

ULOGA IL-17 U MODULACIJI ANTITUMORSKE IMUNOSTI I PROGRESIJI KARCINOMA POVEZANIH SA KOLITISOM

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THE ROLE OF IL-17 IN MODULATION OF ANTITUMOUR IMMUNITY AND PROGRESSION OF COLITIS-ASSOCIATED CANCER

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SAŽETAK

Kolorektalni karcinom je jedan od najčešćih maligniteta u svetu. Smatra se da nastaje na podlozi zapaljenske bolesti creva. Proinflamatorni citokini koje oslobađaju maligne ćelije, ali i tumor infiltrišući leukociti doprinose nastanku, rastu i progresiji tumora. Značajna uloga T limfocita u antitumorskom odgovoru je dobro poznata. CD4⁺ Th limfociti mogu se podeliti na više funkcionalnih fenotipova: T helper 1 (Th1), T helper 2 (Th2), T helper 17 (Th17), na osnovu sposobnosti da sekretuju različite citokine. Th1 limfociti imaju značajnu ulogu u indukciji ćelijskog imunskog odgovora, dok Th2 limfociti suprimiraju ćelijsku imunost pojačavanjem humoralnog imunskog odgovora. Th17 limfociti su važni za nastanak zapaljenja, jer obezbeđuju „regrutovanje“ neutrofilnih leukocita i makrofaga. Polarizacija T imunskog odgovora ima višestruk uticaj na rast tumora. Iako ima dokaza da Th2 citokini mogu da dovedu do akutnog odbacivanja tumora, Th1 citokini obezbeđuju znatno bolji antitumorski efekat i sami mogu da obezbede dugotrajan antitumorski odgovor CD8⁺T limfocita. Međutim, uloga IL-17 u patogenezi karcinoma povezanim sa kolitisom (engl. colitis-associated cancer – CAC) nije u potpunosti definisana. Cilj ovog rada jeste da razjasni ulogu IL-17 u modulaciji antitumorske imunosti i progresiji kolorektalnog karcinoma.

Cljučne reči: kolitis; kolorektalne neoplazme; interleukin-17.

ABSTRACT

Colorectal carcinoma is one of the most frequent malignancies worldwide. There is a strong belief that it is initiated in the inflammatory bowel disease microenvironment. Pro-inflammatory cytokines produced by malignant cells as well as by tumor infiltrating leukocytes facilitate origination, growth and progression of cancer. An important role of T cells in antitumor immunity is well established. CD4⁺ Th lymphocytes can be classified into a few functional phenotypes: T helper 1 (Th1), T helper 2 (Th2), T helper 17 (Th17), according to the ability to secrete different cytokines. Th1 lymphocytes play important role in induction of cellular immunity, while Th2 lymphocytes suppress cellular immunity and enhance humoral immune response. Th17 lymphocytes are the key players in inducing inflammation by recruitment of neutrophils and macrophages. The polarization of T-mediated immune response has multiple effects on tumor progression. Although Th2-type cytokines can induce acute tumor rejection, Th1-type cytokines provide a greater antitumor effect and can promote durable anti-tumor CD8⁺T cell response. However, the role of IL-17 in pathogenesis of colitis-associated cancer (CAC) has not been fully understood. The aim of this paper is to clarify the role of IL-17 in modulation of antitumor immunity and progression of colorectal carcinoma.

Key words: colitis; colorectal neoplasms; interleukin-17.

UVOD

Kolorektalni karcinom je jedan od pet vodećih uzroka smrti među tumorima u svetu. Mehanizmi eliminacije patogenih mikroorganizama i zapaljenja sluznice debelog creva veoma su važni za nastanak i razvoj tumora (1). Tokom hroničnog zapaljenja, infiltrišuće ćelije imunskog sistema oslobađanjem azot-monoksida i slobodnih kiseoničnih radikala indukuju direktno oštećenje DNK i inhibiraju apoptozu čime izazivaju malignu transformaciju ćelija (2,3). Kod nekih tipova tumora, pretpostavlja se da i same genetske promene (aktivacija onkogeni i inaktivacija tumor-supresor gena) tokom maligne transformacije favorizuju razvoj hronične inflamacije u

tumorskoj mikrosredini. Tumorska mikrosredina predstavlja mesto gde različite vrste ćelija, uključujući tumorske i ćelije imunskog sistema, konstantno interreaguju. Virchow je prvi, još 1863. godine, otkrio leukocite u tumorskom tkivu i na granici tumorskog tkiva. Maligne ćelije aktivacijom transkripcionih faktora, među kojima su najznačajniji NF-κB (engl. Nuclear Factor-κB), STAT3 (engl. Signal Transducer and Activator of Transcription 3) i HIF1α (engl. Hypoxia-Inducible Factor 1α), koordiniraju produkciju proinflamatornih citokina, hemokina i proangiogenih faktora (4). Velika količina proinflamatornih citokina koje oslobađaju maligne ćelije, ali i tumor infiltrišući leukociti doprinose rastu i progresiji tumora (4,5).

Studija Liu J. i saradnika po prvi put pokazuje znatno veći procenat IL-17 produkujućih ćelija u tumorskom tkivu pacijenata sa kolorektalnim karcinomom u poređenju sa zdravom intestinalnom sluznicom istih pacijenata (62). IL-17 u tumorskom tkivu su produkovali makrofagi i Th17 limfociti. Ekspresija IL-17 je u korelaciji sa gustinom tumorske mikrocirkulacije. U istom istraživanju VEGF je definisan kao jedan od proangiogenetskih faktora aktiviranih IL-17 posredovanom angiogenezi. IL-17 produkujuće ćelije ubrzavaju rast i razvoj kolorektalnog carcinoma indukujući angiogenezu povećanjem produkcije VEGF-a u tumorskim ćelijama. Girardin A. sa saradnicima pokazao je manju procentualnu zastupljenost efektorskih (CD69+) T limfocita a znatno veću zastupljenost regulatornih (CD25⁺Foxp3⁺) ali i proinflamatornih (IL-17⁺) T limfocita u tumorskom tkivu, u poređenju sa zdravim tkivom intestinuma kod istih pacijenata (1). Takođe su identifikovali malu populaciju T limfocita koji ekspimiraju markere inflamatornih i regulatornih ćelija (CD4⁺IL-17⁺Foxp3⁺) u tumorskom tkivu. Isti autori smatraju da ove ćelije mogu da predstavljaju intermedijalnu populaciju ćelija ili da kontrolišu inflamatornu i regulatornu funkciju infiltrišućih T limfocita. Ma C. sa saradnicima potvrđuje ovaj fenomen (63), tj. prisustvo i znatno veći procentualni udeo Foxp3⁺IL-17⁺ T limfocita u tkivu kolorektalnog carcinoma u odnosu na normalnu mukozu debelog creva. Izolovani Foxp3⁺IL-17⁺ T limfociti pokazali su značajan imunosupresivni kapacitet prema tumor-specifičnim CD8⁺T limfocitima, nakon in vitro kokultivacije.

Hronična inflamacija je povezana sa nastankom i razvojem mnogih tipova karcinoma (4, 64). Najbolji primer povezanosti zapaljenja i karcinoma jeste povećani rizik od kolorektalnog karcinoma kod pacijenata sa hroničnom granulomatoznom bolešću creva (engl. Inflammatory bowel disease – IBD; 65, 66). Jedno od mogućih objašnjenja ovog fenomena jeste da velika količina medijatora zapaljenja, koji se sintetišu tokom zapaljenske reakcije, može da doprinese nastanku, rastu i progresiji kolorektalnog karcinoma. Dakle, pored već postojećeg koncepta da oslobađanje slobodnih radikala tokom zapaljenja može da indukuje akumulaciju mutacija što sledstveno vodi u displaziju, danas se smatra da velike količine citokina i faktora rasta koje tokom zapaljenja stvaraju ćelije imunskog sistema, ali i druge ćelije, takođe mogu da utiču na proces kancerogeneze (67). Hyun Y. S. i saradnici ispitivali su ulogu IL-17 u razvoju karcinoma povezanog sa kolitisom (68). Naime, indukovali su tumor normalnim (wild type) i IL-17A deficijentnim miševima i pokazali da su incidenca i veličina tumora značajno niži u grupi IL-17A deficijentnih miševa. U ovoj grupi životinja izmerene su i niže serumske vrednosti inflamatornih citokina IL-6 i TNF- α kao i ekspresija markera i regulatora proliferacije: cyclin D1, cyclin-dependent kinase 2, cyclin

E, Ki-67 (68). Pojedina istraživanja su pokazala da IL-23 i IL-17, kao proinflamatorni citokini potpomažu zapaljenje creva i prisutni su u visokom nivou kod bolesnika sa inflamatornom bolešću creva (69, 70). Osim toga, aktivacija IL-23/IL-17 puta stimuliše rast i razvoj tumora tako što indukuje lokalnu zapaljensku reakciju (71–74). Zajedno sa drugim proinflamatornim citokinima (TGF- β , IL1 i IL6), IL17 stimuliše infiltraciju neutrofila i makrofaga u tumorsko tkivo. U tumorskoj mikrosredini, ove ćelije produkuju MMPs (engl. Matrix Metallo-Proteases) koje stimulišu remodeliranje tkiva, angiogenezu i rast tumora. Takođe, IL-23 ima važnu ulogu u izbegavanju imunskog nadzora tako što redukuje infiltraciju CD8⁺ T limfocita u tkivo tumora (72). Naša ranija istraživanja pokazala su da je serumska vrednost IL-23 znatno povišena kod pacijenata sa kolorektalnim karcinomom u poređenju sa zdravom kontrolom (75). Povišene vrednosti ovog citokina zabeležene su i kod pacijenata sa karcinomom želuca (76). Naša istraživanja su potvrdila i pozitivnu korelaciju serumskog IL-23 i ekspresije VEGF-a u tumorskom tkivu (75). Smatra se da karcinomi povezani sa kolitisom nastaju između i kao rezultat aktivacije transkripcionog faktora STAT3 koji pokreće prokarcinogeni Th-17 imunski odgovor potpomognut IL-23 (77). Skorije istraživanje je potvrdilo da aktivacija STAT3 transkripcionog faktora indukuje sintezu prokarcinogenih citokina (npr. IL-23), dok inhibira sintezu antikancerogenih citokina (npr. IL-12) (78).

Novija istraživanja ukazuju na to da IL-17 spada u klasu indirektnih faktora angiogeneze, koji stimulišu angiogenezu in vivo, ali nemaju direktan mitogeni efekat na endotelne ćelije in vitro. Smatra se da IL-17 ima značajnu ulogu u T-ćelijski posredovanoj angiogenezi (52), kao i da indukuje angiogenezu povećanjem ekspresije VEGF-a (79). Takođe je pokazana ekspresija IL-17 u tkivu karcinoma ovarijuma, a intenzitet ekspresije korelira sa gustinom vaskulature u tumoru (53). Alexandrakis i saradnici (80) pokazali su povećane serumske vrednosti IL-17 kod pacijenata sa multiplim mijelomom, kao i korelaciju ovih vrednosti sa faktorom angiogeneze VEGF. U našim istraživanjima nismo našli značajnu povezanost IL-17 i VEGF-a kod pacijenata sa kolorektalnim karcinomom (61).

ZAKLJUČAK

Serumska vrednost IL-17 povišena kod pacijenata sa hroničnom zapaljenskom bolešću creva kao i kod pacijenata sa kolorektalnim karcinomom. IL-17 spada u proinflamatorne citokine i ima važnu ulogu kako u patogenezi zapaljenske bolesti debelog creva, tako i karcinoma povezanih sa kolitisom. Među moguće mehanizme kojima IL-17 doprinosi kancerogenezi jesu i: indukcija angiogeneze povećanjem produkcije VEGF-a u tumorskim ćelijama; stimulacija produkuje MMPs (Matrix

Metallo-Proteases) koje remodeliraju tumorsko tkivo i olakšavaju invazivnost, angiogenezu i metastaziranje; akumulacija Foxp3+IL-17+ T limfocita koji poseduju imunosupresivni kapacitet prema tumor-specifičnim CD8+T limfocitima. Takođe, IL-17 može biti novi prognostički faktor za pacijente sa kolorektalnim karcinomom i može poslužiti kao novi terapijski cilj.

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