INFECTIOUS DISEASES (BACTERIAL, FUNGAL, VIRAL, PARASITIC, INFESTATIONS)

MIRNA-146A REGULATES CD11C+CD11BHI MYELOID DC DEVELOPMENT AND CONTROLS TH1/TH17 DIFFERENTIATION MEDIATED BY TLR9 LIGAND CPG-ODN ACTIVATED DCS

Yuling Shi [1] - *Li Zhou* [1] - *Qingsheng Mi* [1]

Henry Ford Health System, Department Of Dermatology, Detroit, United States [1]

Introduction: miRNAs have emerged as a novel class of posttranscriptional regulators that modulate immune cell development and functions. miRNA miR-146a acts as a critical physiological brake to prevent the hyperresponsiveness to microbial infections. Nucleic acids from microbes are generally sensed by Toll-like-receptor (TLR)-7/9 prevalently expressed in dendritc cells (DCs), which results in DC activation. Although previous study showed that miR-146a highly expressed in activated DCs is involved in DC maturation and cross-priming, it is still unknown whether miR-146a regulates TLR9-mediated DCs function in vivo.

Objective: To study the role of miR-146a in regulating TLR9-mediated DCs function in vivo using miR-146a knockout (miR-146aKO) mice.

Materials and Methods: In the case of TLR ligands treated or not, miR146a expression of BMDCs was tested by RT-PCR and the phenotype of DCs were analyzed using flow cytometry; the function of DCs from miR-146aKO and wild type (WT) mice activated with TLR9 agonist were tested by analyzing CD4+ T cell proliferation and differentiation; splenic DCs population from miR-146aKO and WT mice were analyzed by FACS. Bone marrow chimeras was used to test the effect of miR-146a on the development and function of DCs in a cell autonomous fashion.

Results: We observed a strong induction of miR-146a expression in BMDCs activated by TLR9 ligand CpG-ODN, and DCs from miR-146aKO mice significantly enhanced Th1/Th17 differentiation upon CpG-ODN stimulation, but not with TLR4 ligand LPS, compared to that of WT mice. The splenic cDC, especially CD11c+CD11bhi subset, was dramatically reduced in miR-146aKO mice compared to WT mice. Bone marrow transferring experiments indicated that functional changes of CpG-ODN-mediated cDCs and reduced splenic cDCs in miR-146aKO mice were cell-intrinsic.

Conclusions: miR-146a plays a critical role in the maintenance of immune balance by regulating the development and function of cDCs during microbial infection.