DIABETES MELLITUS DIRECTS NKT CELLS TOWARD TYPE 2 AND REGULATORY PHENOTYPE

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DIABETES MELITUS USMERAVA DIFERENCIJACIJU NKT ĆELIJA U PRAVCU TIP 2 I REGULATORNOG FENOTIPA

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ABSTRACT

Diabetes mellitus is chronic disorder characterized by hyperglycaemia. Hyperglycaemia induces mitochondrial dysfunction, enhances oxidative stress and thus promotes reactive oxygen species (ROS) production. Earlier studies suggested that reactive oxygen species (ROS) are involved in the pathogenesis of many diseases. Previous studies have revealed that hyperglycaemia changes the functional phenotype of monocytes, macrophages, neutrophils, NK cells and CD8⁺ T cells. The aim of this study was to investigate whether diabetes affects the functional phenotype of NKT cells.

Diabetes mellitus was induced in BALB/c mice by intraperitoneal injection of streptozotocin at a single dose of 170 mg/kg body weight. The number and functional phenotype of splenic NKT cells was assessed by flow cytometry, 28 days after diabetes induction.

The diabetic condition facilitated the production of antioxidant enzymes, including catalase ($p<0.05$) and superoxide dismutase. Hyperglycaemia enhanced oxidative stress and thus decreased the number of splenic NKT cells but did not change the percentage of splenic CD3⁺CD49⁺ NKT cells that express the activatory receptor NKP46 or produce IFN-γ. However, hyperglycaemia increased the frequency of splenic NKT cells that express KLRG-1 and produce TGF-β, IL-4, and IL-5, and it decreased the frequency of IL-17⁺ NKT cells.

Our study indicates that diabetes mellitus induces oxidative stress and switches the functional phenotype of NKT cells towards type 2 (IL-4 and IL-5 producing NKTs) and regulatory (TGF-β producing NKTs) phenotypes. These findings are correlated with the clinical observation in humans that diabetic patients are more prone to infections and tumours.

Keywords: *diabetes, hyperglycaemia, oxidative stress, NKT cells*

SAŽETAK

Dijabetes melitus je hronično oboljenje koje se karakteriše hiperglikemijom. Hiperglikemija utiče na funkciju mitohondrija, pojačava oksidativni stres i time podstiče produkciju kiseoničnih slobodnih radikala. Ranije studije su pokazale da kiseonični slobodni radikali igraju važnu ulogu u razvoju mnogih bolesti. Hiperglikemija utiče na funcionalni fenotip monocita, makrofaga, NK ćelija i CD8⁺T limfocita. Cilj istraživanja je bio ispitati da li hiperglikemija utiče na funcionalni fenotip NKT ćelija.

Dijabetes melitus je indukovan BALB/C miševima jednom dozom streptozotocina intraperitonealno u dozi od 170 mg/kg. Broj i funkcionalni fenotip NKT ćelija je analiziran protočnom citometrijom 28. dana nakon indukcije dijabetesa.

Dijabetes je povećao produkciju antioksidantnih enzima, katalaze i superoksid dizmutaze. Dijabetes i pojačan oksidativni stres su smanjili ukupan broj NKT ćelija u slezini hiperglikemičnih miševa, dok se procenat NKp46⁺NKT ćelija i NKT ćelija koje produkuju IFN-γ u slezini nije značajno razlikovao u poređenju sa normoglikemičnim miševima. Međutim, hiperglikemični miševi su imali veću procentualnu zastupljenost NKT ćelija koje eksprimiraju KLRG-1 i produkuju TGF-β, IL-4, and IL-5, dok je učestalost IL-17⁺ NKT ćelija bila značajno manja u poređenju sa normoglikemičnim miševima.

Rezultati ukazuju da dijabetes melitus pojačava oksidativni stres i usmerava polarizaciju NKT ćelija ka tipu 2 i regulatornom fenotipu, što je u skladu sa kliničkim studijama koje potvrđuju da su osobe sa dijabetesom sklone razvoju infekcija i tumora.

Ključne reči: *dijabetes, hiperglikemija, oksidativni stres, NKT ćelije*

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