DBT-CDFD study gains deeper insight into TB infection

New Delhi, Nov 27: Mycobacterium tuberculosis is one of the most successful pathogens and has caused more than 1.4 million deaths in the year 2020 (Global TB report 2020, WHO). It infects alveolar macrophages and uses them as their "home" for further multiplication and spread of the infection.

Among other things, the pathogen requires Iron for carrying out its metabolic processes when it is residing inside the host macrophages. Iron alone is the cofactor of more than 40 enzymes of the mycobacterial metabolism.

A team of researchers at DBT-Centre for DNA Fingerprinting and Diagnostics (DBT-CDFD) has identified a novel mechanism by which it acquires iron by manipulating the holotransferrin-mediated iron uptake in macrophage.

In the macrophages, holotransferrin-mediated iron uptake is one of the ways of acquiring iron from the extracellular environment and Hereditary hemochromatosis protein (HFE) is one of the key protein in this process. In endoplasmic reticulum, HFE interacts with beta-2-microglobulin (β2M) which is an important event for the proper folding of HFE and its subsequent surface-localization. At the cell surface, HFE interacts with Transferrin receptor-1 (TFR-1) and forms a HFE-TFR-1 complex. Only the free form of TFR-1 can bind to the iron bound-holotransferrin and facilitate iron intake in the cells and that is how the cells maintain their intracellular iron levels via the HFE-TRF-1-holotransferrin system.

During infection, M. tuberculosis secretes a protein, ESAT-6, which goes to the endoplasmic reticulum of the infected cell and binds with β2M. ESAT-6-β2M interaction creates a deficit of β2M in the endoplasmic reticulum. In the β2M deficit, HFE's folding is greatly impaired and unfolded HFE remains sequestered in the endoplasmic reticulum and is unable to reach the cell surface.

In the absence of HFE at the surface, TFR-1 remains free to interact with iron bound-holotransferrin. As more of the holotransferrin binds with the TFR-1 more iron is taken up by the macrophages resulting in the surge in the intracellular levels of iron in the presence of ESAT-6 protein. Intracellular accumulation of iron is found to be less in macrophages infected with ESAT-6 deficient M. tuberculosis indicating a direct role of ESAT-6 protein in iron uptake.

The findings of the study, thus, suggests that M. tuberculosis targets the holotransferrin-mediated iron uptake pathway in macrophages for iron acquisition during infection by utilizing ESAT-6 protein. This is one of the mechanisms by which M. tuberculosis increases the iron uptake which eventually helps in its better persistence inside host macrophages.

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