GROUP 1 INNATE LYMPHOID CELL INVOLVEMENT IN THE PROGRESSION OF EXPERIMENTAL GLOMERULONEPHRITIS IS INHIBITED BY PPAR-ALPHA

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INTRODUCTION AND AIMS: In anti-glomerular basement membrane (anti-GBM) glomerulonephritis (GN) in rat, glomerular injury caused by activated macrophages (Mø) is induced by CD8+ lymphocytes (CD8+ Lym). However, little is known about the profile of CD8+ Lym, with the exception that they do not express T-cell receptors or CD3. Innate lymphoid cells (ILCs), a recently discovered group of immune cells, are classified into group 1, group 2 and group 3 ILCs based on their phenotypic and functional characteristics of Th1, Th2 and Th17, respectively. Notably, ILCs lack myeloid and dendritic cell phenotypical markers. This study examined the profile of CD8+ Lym, which show features similar to those of ILCs. In addition, we investigated the effects of peroxisome proliferator-activated receptor alpha (PPARα), which has anti-inflammatory effects on anti-GBM GN.

METHODS: Three groups of 4-week-old male Wistar-Kyoto rats were administered fenofibrate (300 mg/kg/day; PPARα agonist), pioglitazone (100 mg/kg/day; PPARγ agonist) or vehicle, respectively, once daily from on day 0, and then injected intravenously with 50 μg anti-GBM antibodies on day 1. Urine and blood samples, and the kidneys were collected on day 8. Cell surface markers and cytokine expression of CD8+ Lym were analyzed by quantitative reverse transcription polymerase chain reaction (qRT-PCR) or flow cytometry.

RESULTS: Immunofluorescence and flow cytometric analyses of isolated glomeruli showed that glomeruli-infiltrated CD8+ Lym were lineage negative cells (CD35 CD43 CD14 CD145R CD103 CD161 HIS48 antigen) (Figure.1). qRT-PCR analysis of cell sorted CD8+ Lym harvested from isolated glomeruli revealed that CD8+ Lym expressed markedly high levels of interferon (IFN)-γ and T-bet mRNA compared to Mø (Figure.2). The glomeruli-infiltrated CD8+ Lym were group 1 ILCs and comprised the majority of cells producing IFN-γ in anti-GBM GN-induced rats. Both PPAR agonists reduced the amount of proteinuria, the numbers of crescentic lesions, infiltrating CD8+ Lym and Mø into the glomeruli, and the level of tumor necrosis factor-α and interleukin-1β mRNA expression in isolated glomeruli. In contrast, PPARα agonist treatment caused significant reduction in the level of IFN-γ mRNA expression in isolated glomeruli.

CONCLUSIONS: This study showed that the CD8+ Lym involved in the progression of rat anti-GBM GN are group 1 ILCs. PPARα attenuated anti-GBM GN by inhibiting production of IFN-γ, which activates Mø, from group 1 ILCs.