PPE2 protein of Mycobacterium tuberculosis inhibits innate defense by decreasing ROS production in macrophages

Study conducted at Centre for DNA Fingerprinting and Diagnostics (CDFD), Hyderabad we have found that one of the PE/PPE family protein of *Mycobacterium tuberculosis* (M. tb), PPE2, can limit oxidative stress mediated by reactive oxygen species (ROS). PPE2 is shown to be a secretory protein. Bioinformatics analysis revealed the presence of eukaryotic like SH3 domain and a PxxP motif in PPE2. PPE2 protein interacted with $p67^{phox}$ subunit of NADPH oxidase in the cytosol and hindered the migration of cytosolic subunits $p47^{phox}$ and $p67^{phox}$ from cytosol to membrane.

Unavailability of subunits $p47^{phox}$ and $p67^{phox}$ at the membrane resulted in faulty assembly of NADPH oxidase complex and as a result inhibition in ROS production was observed (**Figure**). Further, to investigate the role of SH3-like domain and PxxP motif in PPE2 mediated ROS inhibition, we mutated conserved residues in SH3-like domain (Y209A, W236A, and P249A), deleted a PxxP motif (Δ540-543). Team observed that W236A mutation could not inhibit ROS generation, also, it failed to inhibit PPE2-$p67^{phox}$ interaction. This suggested that W236 residue in SH3 like domain of PPE2 is probably crucial for PPE2-$p67^{phox}$ interaction. PPE2 expression in *M.tb* improves the intracellular survival of *M.tb* as PPE2-deficient *M.tb* poorly survive inside macrophages. This suggests that PPE2 is important for intracellular survival of *M.tb* in macrophages.

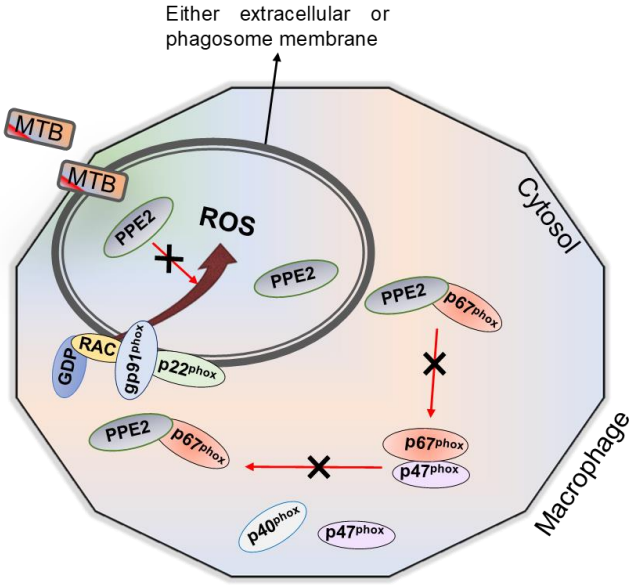

Figure showing the mechanism of ROS inhibition by PPE2 during *M. tuberculosis* (MTB) infection

In macrophages, assembly of NADPH oxidase complex is required for ROS generation. In *M. tuberculosis*-infected macrophages, PPE2 is secreted out and interacts with cytosolic subunit

$p67^{phox}$ preventing the translocation of $p47^{phox}$ and $p67^{phox}$ at the membrane to form a complex with gp 91^{phox}. Thus, NADPH oxidase activity is reduced causing poorer ROS generation.

The study suggested that PPE2 may be an important target for the development of novel drugs against M. tb. PPE2 inhibits the production of ROS in a very coordinated manner to diminish oxidative stress. Further studies on PPE2 will expand our understanding of host and mycobacterial interactions and the role of oxidative stress in TB pathogenesis which may help in the development of new drugs to control tuberculosis.

The M. tb is one of the most successful pathogens of humans and causes tuberculosis (TB) disease. M. tb has evolved several adaptive skills and evasion mechanisms to hijack the immunologically educated host to suit its intracellular lifestyle inside macrophages. Macrophages phagocytosize mycobacteria and gets trapped inside the phagosome. Phagosome gets associated with lysosome. During this process, there are production of reactive oxygen species (ROS) creating an oxidative stress which mount an effective host-defense mechanism to kill mycobacteria. However, M. tb has evolved strategies to avoid oxidative stress caused by “ROS”.

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