During an infection, interplay between the host immune response and the virus (virulence factors, capacity to evade the host immune response) plays an essential role in influencing the disease outcome. Innate immune response represents the first line of defence, and it is triggered at the first instance of pathogen exposure by peripheral antigen presenting cells [APCs; macrophages and Dendritic cells (DCs)] and innate lymphocytes - CD56⁺ natural killer/natural killer T (NK/NKT) cells. On viral infection, these cells undergo maturation and activate a cascade of anti-viral immune responses as well as act as the scaffold for establishment of adaptive response.

Japanese encephalitis virus (JEV) is a mosquito-borne, single-stranded RNA (~11kb, monopartite, linear) virus belonging to family Flaviviridae and genus Flavivirus. Japanese encephalitis is a major seasonal health problem in many parts of rural India and other parts of Asia and Pacific with 30,000-50,000 cases reported annually. An important feature of human JEV infection, in endemic regions, is that, a large number of JEV-infected individuals do not develop encephalitis, but manifest subclinical infection and develop a beneficial adaptive immune response. The question as to how innate immune system handles and restricts the virus has been a major question.

The aim of this study was to determine (i) the interaction between JEV strains and peripheral APCs (i.e. APCs functional activation), and (ii) differential ability of different JEV strains (pathogenic wild-type and attenuated vaccine strain) to induce and/or respond to innate anti-viral response. Two in-vitro models of innate response i.e., (i) JEV-macrophage interaction with type-I interferon (IFN) and
nitric-oxide as anti-viral mechanism, (ii) JEV-DCs interaction with NK/NKT (CD56+) cells as anti-viral mechanism was studied using cells obtained from human peripheral blood mononuclear cells (PBMCs). It was hypothesized that pathogenic (i.e. wild-type / clinical isolate) JEV strain might hamper innate immune response activation or might be less-sensitive to innate anti-viral response as compared to the vaccine JEV strain.

Major findings of the studies are as follows

1) Both JEV strain replicated in MDMs (monocyte derived macrophage) and MDDCs (monocyte derived DCs). JEV growth in MDMs was influenced by viral virulence since vaccine-JEV strain showed decreased replication potential than wild-type JEV strain. In MDDCs, JEV growth was dependent on the DC maturation status rather than viral virulence, since both wild-type and vaccine JEV strain did not show a differential replication potential in immature-MDDCs; while, mature-MDDCs did not supported either of JEV replication. Therefore, JE-viral strain and APC-maturation status influence productive JEV replication in APCs.

2) JEV infection induced phenotypical maturation, secretion of pro-inflammatory cytokines, type-I IFN, and chemokines from MDMs, and MDDCs. This ability was dependent on viral replication and host kinases (PI3K and p38).

3) IL2-activated NK/NKT cells imparted both immunomodulatory (via direct cell-to-cell contact, and TNFα) and anti-viral (via direct cell-to-cell contact) effect during JEV infection.

4) JEV strains showed varied ISGs inducing ability, and sensitivity to innate anti-viral response. Vaccine-JEV strain was more susceptible to innate anti-viral response (type-I IFN, nitric-oxide, and NK/NKT cytotoxicity) even at subordinate concentration levels than the wild-type JEV strain. Vaccine-JEV strain also induced comparatively efficient Mx-protein and total-STAT1 levels in MDMs than the wild-type JEV.

5) Ability of wild-type JEV to circumvent innate anti-viral response is not absolute – a higher dose of type-I IFN / nitric-oxide or cell concentration of NK/NKT cells brought about decrease in wild-type virus load. In addition, the wild-type JEV strain neither inhibited phosphorylation of STAT1 nor induced degradation of total STAT1 during IFNα mediated anti-viral mechanism; nor inhibited NK/NKT degranulation ability.
Therefore, these observations suggest that JEV infection results in overall activation of the peripheral innate immune response; however, the virulence of JEV might be related with replication fitness and a decreased susceptibility to innate anti-viral effects. This reduction in infectious virion production and increased sensitivity towards innate anti-viral mechanism of vaccine JEV strain could play a potential role in limiting viral spread into additional target tissues and thus aid in mounting up of beneficial immune response.