In this issue

Tuberculosis

Tuberculosis (TB) is a global health concern. In India, the number of people infected with TB is large, and is an important public health issue. Articles in this special section have contributions from a mix of researchers and clinicians, reflecting the advances made in this field, current challenges and way forward to handle this global health burden.

Kashyap *et al.* (**page 597**) briefly discuss problem and challenges associated with control of TB in India. They report that despite various efforts from health-policy makers in controlling TB, India still accounts for majority of overall TB cases and higher mortality rates. They highlight certain major issues explaining the high burden of TB in India, which includes unavailability of rapid diagnostic tools, low efficacy of BCG, emergence of drug resistance along with prevalence of other factors like latent TB, poverty, unhygienic living conditions and co-infection with HIV. They discuss problems associated with the above factors with special focus on issues related to TB diagnosis and TB vaccine development. They discuss the need for new and rapid strategies for early diagnosis against different TB forms and also the need of properly monitored treatment which are essential for any TB control programme to be executed. They also state need for revision in existing TB vaccination policies towards improving efficacy of BCG and reducing the burden of TB in India.

M. tuberculosis, the etiological agent of the highly infectious bacterial disease TB, owes its success as a pathogen in no small measure to its ability to survive for prolonged periods, sometimes even decades, in a state of 'dormancy'. It is estimated that approximately one-third of the world's population harbours a latent TB infection. Therefore a key challenge in combating TB is to fight latency and eradicate the huge reservoir of TB bacilli harboured by latently infected individuals. Towards this, it is important to understand the physiologic and metabolic states of 'dormant' bacilli residing within the host. The TB bacillus is likely exposed to multifarious stresses within the granuloma including hypoxia, nutrient limitation, oxidative and nitrosative stresses, iron starvation and exposure to other gaseous stresses such as nitric oxide and carbon monoxide. Several *in vitro* 'dormancy' models that mimic one or more of these stresses have been exploited to decipher the bacterial adaptive responses that are crucial for their intracellular survival. *In vitro* models have their own limitations and therefore cell infection 'dormancy' models have been developed, of which the ascorbic acid-based model was the first cell-infection based 'dormancy' model to be described. Other models include THP-1 cells infected with hypoxic 'dormant' bacteria and an *in vitro* human granuloma model. Various models that have contributed to our understanding of the mechanisms underlying *M. tuberculosis* 'dormancy' are briefly described by Sikri and Tyagi (**page 607**).

With the rising incidence of drug resistance associated with TB, and the drawbacks of the currently available drugs, it is acknowledged that alternate strategies for therapeutic intervention are needed. A possible alternate approach could be to manipulate the host immune response, which requires understanding of the interplay between the pathogen and its host. Kundu and Basu (**page 617**) highlight some of the advances made in our understanding of this interplay and its role in the outcome of infection. The checkpoints of the macrophage include oxidative and nitrosative stress and killing of the bacterium in phagolysosomes. Bacterial virulence factors overcome these checkpoints. The bacterium also exploits host metabolism to establish a persister population, using host-derived lipids as a source of nutrients and as precursors for cell-wall lipids. The role of arachidonic acid metabolites in TB and the recent finding that SNPs in the leukotriene A4 hydrolase gene are associated with protection against TB are highlighted. The interplay between pattern recognition receptors and mycobacterial ligands in the innate immune response is discussed in some detail, while at the same time, bringing into focus our knowledge of the role of mycobacterial ligands which dampen the innate immune response. Finally, the potential to modulate autophagy as a means of improving the efficacy of vaccines and the potential of microRNA-linked therapeutics in modulating the immune response are discussed.

Singh and Rao (**page 626**) discuss the importance of foamy macrophages (FM) in the infection biology of *Mycobacterium tuberculosis*. Work done in authors' laboratory identifies the *M. tuberculosis* secretory protein, ESAT-6 as a critical mediator of FM differentiation, thus adding a new role by which this protein contributes towards the expression of mycobacterial virulence. The authors show that macrophages infected by virulent strains of *M. tuberculosis* secrete a ligand for the anti-lipolytic G-protein coupled receptor, GPR109A which causes feedback activation of this receptor. The receptor activation leads to reduction in triacylglycerol lipolysis and causes a buildup of lipid bodies (LB) within the *M. tuberculosis*-infected macrophage which impart the foamy phenotype to the infected macrophage. They also show that targeting such key host factors provides a viable and potentially useful approach for the chemotherapy of TB. This strategy was equally effective against diverse *M. tuberculosis* genotypes

and was also insensitive to the drug-sensitivity profile of the infecting strain. The results give hope that the problem of drug-resistance in TB might be addressed in the near future.

Transcription is the first step leading to the expression of genes. Gene expression is regulated precisely in temporal manner to ensure that appropriate levels of the gene products are present in the cells to carry out specific functions. Hence all organisms have evolved elaborate strategies to regulate gene expression at various stages of transcription. Much of these strategies are invested on controlling transcription initiation, the first step of gene expression. While there is large body of literature on transcriptional regulation in *Escherchia coli* and a number of diverse organisms over the last several decades, the studies with mycobacteria are more recent. Understanding the transcription process and its regulation in these groups of organisms is important to appreciate their distinct life style, survival mechanisms and also to develop newer strategies to combat the disease. Tare and Nagaraja (**page 632**) have reviewed the recent advancements in transcription initiation in mycobacteria. The article highlights the distinctive features of the process in mycobacteria while comparing with other well-studied systems. It appears that some of the features may have been tailored by these organisms to suit their life style.

Organisms have the ability to sense and respond to the environmental fluctuations to regulate their survival and small nucleotides play important roles in this direction. Other than the major role that nucleotides perform to synthesize nucleic acids, it is increasingly being felt that they act as signalling molecules, which are connected with the bacterial persistence and pathogenesis. Second messengers in prokaryotic cells are generally of three types, cAMP, ppGpp known since 50 years and c-diGMP which has completed 25 years since its discovery. It is interesting to note that guanosine derivatives exhibit a pelthora of functions in biology and a structure–function relationship of this important nucleotide is in order. Regulation of c-diGMP synthesis is maintained by two enzymes appear in tandem under the same promoter in Gram-positive bacteria. However, in Gram-negatives the synthesis and degradation of the nucleotide take place in two different genes and there are multiple copies of the genes in addition. Bharati and Chatterji (**page 643**) make an attempt to discuss several function of c-diGMP, particularly its connection with bacterial persistence, pathogenesis and bio-film formation. An extra effort has also been put to find out the roles of other nucleotides in pathogenecity in bacteria and similarity between ppGpp and c-diGMP, two second messengers.

Narendran and Swaminathan (**page 657**) discuss the recent advances and changing concepts in the management of Tuberculosis Immune Reconstitution Inflammatory Syndrome (TB-IRIS) among HIV-TB co-infected patients, also known as paradoxical reaction, in the past. They provide a succinct description of the evolution and progression of a cytokine storm that culminates in inflammatory manifestations referred to as IRIS. It explains about who is vulnerable and what predisposes to IRIS among dually infected patients. The authors review the current state of knowledge on risk factors, pathogenesis, clinical features and management of TB-IRIS. They also alert the reader to rule out conditions that closely mimic this syndrome. This article assumes importance as the occurrence of TB-IRIS has increased subsequent to the recommendation to initiate ART during the early phase of TB treatment. The authors review both Indian and global experience on the causes for the occurrence of this syndrome, its management and ways to effectively reduce the associated morbidity.

Pathogens utilize a multitude of sophisticated mechanisms to overcome defence mechanisms of the host. Mycobacteria are very versatile in their ability to infect and remain dormant in the human host for many years and mechanisms by which this is achieved remain an intensive area of study. Mycobacteria synthesize high amounts of cAMP, a universal second messenger, and mycobacterial genomes harbour a number of genes coding for enzymes involved in cAMP metabolism. Zaveri and Visweswariah (**page 666**) present a review on recent advances in understanding the effects of cAMP on mycobacterial physiology and virulence, with a special focus on the proteins that are directly regulated by cAMP. They discuss structural and biochemical studies on these proteins which include canonical transcription factors and a cAMP-regulated protein lysine acetyltransferase. The CRP-like (catabolite repressor protein-like) transcription factors in mycobacteria regulate genes involved in metabolism. The cAMP-regulated protein lysine acetyltransferase is the first lysine acetyltransferase described in this organism and has been shown to function by an elegant allosteric switch-like mechanism. These cyclic nucleotide-binding proteins appear to have adapted to the high levels of cAMP in the mycobacterial cell, either by relaxing their dependence on cAMP for activity, or by reducing their affinity for cAMP. Thus, mycobacterial cAMP effectors diverge from their counterparts in other organisms. Given the multitude of proteins involved in cAMP signalling in mycobacteria, with many of them still uncharacterized, future research directions are also delineated by the authors in the article.