Abstract—Tuberculosis is caused by *Mycobacterium tuberculosis* (Mtb) infection. Mtb is one of the oldest human pathogens, and evolves mechanisms implied in human evolution. There have been several studies discussing the functions of Mφs and DCs during Mtb infection, but the genome-wide pathways and networks are still incomplete. Therefore, we analyzed the cross-talk genome-wide genetic-and-epigenetic interspecies networks (GWGEINs) between Mφs vs. Mtb and DCs vs. Mtb to determine the varying mechanisms of both the host and pathogen as it relates to Mφs and DCs during early Mtb infection. We investigated the underlying cross-talk mechanisms between the host and the pathogen to determine how the pathogen counteracts host defense mechanisms in Mφs and DCs during Mtb H37Rv early infection. Based on our findings, we propose Rv1675c as a potential drug target because of its important defensive role in Mφs. Furthermore, the membrane essential proteins v1098c, and Rv1696 (or cytoplasm for Rv0667), in Mtb could also be potential drug targets because of their important roles in Mtb survival in both cell types. We also propose the drugs Lopinavir, TMC207, ATSM, and GTSM as potential therapeutic treatments for Mtb infection since they target the above potential drug targets.

**FIGURE 1** Comparison of the HPCNs in Mφs and DCs infected with Mtb during early infection. Host-pathogen core networks (HPCNs) contain the major structure of GWGEINs via the principal network projection (PNP) method, which allowed investigation of the underlying mechanisms of the host and pathogen. HPCNs highlight the different signaling pathways between Mφs and DCs during Mtb infection. The upper half shows the pathogen network and the lower half the host network. The edges with solid black lines represent presence in both cell types.

**FIGURE 2** The defensive mechanisms of the host and pathogen and the dysfunction of the host in Mφs and DCs during early Mtb infection. The upper figure summarizes the defensive mechanisms of the host in Mφs during early Mtb infection. The defensive proteins (Rv1438, Rv0762c, and Rv0667) and metal-dependent homeostasis signaling pathway of Mtb within Mφs counteract the host defense mechanisms. The lower figure summarizes the defensive mechanisms of the host in DCs during early Mtb infection. The defensive proteins (Rv1438, Rv0762c, and Rv0667) and metal-dependent homeostasis signaling pathway of Mtb within DCs influence host defense mechanisms. We observed that the defensive mechanisms of Mφs are more easily influenced by Mtb than DCs, indicating that Mφs are more susceptible to Mtb than DCs. In addition, the dysfunction in Mφs such as DNA repair and cell growth caused by Mtb may easily cause the accumulation of mutations in Mφs. Thus, Mtb infection of Mφs may promote progression from TB to lung cancer.