Dysfunction Of CD8+PD-1+T Cells in Type 2 Diabetes Caused by the Impairment of Metabolism-Immune Axis

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Abstract:

Background:

The metabolic changes and dysfunction in CD8+T cells may be involved in tumor progression and susceptibility to virus infection in type 2 diabetes (T2D).

Objectives:

We conducted this study to investigate peripheral CD8+T cells derived from the patients with T2D and their alterations by the treatment with metformin by evaluating the cytokine production and metabolic states by flux analyzer.

Study Design:

Randomized control trial

Methods:

We recruited the hospital in-patients with T2D, who were not less than 20 years old and not more than 75 years old and who did not receive metformin. We randomly assigned the patients with T2D to metformin group, Met(+) (n=9), non-metformin group, Met(−) (n = 10). In the metformin group, the initial dose was 500 mg/day (250 mg twice daily), and the dose was increased up to 1,500 mg/day (500 mg thrice daily) over 2 weeks by confirming the absence of adverse efects. Blood samples were collected at baseline, 1 week at hospital and 2 months at out-patient clinic, to evaluate the function of CD8+T cells.

Results:

In C57BL/6JJcl mice fed with high fat-high sucrose chow (HFS), multifunctionality of CD8 + splenic and tumor-infltrating lymphocytes (TILs) was impaired and associated with enhanced tumor growth, which were inhibited by metformin. In CD8 + splenic T cells from the HFS mice, glycolysis/basal respiration ratio was signifcantly reduced and reversed by metformin. In the patients with T2D (DM), multifunctionality of circulating CD8+PD-1 +T cells stimulated with PMA/ionomycin as well as with HLA-A*24:02 CMV peptide was dampened, while metformin recovered multifunctionality. Both glycolysis and basal respiration were reduced in DM, and glycolysis was increased by metformin.

Conclusion:

The disturbance of the link between metabolism and immune function in CD8 +PD-1 +T cells in T2D was proved by recovery of antigen-specifc and non-specifc cytokine production via metformin mediated increase in glycolytic activity.

Keywords:
T2D, metformin, CD8+PD-1 +T cells, tumor progression.