activation lead to multisystem tissue damage. Plasmacytoid dendritic cells (pDCs) play a central role in the pathogenesis of SLE through dysregulated type I IFN production, together with activated myeloid DCs (mDCs), amplifying vicious spiral of autoimmune disorders(1). Therefore, control of the aberrant DC activation may provide an alternative treatment strategy against SLE.

Objectives: Mycophenolate mofetil (MMF), which has been used to treat lupus nephritis, specifically blocks proliferation of B and T lymphocytes by inhibition of inosine-5-monophosphate dehydrogenase (IMPDH). In addition, although there is evidence indicating the immunosuppressive effects of MMF on human monocyte-derived dendritic cells(2,3), there are no reports showing its effects on human blood DC subsets. Here we focused on the effects of MMF on the functions of the blood pDCs and mDCs.

Methods: We isolated human blood DCs from healthy donors using cell sorting(4) and examined the function of mycophenolic acid (MPA), which is metabolitic products of MMF, on DC subsets in response to TLR-ligands and serum from patients with active SLE. Written informed consent was obtained from all healthy adult donors and SLE patients.

Results: We found that therapeutic plasma concentration range of MPA down-regulated expression of CD40, CD80 and CD86 dose-dependently on mDCs and pDCs without inducing apoptosis, in response to R848(TLR7/8 agonist) and CpG2216(TLR9 agonist), respectively. Of note, MPA profoundly suppressed IL-12 production and STAT4 expression in the mDCs and IFN-α production and IRF7 expression in the pDCs(Fig 1). We also observed inhibition of nuclear translocation of IRF-7 in pDCs treated with MPA by confocal microscopy(Fig 2). Furthermore, we identified that MPA had an inhibitory effect on SLE serum-induced IFN-α production by human PBMCs.

Conclusion: Our data suggest that MMF can drive a wedge into the vicious spiral of autoimmune disorders through regulating the function of not only lymphocyte but also DC subsets. Thus, we unveiled a part mechanism of the therapeutic ability of MMF against SLE.

References:


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