IGIB Swarnajayanti fellow to investigate how fats in cells can boost immune response to TB

Dr. Sheetal Gandotra, Scientist from CSIR- Institute of Genomics and Integrative Biology, Delhi, who has been awarded the Swarnajayanti Fellowship funded by the Department of Science and Technology will investigate the mechanism of how fats in cells can boost the immune response to Tuberculosis infection.

As one of the 14 scientists associated with projects containing innovative research ideas and potential of making an impact on R&D, she, with a background of working on host-pathogen interaction, will look at how proteins can localise lipid droplets thereby regulating the immune response of macrophages to infection.

Dr. Gandotra is interested in studying host-pathogen interaction with a focus on the cross-talk between the host and mycobacterial metabolism, especially lipid metabolism. Her major interests are Macrophage triglyceride metabolism induced by *M. tuberculosis,* which is crucial for the innate immune response in TB. She will be working on providing a link between the infection-induced pathology which leads to lipid droplet accumulation, and the role of lipid droplet localized proteins in enabling the pathogenic immune response.

Knowledge of mechanisms that regulate the immune response via association with lipid droplets will provide specific means to manipulate the immune response in favour of the host's ability to contain the infection and suppressing the damaging immune response elicited by the bacteria. Her approach is a step forward towards developing host-directed therapies against Tuberculosis.

Fats play an important role in human health, and how they are stored and mobilized in the human body governs facets of our well-being. Even for a major infectious disease such as Tuberculosis, this aspect of physiology now seems to be important. *Mycobacterium tuberculosis*, the bacterium that causes
Tuberculosis in humans has a large number of genes involved in lipid metabolism.

This is not surprising, given that the pathology in Tuberculosis involves local accumulation of neutral lipids within macrophages, the cells of the immune system that are meant to engulf and destroy bacteria.

This lipid is stored in the form of specialized structures within the cell called 'lipid droplets.' For a long time, it was assumed that these lipid droplets would serve as depots of carbon sources for the bacteria and therefore evolutionarily advantageous for the bacteria to induce these pathological changes.

Dr. Gandotra's lab has demonstrated that it is the ensuing damage of the host cells by the bacilli that leads to the differentiation of macrophages to lipid-rich macrophages. One of the findings

that emerged from her work was that depleting lipid stores of the host cell did not impact the survival of intracellular bacteria, while the amplitude of the inflammatory response against bacteria declined.

So the question arose, how lipid storage depots could regulate such a central feature of the macrophage. She started her work by asking whether other functional components of these storage depots are changed upon infection. This involved measuring the abundance of proteins that localize to the lipid droplet in an infection dependent manner. It led to the discovery of not only an exhaustive lipid droplet proteome, which is the composition of proteins present on the lipid droplet surface but also revealed changes that are actively induced by *Mycobacterium tuberculosis*. In her research, she found out that not all proteins that changed in abundance had functions associated with lipid metabolism. Functions as far-ranging as vesicular transport and protein synthesis seemed to be associated with lipid droplets of infected cells.

This study has opened up the potential reliance of these cellular functions on the presence of lipid droplets. Dr. Gandotra plans to study how localization of these proteins to the lipid droplet can regulate the immune response of macrophages to infection. Multiple locations of these proteins within the cell make answering this question challenging, and therefore robust assays to ascertain the function of the lipid droplet localized fraction of the proteins is the central theme of her plan. This fellowship will support her to take on this challenging task, which involves a combination of approaches and model systems.