Gene name: **NLRP3** **Previous HGNC Symbols for NLRP3 Gene:** C1orf7, CIAS1, DFNA34

External Ids for NLRP3 Gene: HGNC: 16400 NCBI Gene: 114548 Ensembl: ENSG00000162711 OMIM®: 606416 UniProtKB/Swiss-Prot: Q96P20

NCBI Gene Summary for NLRP3 Gene: This gene encodes a pyrin-like protein containing a pyrin domain, a nucleotide-binding site (NBS) domain, and a leucine-rich repeat (LRR) motif. This protein interacts with the apoptosis-associated speck-like protein PYCARD/ASC, which contains a caspase recruitment domain, and is a member of the NLRP3 inflammasome complex. This complex functions as an upstream activator of NF-kappaB signaling, and it plays a role in the regulation of inflammation, the immune response, and apoptosis.

GeneCards Summary for NLRP3 Gene: NLRP3 (NLR Family Pyrin Domain Containing 3) is a Protein Coding gene. Diseases associated with NLRP3 include Muckle-Wells Syndrome and Cinca Syndrome. Among its related pathways are SARS-CoV-2 Infection and Inflammasomes. Gene Ontology (GO) annotations related to this gene include *peptidoglycan binding*. An important paralog of this gene is NLRP12.
UniProtKB/Swiss-Prot Summary for NLRP3 Gene: Sensor component of the NLRP3 inflammasome, which mediates inflammasome activation in response to defects in membrane integrity, leading to secretion of inflammatory cytokines IL1B and IL18 and pyroptosis.

Cellular localization: golgi apparatus, cytosol, nucleus, mitochondrion, cytoskeleton

The **NLRP3** gene encodes the **NOD-like receptor pyrin domain-containing 3** protein, a crucial component of the innate immune system. NLRP3 is integral to the formation of the **NLRP3 inflammasome**, a multiprotein complex that detects pathogenic microorganisms and stress signals, subsequently activating inflammatory responses.

In sepsis—a severe systemic inflammatory response to infection—the NLRP3 inflammasome plays a dual role:

- **Inflammatory Activation:** Upon recognizing pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs), the NLRP3 inflammasome assembles and activates caspase-1. This activation leads to the maturation and secretion of pro-inflammatory cytokines, such as interleukin-1β (IL-1β) and interleukin-18 (IL-18), amplifying the inflammatory response.
- **Pyroptosis Induction:** Activation of the NLRP3 inflammasome can trigger pyroptosis, a form of programmed cell death associated with inflammation. While this process aids in controlling infections by eliminating infected cells, excessive pyroptosis can contribute to tissue damage and organ dysfunction in sepsis.

The NLRP3 inflammasome is involved in several key pathways during sepsis:

- **NF-κB Signaling:** Activation of pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs), leads to NF-κB-mediated transcription of NLRP3 and pro-inflammatory cytokines, priming the inflammasome for activation.

- **Caspase-1 Activation:** Upon assembly, the NLRP3 inflammasome activates caspase-1, which processes pro-IL-1β and pro-IL-18 into their active forms, facilitating their secretion and promoting inflammation.

Diagnostic and Prognostic Role:

- **Diagnostic Marker:** Elevated serum NLRP3 levels have been observed in sepsis patients, particularly those complicated with acute respiratory distress syndrome (ARDS). Studies suggest that serum NLRP3 concentration may serve as a useful diagnostic biomarker for sepsis patients with ARDS.
- **Prognostic Indicator:** Higher serum NLRP3 concentrations have been associated with increased severity of sepsis and poorer outcomes. Baseline serum NLRP3 levels have shown significant predictive value for 28-day mortality in sepsis patients complicated with ARDS.

Therapeutic Implications: **Inflammasome Inhibition:** Modulating NLRP3 activity could mitigate excessive inflammation in sepsis. Therapeutic strategies may include the use of IL-1β and IL-18 antagonists or inhibitors targeting downstream components of the NLRP3 inflammasome pathway.