Molecular Docking and Dynamics Simulation Studies of a Dataset of NLRP3 Inflammasome Inhibitors

Stefano Fiorucci

Departments of Medicine and Surgery University of Perugia, Perugia, Italy

In this issue of RAIAD, dos Santos Nascimento and colleagues [1], report on the structural characterization of a novel NLRP3 inhibitor paving the way for its development in NLRP3-mediated disorders. The NLRP3 (NOD-, LRR-and pyrin domain-containing protein 3) inflammasome is an intracellular sensor activated by a wide array of microbial motifs and endogenous danger signals. The NLRP3 inflammasome consists of a sensor (NLRP3), an adaptor module (ASC) and an effector module (caspase 1). NLRP3 is a tripartite protein that contains an amino-terminal pyrin domain (PYD), a central NACHT domain (domain present in NAIP, CIITA, HET-E and TIP1) and a carboxy-terminal leucine-rich repeat domain (LRR domain). Importantly, gain-of-function mutations of NLRP3 are the cause of an inherited autoinflammatory disease known as Cryopyrin-associated Periodic Syndrome (CAPS) [2].

The NACHT domain of NLRP3 consists of an ATPase activity, that is essential for NLRP3 self-assembly and function, whereas the LRR domain is thought to induce autoinhibition by folding back onto the NACHT domain. The ASC module has two protein interaction domains, an amino-terminal PYD and a Carboxy-terminal Caspase Recruitment Domain (CARD) which, in turn, recruits a full-length caspase 1 by interacting with the amino-terminal CARD domain of this caspase. Upon stimulation, NLRP3 oligomerizes through homotypic interactions between NACHT domains. The oligomerized NLRP3 recruits ASC through homotypic PYD-PYD interactions and nucleates helical ASC filament formation, which also occurs through PYD-PYD interactions. Assembled ASC recruits caspase 1 through CARD-CARD interactions and enabling proximity-induced caspase 1 self-cleavage and activation, leading to caspase 1-dependent release of two pro-inflammatory cytokines: IL-1β and IL-18, as well as to gasdermin D [3, 4]. This complex mechanism of auto-assembly has emerged as a potential therapeutic target in the treatment of NLRP3-related disorders [5, 6]. Indeed, while there is a wide array of NLRP3 activators ranging from PAMPs (cholesterol crystals, monosodium urate crystals, calcium pyrophosphate dihydrate and oxalate crystals, uric acid, cathelicidin, α-synuclein, amyloid-β, serum amyloid A, prion protein, biglycan, hyaluronan, islet amyloid polypeptide, lysophosphatidylcholine, ceramides, oxidized phospholipids and sphingosine, among others) and DAMPs of bacterial, viral and fungal origin, endogenous inhibitor of NLRP3 are relatively few and the list is restricted to prostaglandin E2, GPBAR1 a bile acids activated receptors and dopamine among the others [7, 8].

By docking analysis and molecular dynamics simulation, dos Santos Nascimento and colleagues [1], have provided structural information on the binding mode of NP3-146 a novel NLRP3 inhibitor, generated from the scaffold of MCC950, a now abandoned NLRP3 inhibitor [7], showing structural requirement for inhibition of the ATPase nucleotide-binding oligomerization. This study is therefore useful to support design and further development of NLRP3 inhibitors. In addition to CAPS, the Muckle-Wells syndrome and the neonatal-onset Multisystem Inflammatory Disease (NOMID) [2, 7], NLRP3 is involved in the development of a number of complex inflammatory and auto-immune disorders, ranging from crystalline arthropathies to pulmonary disorders. Acute gouty arthritis is induced by the deposition of monosodium urate crystals in articular and periarticular tissues. Similarly, the inflammatory joint disorder known as pseudogout is caused by deposition of calcium pyrophosphate dihydrate crystals. The presence of crystals in the joint cavity promotes an acute inflammatory response that is partially mediated by NLRP3 inflammasome activation and IL-1β secretion [7]. In addition to the crystalline arthropathies, several other disorders can be attenuated by NLRP3 inhibitors, including silicosis, asbestosis, type II diabetes, Familial Mediterranean Fever (FMF) and pyogenic arthritis, among others [9, 10]. Cholestasis is also thought to be associated to NLRP3 activation [8]. Therefore inhibition of NLRP3 by small molecules holds promise in the treatment of several disorders and is less invasive than cytokine blockade. The diaryl sulfonylurea derivative MCC950 is a potent and specific NLRP3 inhibitor that specifically inhibits its canonical and non-canonical NLRP3 and was shown effective in attenuating inflammation in preclinical models.
of inflammation, including experimental autoimmune encephalomyelitis, Alzheimer disease atherosclerosis [5] and colitis [11], but its clinical development in rheumatoid arthritis has been terminated because its intrinsic liver toxicity [5, 10]. Thus development of novel NLRP3 inhibitors remains an important therapeutic target for which also several natural compounds have been investigated [12, 13]. The study of dos Santos Nascimento [1] paves the way for rational design and further development in this therapeutic arena.

REFERENCES


DISCLAIMER: The above article has been published, as is, ahead-of-print, to provide early visibility but is not the final version. Major publication processes like copyediting, proofing, typesetting and further review are still to be done and may lead to changes in the final published version, if it is eventually published. All legal disclaimers that apply to the final published article also apply to this ahead-of-print version.