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GTPases: prerequisite molecular target in virulence and survival of *Mycobacterium tuberculosis*

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Short summary of gtpases

Proteins binding to guanine nucleotide such as guanosine diphosphate (GDP) and guanosine triphosphate (GTP) are termed as GTP binding protein or G protein. G proteins are enormous in both eukaryotes and prokaryotes and are known to play vital role in various fundamental process of life as cell proliferation, signal transduction, protein translation, etc by regulating the activity of GTPase.[1] G proteins are hetrotrimeric structurally and are composed of three subunits Gα, Gβ and Gγ; with Gα carrying active site for binding of nucleotides. G-proteins coupled receptors (GPCRs) are group of seven transmembrane proteins that on binding to relevant ligand brings about conformational change in structure of G protein that assists binding of GTP/GDP with G proteins.[2] In eukaryotes GTPases are basically involved in various translational steps, while prokaryotic GTPase are eminent regulators of ribosomal functions and are distributed in daughter cell during cell division.[3]

GTPase constitutes of a protein super family having highly conserved molecular switches involved in several cell function. GTPase undergoes three conformational changes, GDP on binding with the α-subunit keep the protein in inactive form as it remain bound with other two β and γ subunits. On binding of GTP with α subunit, brings about conformational change in the protein structure by dissociating the α-subunit from β and γ subunits; thus in turn allowing the protein to bind with the target molecule or ligand. Further this GTP on action by GTPase gets hydrolyzed form GDP thus resulting in protein's inactivation.[4]

There are 13 universally conserved core GTPases known in bacteria till date. According to the reports it has been stated that these core GTPases are either involved in ribosomal function or signal transmission.[5] These core GTPases protein are elongation factor G(Ef-G), elongation factor Tu(Ef-Tu), initiation factor 2(If-2),YihA, LepA, Thd F/ Trm E, Ffh, FtsY, Obg, Era, EngA, Der and Ych F that are found in prokaryotes and are involved basically in ribosomal functions.[6] In many bacteria several GTPases among these are very important for cell viability itself. In *M. Tuberculosis* Ef-Tu, LepA, Ffh, FtsY, Obg, Era and EngA are few GTPase protein found that play significant role in its virulence and also aids in the survival of bacterium under stress condition.[7,8] *M. Tuberculosis* Ef-Tu (*Mtb* Ef-Tu) has not yet been characterized although it has been found to remain associated with the cell wall[7] and induce under anaerobic condition with high iron containing media.[7,9] Also it has been reported to bind with human plasminogen.[7,10] Phosphorylation mediated *Mtb* Ef-Tu play cogent role in dormancy of *M. tuberculosis* by down-regulating the binding with GTP thus, adversely affecting protein synthesis.[7]

LepA gene codes for highly conserved protein in bacteria and acts as an essential elongation factor.[1] This protein has been reported to play crucial role in survival of *Helicobacter pyroli* in acidic condition by signalling the environmental change outside the bacterium.[8] In *Mycobacterium avium (M. Avium)* mutated gene MAV_1778 which functions as LepA GTP binding protein have shown enhanced growth rate in neutral to acidic pH[11] which depicts the idea that presence of LepA in *M. Tuberculosis* may also enable its survival inside host even in adverse condition.

Ffh is homolog of 54kDa eukaryotic protein that binds to single sequence of pre-protein (SRP) which aids in recognition of single sequence of polypeptide emerging from ribosome.[12] Ffh protein can be categorized into three domains; M domain which is methionine rich, interacts with single peptide; G domain involving in GTPase activity that aids in docking action and subsequently releases peptide at translocon; finally the highly conserved N domain plays important role in control of the GTP occupancy of G domain.[13] FtsY in bacteria is homolog of Ffh gene having similar G and N domain region[13] and have complimentary role in membrane bound signal recognition.

Obg is monomeric G protein found in case of both eukaryotic as well as prokaryotic organism. Gene encoding Obg was firstly identified in *Bacillus subtilis* and was reported to implement sporulation, mycelium development, stress response and chromosome partitioning and its orthologues has been reported in case of *Streptomyces griseus*, *Streptomyces coelicolor*, *Caulobacter crescentus*, *Echerichia coli* and *Vibrio harveyi*.[8,14] In case of *M. tuberculosis* gene Rv2240c encodes for Obg protein which has elevated expression and resulted in 5 fold more division in log as well as in stationary phase thus being hypothesised it significant role in bacterial membrane assembly. Also, Obg has been found associated with ribosomal subunit (30S, 50S) and simultaneously binds with stress protein UsfX.[14] Era protein derives its name from *E. Coli* is a G protein which is also found in *Salmonella typhimurium* and *Streptococcus mutans* and acts as an important growth factor in these organisms.[8,15] In *M. tuberculosis* replacement of position in alanine residue has shown loss in GTPase activity thus indicating its importance in bacteria.[8] Eng A consists of two GTP binding domain and was firstly discovered in *Neisseria gonorrhoeae (N. Gonorrhoeae)* and in study of *S. Typhimurium* this protein was found to interact with the smaller ribosomal subunit 30S in S7 and S9 which focus the concept of its involvement in ribosomal assembly. In *M. Tuberculosis* Eng A protein has shown intrinsic GTP binding and hydrolysing property by its molecular characterization is yet to be done to reveal its exact role.[16]

In conclusion, we would like to summarize that Guanine nucleotide are active signalling molecules targeting GTP by hydrolyzing it and regulates intracellular level of GDP and GTP in many prokaryotes. Several core GTPases are highly conserved in infectious bacterium like *M. Tuberculosis,* thus could be characterized on molecular level, which in turn would aid in understanding the key mechanism of mode of action in causing infection and survival of organism inside host in stressed condition. Further more detailed study may be required to understand the physiological functions of GTPases family proteins to develop anti-TB drugs.

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Conflict of interest

Author declares that there is no conflict of interest.

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