Abstract

Nucleotide binding domain, leucine rich repeat containing proteins (NLRs) were discovered by the genomic mining of evolutionary conserved structurally similar protein families in both plants and animals. NLRs are a family of pattern recognition receptors involved in major innate immune defense mechanisms. NLRs play key roles in several cancers, autoimmune and inflammation associated diseases. There are 22 different NLRs in humans. These are conserved in structure in organisms as diverse from sea urchins to humans. The primary function of NLRs is to recognize heterogeneous self and non-self-patterns shared by pathogens, endogenous molecules and irritants. These conserved structures are referred to as damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) respectively. NLRs have a tripartite structure with central NACHT domain, N-terminal effector domain and c-terminal leucine rich repeats (LRRs). Each NLR can function either independently or by forming a multiprotein complex with adaptor protein, Apoptosis-associated speck-like protein containing a C- terminal caspase recruitment domain (ASC) and pro-caspase-1 called as inflammasome. Gain-of-function mutation in one of the inflammasome forming NLR i.e. NLRP3 causes autoinflammatory diseases such as neonatal onset multisystem inflammatory disease (NOMID), Muckle-Wells syndrome and familial cold autoinflammatory syndrome. The association of NLR with autoinflammatory diseases further confirms the role of NLRs in inflammation and immunity.

The study focuses on the role of NLRs associated inflammation in two different scenarios. Firstly, to identify the role of adapter protein, ASC in nanosilica mediated cell cytotoxicity and inflammation in various human cell populations. Secondly, we identified the differential expression of various NLRs and associated proteins in human glioma tissues. Our study also quantified the levels of inflammatory cytokines, angiogenesis and proliferation associated markers involved in glioma pathogenesis.

Nanosilica particles are being widely used in different industries such as cosmetics, food, agriculture and biomedical purposes such as drug delivery, dental fillers and implants4. They have large surface to volume ratio and higher reactivity as compared to corresponding bulk form. The disorders related to crystalline nanosilica such as silicosis has been identified and extensively studied. However, amorphous nanosilica owing to its stability and bio-inert nature considered not to be harmful. In the present study we are utilizing two amorphous silica nanoparticles with two different sizes i.e. 12nm and 22nm, to study their effect on cell cytotoxicity in different cell population. In this study, I have also investigated the role of intracellular adaptor protein, ASC in the presence of amorphous silica nanoparticles on human cell population. I have also evaluated the size dependent differences in cytotoxicity, spatial localization of ASC and cellular uptake of silica nanoparticles in endothelial cells.

Role of NLRs have been well established in various neurodegenerative diseases such Alzheimer's disease, Parkinson's disease as well as in traumatic brain injury but their role in glioma is yet to be identified. Grade IV glioma or glioblastomas are the most aggressive primary brain tumor with a median survival of 15 months from the time of diagnosis. The standard treatment strategy mainly consists of surgical resection followed by radio- and chemotherapy. Inflammation intensely regulates the severity of glioma at different stages. Our study evaluated the heterogeneous expression levels of NLRs and associated proteins in cell specific manner such as in astrocytes and microglia. Role of NLRP12 protein was identified in the glioma proliferation and invasion. Multiplex bead based assay was utilized to identify protein levels cytokines, growth factors and angiogenesis factors associated with glioma.

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