The PI3K-Akt/mTOR Signaling Pathway Roles in Tuberculosis Pathogenesis - The First System Biology Insight

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Dear Editor,

Tuberculosis (TB) is remains as major public health concern. According to WHO reports in 2018, it estimated 10.7 million TB cases throughout the worldwide. Also there are 1.6 million died from TB and 558,000 rifampin-resistant TB (RR-TB) in 2017 [1]. Furthermore, approximately 2 billion people have contaminated with *Mycobacterium tuberculosis* (Mt) without clinical symptoms as latent-TB infection (LTBI); about 5-10% of these individuals have develop to active tuberculosis during their lives [2]. There are several serious challenges for control of tuberculosis including HIV/AIDS pandemic, inefficacy of BCG vaccination in adult pulmonary-TB or spread of drug-resistant TB strains which cause to failure to control of tuberculosis in recently decades [1,3].

The system biology and cellular transcriptomic information has efficient tool for acquisition of novel insights for developing diagnosis methods, treatment monitoring and development of novel therapeutic options [4]. The phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K-Akt-mTOR) signaling pathway has key role in cell growth, differentiation, apoptosis, autophagy, metabolism and infectious disease particularly tuberculosis [5]. According to review of literatures, dysregulations of the PI3K-Akt/mTOR signaling pathway have shown in tuberculosis individuals [6]. For example, Ouyang et al. have shown that the PI3K-Akt/mTOR pathway is down regulation of T regulatory production via inhibition of transcription factor Forkhead 03α (Foxo1, 3α) [7]. Recently studies have suggested that down-regulation of the PI3K-Akt/mTOR pathway in tuberculosis patients can cause to changes T reg cells and play important role in development to active tuberculosis [5,8,9]. In the present study, we accomplished system biology for analysis of the PI3K-Akt/mTOR expression changes in active-TB and latent-TB patents as well as healthy individuals.

The gene expression profiles of CD4+ T-cells of tuberculosis and healthy individuals was obtained from Gene Expression Omnibus (GEO) database (Accession number: GDS4966; GPL570 platform). Subsequently, the GEO2R analysis was performed for detection of differentially expressed genes (DEGs) from three categorized consisting active-TB, LTBI and healthy controls given that Benjamini-Hochberg FDR-adjusted p-values <0.05 [4]. Then, the AKT3, PI3K, BCL2, CDK6, CREBS, NRAS, mTOR and NF_kB expression levels are remarked according to KEGG pathway (hsa04151). Finally, the Protein-Protein Interaction Networks (PPIN) was conducted using STRING online server. According to our analysis, inflammatory cytokines, JAK-STAT signaling, MAPK signaling pathway, autophagy gene expression profiles were different among TB, LTBI and healthy donors. In heat map diagram it’s obvious to decrease in immune-related genes expression fold from healthy donors to active-tuberculosis patients. In contrast the several genes including Foxp3, CTLA-4, TIM1, JAK1, Cox11, BCL11A, TMX3, CXL10 or PDL2 are over expressed in active-TB compared than LTBI and health group respectively. Moreover, there are significant difference (based on the adjusted p-values <0.05) in fold expression levels of PI3K-Akt/mTOR signaling related genes such as AKT, BCL2, CDK6, CREBS, mTOR, PIK3, NRAS, NF_kB (Figure 1, Table 1).

Based on the signaling network analysis, there are several PI3K-Akt/mTOR signaling related genes in central nodes of PPIN (such as mTOR, AKTs, CREBS, RICTOR, PIK3, MITF, NRAS or IKZF3) which are surrounded by various genes that regulated vital cell process including apoptosis, autophagy, cell-growth, p53 signaling pathway, NF_kB related genes (Figure 2).

Overall, according to present study, it’s obvious different expression profiles of the PI3K-Akt/mTOR signaling pathway in three groups of active-TB, LTBI and healthy individuals. Autophagy related genes (ATG), inflammatory cytokines, NF_kB pathway or MAPK signaling pathway are down-regulated from healthy donors to LTBI and active-TB patients. In contrast, apoptosis related genes, cell growth, P53 signaling pathway and cell proliferation were over-expressed in active-TB compared that LTBI and health individuals. The present study was the first document for explain of the PI3K-Akt/mTOR signaling pathway roles in different stages of tuberculosis disease.
Figure 1: The different expression of the AKT, BCL2, CDK6, CREB5, mTOR, PI3K, NRAS, NF-κB as separate diagrams from A to H respectively.

Figure 2: The PPIN conducted for the PI3K-Akt/mTOR signaling pathway related genes.
In summary, or funding imply that expression amounts of the PI3K-Akt/mTOR signaling pathway is changed during tuberculosis pathogenesis; the PI3K-Akt/mTOR signaling pathway is influenced cell process particularly introduction of T regulatory cells via FOXO1. Previous reports are suggested that T reg cells are over expressed in active-TB patients who suppressed Th1 response. Therefore, expression of the PI3K-Akt/mTOR signaling pathway is important for determination of tuberculosis outcomes and monitoring of tuberculosis progression in LTBI cases.

**Ethical Considerations**

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

**References**


### Table 1: Different expression amounts of the PI3K-Akt/mTOR signaling genes in three groups of active-TB, latent-TB and health group.

<table>
<thead>
<tr>
<th>Genes</th>
<th>Active-TB</th>
<th>LTBI</th>
<th>Health group</th>
</tr>
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<tbody>
<tr>
<td>AKT</td>
<td>9.74</td>
<td>10.13</td>
<td>10.8</td>
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<tr>
<td>BCL2</td>
<td>2.52</td>
<td>3.55</td>
<td>3.31</td>
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<td>CDK6</td>
<td>9.85</td>
<td>9.56</td>
<td>9.48</td>
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<td>CREB5</td>
<td>9.08</td>
<td>8.03</td>
<td>8.13</td>
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<tr>
<td>mTOR</td>
<td>8.71</td>
<td>8.83</td>
<td>8.76</td>
</tr>
<tr>
<td>PIK3</td>
<td>4.41</td>
<td>4.48</td>
<td>4.66</td>
</tr>
<tr>
<td>NRAS</td>
<td>14.91</td>
<td>14.81</td>
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<tr>
<td>NF_kB</td>
<td>10.05</td>
<td>10.21</td>
<td>10.23</td>
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