya uning TLR4 retseptorlari bilan o'zaro ta'sirini sezilarli darajada kamaytiradi va TLR4 retseptorlari orqali signalizatsiya yo'llari orqali tanib olishdan qochishga imkon beradi [14, 18]. TLR4 agonistining faolligi lipopolisaxarid yadrosining glikozillanish yo'li bilan TLR4 MD-2 retseptorlari va brutsella lipopolisaxaridi o'rtasidagi o'xshashlikni kamaytiradi [19, 20].

Komplementning faollashuvi va bakterial xoslikka ega TLR lar birgalikda ishlaydi va makroorganizmga xavf omiliga nisbatan mos javob berishda alohida o'rin egallaydi (neytrofillar oqimi va boshqalar) [22]. Komplement sistemasi bakteriya hujayra devoridagi lipopolisaxarid bilan o'zaro tasirlanganda ishga tushadi [14, 18, 23]. *Brucella* lipopolisaxaridi tarkibida gomopolimer qoldiqlardan tashkil topgan O-polisaxaridi mavjud bo'lib, bu polimer C3 komplement sistemasi bilan to'liq birikmaydi, bu jarayon C3a va C5a komplement tizimining yallig'lanishga qarshi mahsulotlarini ishlab chiqarishini to'xtatadi [14, 18, 23].

Brucella harakatsiz bakteriya bo'lsada, uning genomlari nomalrum funksiyaga ega noan'anaviy flagellin (ipchalar) tarkibiy qismlarini kodlaydi, TLR5 retseptorida ushbu flagellinni tanib olish uchun zarur bo'lgan domen yo'qligi sababli bakteriya sezilmasdan qoladi [18, 15]. Biroq, sitozolik NLCR4 retseptorlari brutsella flagellinini aniqlay olishi va *in vivo* ravishda infektsiyani nazorat qilish uchun muhim ekanligi ko'rsatilgan [21]. TLR4 ga qo'shimcha ravishda TLR2 va TLR9 signal yo'li brutsellyoz infektsiyasini aniqlashda ishtirok etadi [24].

Brucellaning immun tizim orqali tanib olinishiga faol to'sqinlik qilishi quyidagi oqsillarning ishlab chiqarilishi bilan bog'liq: *Br. abortus*da TIR domeni Btp1/BtpA, *Br. melitensis*da TcpB. Btp1 va TcpB MyD88 adapterining (MAL) o'tkazuvchanlik funksiyasiga salbiy ta'sir qiladi, bu esa TLR2 va TLR4 signalizatsiyasi uchun zarurdir [25, 26]. Natijada, bu oqsillar dendritik hujayralarning yetilishini va yallig'lanishga qarshi sitokinlarni ishlab chiqarishni ingibirlaydi, bu esa brutsellaning uzoq muddatli saqlanishi yordam beradi.

Brutsellalarning barcha turlari virB1-virB12 genlari tomonidan kodlanadigan T4SS (IV turdagi sekretiya tizimi) muhim virulentlik omiliga ega. Ushbu omil bakteriyaga hujayra ichida omon qolishga imkon yaratadi [18, 27, 28].

T4SS ning hal qiluvchi roli virB genlari mutatsiyaga uchragan brutsella bakteriyalarining sichqon [29, 30] va echki modellarida [31] *in vivo* hujayra ichida ko'payish qobiliyatiga ega emasligida tasdiqlangan. T4SS shuningdek, *Brucella* uchun maxsus ER bilan bog'liq replikatsiya sohasini yaratishda ishtirok etadi, virB geni mutatsiyaga uchragan bakteriyalar esa makrofag lizosomalari ichida parchalanadi [3, 32].

T4SS transmembrana oqsilli "pushka" ni hosil qiladi, bu protein effektor molekularini makroorganizm hujayrasi sitoplazmasiga ko'chirishni amalga oshiradi, bu ularning turli funksiyalarini ta'minlaydi va hujayra ichidagi infektsiyani rivojlanishi va saqlanishiga ta'sir qiladi. Ko'pgina tadqiqotlarda bir necha o'nlab *Brucella* T4SS effektor oqsillari makroorganizm sitoplazmasiga ko'chirilishi paytida aniqlangan [7, 33, 34, 35, 36]. T4SS oqsillarining kasallikni qo'zg'atish uchun va albatta hujayra ichida saqlanib qolishi uchun bevosita va bilvosita muhim ekani bir qancha ilmiy ishlarda tasdiqlangan [5, 10, 34, 35, 36].

Yaqinda BtpA oqsillari (Btp1/TcpB) eukariotik Toll/interleykin-1 retseptorlari, TIR domeni bilan gomologiyaga ega bakterial oqsillar sinfiga mansubligi va brucellaning makroorganizm hujayralariga penetratsiyasi bilan ajralib chiqishi aniqlangan [24, 25, 35].

Konservativ TIR domeni eukaryotik TLR oqsillarida va immun signalizatsiyasida muhim rol o'ynaydigan MAL (MyD88) sitozolik adapter oqsilida mavjud. Ushbu *Brucella* effektor oqsillari MAL signal o'tkazuvchan adapter oqsilining degradatsiyasiga olib keladi, bu esa TLR2 va TLR4 signallarining ingibitsiyasiga va NF-kB transkripsiya faktorining faollashmasligiga olib keladi. Natijada, yallig'lanishga qarshi muhim TNF-alfa va IL-12 sitokinlarining ishlab chiqarilishi pasayadi, dendritik hujayralarning yetilishi va faollashishi kechikadi, bu infektsiyaning rivojlanishi va davom etishi uchun sharoit yaratadi [11, 37, 38].

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