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**Supplementary Figure 1: (a) Schematic representation for the construction of *dkppx* mutant strain of *M. tuberculosis*.** The *dkppx* strain of *M. tuberculosis* was constructed using temperature sensitive mycobacteriophages.In *ppx1* strain, the open reading frame for *ppx1* has been replaced by hygromycin resistance gene. The *dkppx* strain was constructed by replacing PPX2 open reading frame with kanamycin resistance gene in the genome of *ppx1* strain. **(b)** Disruption of *ppx1* and *ppx2* in their respective single and *dkppx* strain was confirmed by PCR using locus specific primers. **(c)** For Southern blot analysis, genomic DNA of parental and *dkppx*strainsof*M. tuberculosis*was digested with either *BamH I*for *ppx1* locus or *Pvu* II for *ppx2* locus. The digested DNA was separated on a 1.2% agarose gel, transferred to a nylon membrane and probed with locus specific probes. The *ppx1* locus specific probe hybridized to a band of 3.2 kb in the case of parental strain and 3.9 kb in the case of *dkppx* strain. The *ppx2* specific locus probe hybridized with 2.2 kb and 4.1 kb in the case of parental and *dkppx* strain, respectively.

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**Supplementary Figure 2: (a) Effects of deletion of *ppx* genes on the transcription of *ppk1* and *ppk2* in *M. tuberculosis.***qPCR of *ppx1, ppx2*, *ppk1* and *ppk2* was performed using mRNA isolated from mid-log phase cultures of wild type, *ppx2* and *dkppx* strains of *M. tuberculosis.* Data shown is mean + S.E. of fold change in mutant strains relative to the wild type strain obtained from two independent experiments. **(b) Effect of deletion of *ppx* genes on colony morphology of *M. tuberculosis*.** Colony morphology of parental and *dkppx* strains of *M. tuberculosis* was determined by plating 10.0 fold serial dilutions on MB7H11 plates and incubation of plates at 37oC for 3-4 weeks. Scale bar, 1.0 cm **(c) Susceptibility of various strains to different stress conditions:** Early-log phase cultures were exposed to either oxidative stress (5 mM H2O2, 1 day); nitrosative stress (5 mM NaNO2, 3 days); acidic medium (pH-5.2, 7 days). For bacterial enumeration, 10.0-fold serial dilutions were prepared and 100 l was plated on MB7H11 plates for 3-4 weeks at 37oC. **(d)** Early-log phase cultures were exposed to either 0.25% SDS for 3 days; 2.5 mg/ml lysozyme for 3 days; 500 M CuSO4 for 7 days. At designated time points bacterial enumeration was performed as described above and data shown in this panel is mean + S.E. obtained from three independent experiments.



**Supplementary Figure 3: (a and b) Susceptibility of parental, mutant and complemented strains upon exposure to nutritional or low oxygen growth conditions.** **(a)** Early-log phase cultures of various strains was harvested, washed and resuspended in 1x TBST for 14 days. **(b)** Early-log phase cultures of parental, *ppx1* and *ppx2* strains were exposed to low oxygen as previously described. At designated time, points 10.0 fold serial dilutions were prepared and 100 µl was plated on MB7H11 plates. The data depicted in this panel is mean ± S.E. of log10cfu obtained from two independent experiments. **(c) Influence of the deletion of *ppx1* and *ppx2* genes on the survival of *M. tuberculosis* in macrophages.** THP-1 macrophages were infected with either parental or *ppx1* or *ppx2* strains at an MOI of 1:1. At designated time points, triplicate wells of infected macrophages were lysed in 1x PBS with 0.1% Triton-X-100. The bacterial counts were determined and data shown in this panel is mean + S.E. obtained from two independent experiments. **(d)** **Susceptibility of various strains upon exposure to isoniazid.** For *in vitro* drug-tolerance experiments, mid-log phase cultures of various strains were exposed to either 10 g/ml levofloxacin or 10 g/ml isoniazid. After 14 days of exposure, 10.0-fold serial dilutions were prepared and 100 l was plated on MB7H11 plates at 37oC for 3-4 weeks. Percent survival was measured as number of CFU/ml in the culture after incubation with the drug relative to the CFUs of the culture before the addition of drug. Data shown in this panel is mean + S.E. obtained from at least two independent experiments performed in triplicates. Significant differences were observed for the indicated groups (paired, two-tailed, t-test \*p<0.05).

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**Supplementary Figure 4: The effect of PolyP on autophosphorylation of *M. tuberculosis* sensor kinases.** Various sensor kinases (PdtS, KdpD, MtrB and PrrB) were purified and autophosphorylated with32PATP in presence of 1.0 mM PolyP. The reactions were resolved by SDS PAGE and visualized by either autoradiography or CBB staining. The data shown is representation of two independent experiments.

**Supplementary Table 2:** List of oligonucleotides used in the study

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|  | Forward Primer (5’ – 3’) | Reverse Primer (5’-3’) |
| *Rv0496* Upstream | gggaggcctagggtggtcttgaggatttcgg | gggtctagacgggtggccgccgcggtgggcatcg |
| *Rv0496* Downstream | gggaagcttaaccgatcgagaggcagcaaacc | gggactagtccactatgctgttccagcgccac |
| *Rv1026* Upstream | gggaggccttgcgccgccagatcgctgacctgg | gggtctagagtcgatcgcggcgacccgggttagc |
| *Rv1026* Dnstream | gggaagcttgacggcatcgcgttgtcactggc | GGGACTAGTggcgtaacaccgcggccgccgag |
| *Rv0496* ORF | gggtctagagtggtcgatgcccaccgcggcgg | gggaagctttcatggtttgctgcctctcgatcgg |
| *Rv1026* ORF | gggtctagagtggcgctaacccgggtcgccgcg | gggaagcttttatccggccagtgacaacgcg |
| Primers used for qPCR analysis | | |
|  | Forward Primer (5’ – 3’) | Reverse Primer (5’-3’) |
| *sigA* | acgaagaccacgaagacctcgaa | gtaggcgcgaaccgagtcggcgg |
| *Rv1738* | ACTCGGGCGAAGGCACGGCTGCG | TCAATACAACAATCGCGCCGGC |
| *Rv2007c* | CGAGTGCGTGGATTGTGGTGCGTG | CCGGCGAACCCAGCGGAGCCACTC |
| *Rv2030c* | GGGACTTCCGGCAGGTCACCGAC | GCATCGCCGACCAGCTCCGCC |
| *Rv2031c* | CCGTCATTCGCCGGACTCCGGCCC | GCGAACGAAGGAACCGTACGCGA |
| *Rv3130c* | GGGCTCTCCGATGAAAGTATGAG | GGCGGGACTTAGCACGCCGGCCG |
| *Rv3134c* | GGGCAACCGGTCAAGATCGAAACGG | CGGCCGGCGACGGGTGAATCACCG |
| *dosR* | GGTCGATGACCACGAGGTGGTGCGT | TCGCATCTAGCATGGCCTCGTCAGA |
| *Rv0079* | GACACCCCATTAAGGGCGCAGG | CGGGGTTGCGCGCCTTAGCACG |
| *Rv0081* | GGAGCTGCTGGTCGAGCGGGAC | CGTGCCGCGACAACACCCGCC |
| *Rv2623* | GTTCCCACATTGGTCGACATGTC | CGCCAACTAGCACCGGCGCTTG |