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Letter to Editor

The Novel Insight of Programmed Death Ligand 1 Over-Expression in Tuberculosis Patients From System Biology

Masoud Keikha[1,2*]

[1]Department of Microbiology and Virology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[2]Antimicrobial Resistance Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
***Corresponding Author:** Masoud Keikha, Tel: +989386836425, Email: masoud.keykha90@gmail.com

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Dear Editor,

Tuberculosis (TB) remains one of the 10 leading causes of morbidity and mortality in the world. It is estimated that 2 billion of world's population are infected with *Mycobacterium tuberculosis* as asymptomatic (latent TB) during their lives, of whom, 5-10% progress to active TB (1). The immune response influenced host reaction to *M. tuberculosis* infection; particularly CD4+ T cells that are responsible for resistance to TB infection but there are several questions that remain unanswered about dysregulation of the balance between protection and reactivation of previous TB infection; understanding this process lead to development of monitoring of TB progression in latent-TB infection (LTBI) and appropriate treatment (2,3).

The programmed cell death protein 1 (PD-1 or CD279) is a surface molecule which interacts with PD-L1, PD-L2, CD80, CD86 or PDCD1 surface receptors followed by down-regulating the immune system via promoting apoptosis or reducing T regulatory cell death (T regulatory inhibits Th1 activities by suppressing cytokine, e.g. IL-10 and TGF-β) (2,4). According to the literature, the PD-1/PD-L1 interaction dysregulates IFN-γ production and suppresses CD8+ T lymphocytes via stimulating apoptosis reaction (4,5). In addition, the PD-1 is over-expressed in active TB patients compared with healthy individuals (4,6). PD-1 overexpression reduces the expression of IFN-γ and development of TB progression in LTBI cases (4). In the present study, we analyzed the PD-1 and the expression of its ligands among active-TB and LTBI patients and healthy individuals as well as changes in IFN-γ, FOXP3, IL-10 and TGF-β in these population using a system biology study.

First, the gene expression profiles of active-TB and LTBI patients and healthy individuals were obtained from Gene Expression Omnibus (GEO) database (Accession number: GDS4966, GPL570 platform). Then, the GEO2R and GEO profiles were employed to determine differentially expressed genes (DEGs) of PD-1, PD-L1, PD-L2, PDCD1, CD80, CD86, IFN-γ, Foxp3, IL-10 (based on the KEGG pathway, hsa04151) and TGF-β for three categories using Benjamini-Hochberg FDR-adjusted *P* values <0.05. In addition, the protein-protein interaction network (PPIN) was constructed using STRING (Search Tool for the Retrieval of Interacting Genes) online server. According to our analysis, the PD-1/PD-L2 is over-expressed in active-TB compared to LTBI and healthy individuals, which has also been confirmed by previous reports (2,4-6). In addition, IFNG is down-regulated in active-TB (Table 1). In contrast, PF-L1, PDCD1 and CD4+ T cells on surface molecules CD80 and CD86 were down-expressed in active-TB group, which could be the cause of CD4+ T cell death under the influence of PD-1 over-expression in this group or the potential PD-1 interaction with alternative receptors but the expression amount of Bax (apoptotic biomarker) was down-expressed in active-TB patients, which confirms increased cell death (due to PD-1, etc) in active TB patients. But Foxp3, IL-10 and TGF-β were down-regulated in active-TB patients compared to LTBI patients and healthy individuals. According to previous reports, Foxp3 is a reliable biomarker for production of T regulatory cells that is recruited in granuloma lesion in the lungs of TB patients and is decreased in peripheral blood mononuclear cells (7,8); therefore, the decrease in the expression of Foxp3, IL-10 and TGF-β in this study is logical (Table 1).

The PPIN confirmed the close relationship between PD-1 and CD4+ T cell receptors that influenced acquired immune system, particularly CD4+ T cells. According to the interaction network, the PD-1 could influence PDCD1, PDCD1LG2, CD274 and CD80 surface molecules which regulates the immune system including T cell stimulation, cell death and proliferation, IL-2

Table 1. Different Profiles of Gene Expression in Active-TB, LTBI and Health Groups

Genes	Expression Amounts in 3 categorizations		
	Active-TB	LTBI	Health donors
PD-1	84.44	82.33	81.66
PD-L1	72.77	81.5	82.16
PD-L2	18	11	11
PDCD1	37.66	48.33	47.33
CD80	38.11	71.66	70.16
CD86	87.55	92.33	92.83
IFNG	13.44	15.66	22.83
Foxp3	19.88	24	17.5
IL-10	44.55	60.16	76.16
TGF-β	63.33	66	66.33
Bax	82.66	74.5	71.66

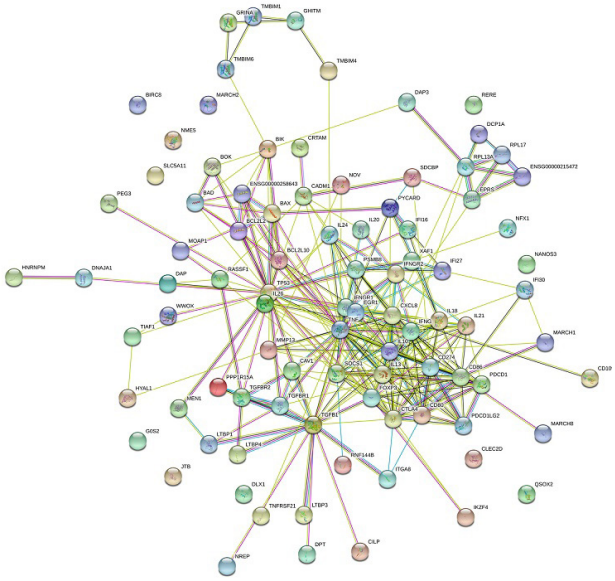

Figure 1. The Protein-Protein Interaction Networks of PD-1 and its Related Protein During Tuberculosis Pathogenesis.

induction and pro-inflammatory cytokines production. There are PD-1 and its ligands in the central nodes which have been surrounded by numerus genes which indicates vital cellular processes such as apoptosis, T regulatory production, p53 signaling pathway, and inflammatory cytokines (Figure 1).

In summary, the PD-1 is over-expressed in active TB patients compared to LTBI patients and healthy individuals, which stimulates CD4+ T cell death via apoptosis and production of T regulatory cells. Overall, our system biology study confirmed previous reports that have indicated the PD-1 is over-expressed in active-TB patients. In addition, there are novel insights about numerous immune system changes mediated by PD-1 over-expression that lead to progression from LTBI to active-TB particularly T regulatory production or CD4+ T cell apoptosis during TB pathogenesis. The PD-1 is considered as a reliable biomarker for TB progression and as a novel therapeutic target for TB treatment.

Ethical Approval

The Ethics Committee of Mashhad University of Medical Sciences approved the study.

Conflict of Interest Disclosures

None.

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