Innate immunity is the frontline for the host to defend against infections. This process entails the cooperation among pathogen recognition receptors, adaptor proteins, kinases, and transcription factors that elicit the production of effector cytokines. As an important transcription factor, IRF5 was known to be essential for the host cytokine production in response to various ligands and SNPs in IRF5 have been closely related to autoimmune diseases. However, the mechanism by which IRF5 is activated is not well understood. In the first part of this dissertation, I presented evidence that the kinase IKK2 phosphorylates IRF5 on Serine 445, leading to its dimerization and nuclear translocation.

cGAMP is the first cyclic di-nucleotide discovered in metazoan. It is produced by the cytosolic DNA sensor cGAS in response to pathogen or self DNA as a second messenger to activate STING. cGAMP has been proven to be very important in anti-viral response and anti-tumor process. In the second part of the dissertation, I used next-generation sequencing techniques and presented that STING is the predominant receptor for cGAMP and innate immune response.

As the essential and general DNA sensor, cGAS was purified and identified from cellular cytosols. Upon DNA binding, cGAS utilize ATP and GTP to synthesize cGAMP. However, the regulation of cGAS activity in cells are still poorly understood. Here I presented that certain RNA species that is interferon inducible could inhibit cGAS catalytic activity in vitro and probably regulate cGAS mediated immune response in cells. Besides, I have discovered that during cell cycle, cGAS is recruited and co-localize with chromosome and in actively dividing cells, cGAS remains in the nucleus. I further presented evidence that certain protein(s) in the nucleus can inhibit cGAS activity thus prevent cGAS from being activated by host DNA in the nucleus.

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