# 1

# Introduction

Innate immunity is the first line of defense against infection and tissue injury. A typical innate immune response consists of an inducer, sensors, mediators, and effectors [Medzhitov, 2008]. Inducers are evolutionary conserved patterns against which the host has evolved receptors called Pattern-recognition receptors (PRRs) (Figure 1.1). These inducers are classified into Pathogen associated molecular patterns (PAMPs); Danger associated molecular patterns (DAMPs) and irritants. PRRs fall into four distinct genetic and functional clades: Toll-like receptors (TLRs), C- type lectin receptors (CLRs), retinoic acid-inducible gene (RIG) – I- like helicase (RLHs) and nucleotide-binding domain, leucine-rich repeat-containing proteins (NLRs)[Davis *et al.*, 2011]. Activation of PRRs is known to regulate an array of immune signaling pathways by the release of cytokines and chemokines as well as regulating adaptive immune responses.

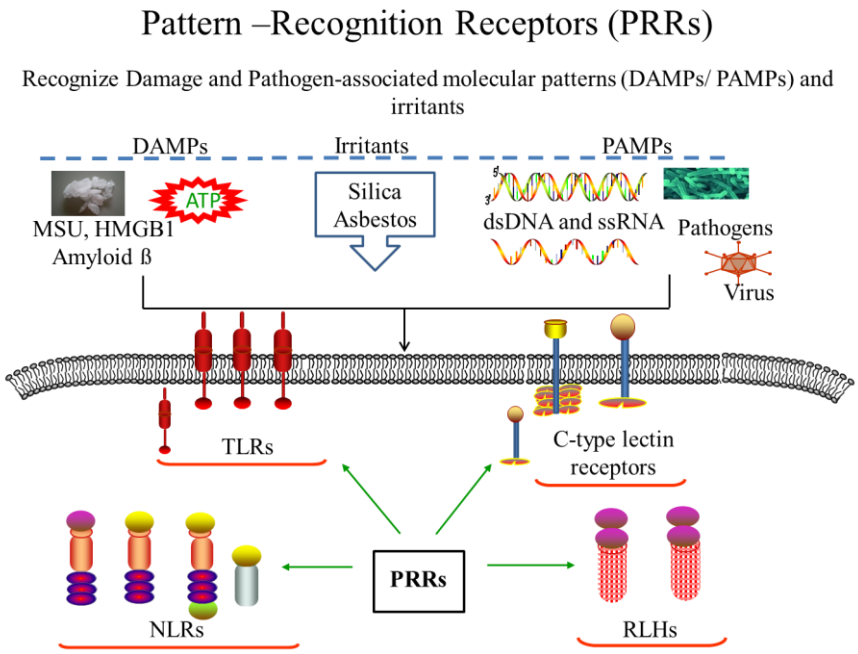


Figure 1.1 Activation of pattern recognition receptors (PRRs): The PRRs fall into at least four distinct genetic and functional clades: Toll-like receptors (TLRs), C- type lectin receptors (CLRs), retinoic acid-inducible gene – I- like helicase (RLHs) and nucleotide-binding domain, leucine-rich repeat-containing proteins (NLRs) which gets activated with an array of DAMPs such a monosodium urate crystals (MSU), amyloid β, PAMPs (such as DNA and RNA) and irritants

## 1.1 Purpose of this study

NLRs are important members of the PRR family that are evolutionarily conserved with structural similarities with plant disease resistance (*R)* genes [Ting and Davis, 2005]. There are about 22 members of NLRs found in humans, and they spread across eight chromosomes [Proell *et al.*, 2008]. *NLR* genes encode a tripartite structure with a conserved central nucleotide-binding domain, a variable number of C-terminus leucine-rich repeats (LRRs) and variable N-terminus domains [Jha and Ting, 2009; Singh and Jha, 2018; Ting and Davis, 2005]. NLRs elicit a host defense response by the activation of several signaling pathways including; inflammatory caspases, NF-κß pathway, mitogen-activated protein kinase (MAPK), and type-I interferon (IFN) pathways [Zhong *et al.*, 2013]. Mutations in some NLRs cause auto-inflammatory diseases reaffirming their essential role in inflammation. The role of NLRs have been well defined in various cancers, immunological and neurological disorders; however, their role in glioma pathology remain largely unknown [Davis *et al.*, 2011; Sharma and Jha, 2016]. This study aims to recognize the importance of NLRs and associated proteins in two different scenarios: 1) Inflammatory response to amorphous nano-silica particles 2) In cancer specifically glioma pathophysiology.

## 1.2 BRIEF RESULTS, SCOPE AND FUTURE PROSPECTS OF THE WORK

### 1.2.1 Chapter 3: Investigation of cellular and molecular pathways of innate immunity in response to amorphous nanosilica particles on different cell types

Silica nanoparticles have wide consumer and industrial applications ranging from medicine, cosmetic, food to cement industries [Salata, 2004; Singh *et al.*, 2015]. The current study identifies the cytotoxic effects of amorphous silica nanoparticles (12nm and 22nm) on different cell population. Differential activation and nuclear localization of adaptor protein, apoptosis-associated speck-like protein containing CARD domain (ASC) was also observed following silica nanoparticles exposure. The 12nm silica nanoparticles elicit a higher cytotoxic response as compared to 22nm silica nanoparticles in a cell-specific manner. The study infers amorphous nanosilica particles treated cells undergo size-dependent cell death pathways.

### 1.2.2 Chapter 4: Investigation of cellular and molecular pathways of innate immunity in the context of glioma pathophysiology

NLR associated with inflammatory response has been studied in the case of various cancers except in glioma pathology [Sharma and Jha, 2016; Zitvogel *et al.*, 2012]. In the current study, we identify the expression of various NLRs and associated proteins in human glioma tissues in a cell-specific manner. We also quantified multiple chemokines and cytokines responsible for angiogenesis, proliferation, and inflammation in human glioma tissues. Overall we recognize the potential of NLRs associated pathways as a potential therapeutic target to ultimately delay glioma progression.