Targeting NLRP3 inflammasome: development of new covalent and non-covalent inhibitors of ATPase activity

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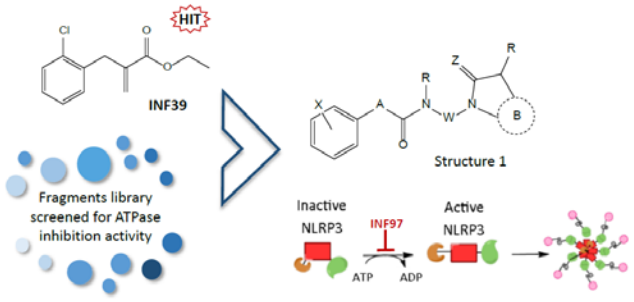
NLRP3 inflammasome is a multiprotein complex playing a key role in the intracellular activation of the innate immune system through activating cleavage of pro-inflammatory interleukins (IL)-1β, IL-18 and triggering of pyroptotic cell death[1]. In the last decades, several studies have highlighted the pivotal role of inflammasomes in the molecular control of inflammatory processes and the pathological role of NLRP3 inflammasome has been well established in different pathological settings.

Aims

The discovery of agents able to prevent inflammasome activation is a promising therapeutic strategy to decrease chronic inflammation and associated damage.

Methods

NLRP3 and few others inflammasome possess ATP-binding potential and intrinsic ATPase activity. Mutations in ATP-binding regions abolished their ATP-binding and ATPase activities and thereby resulted in impaired IL-1β maturation. From a screening of different molecular fragments on recombinant human (rh)NLRP3 protein, a benzo[d]imidazol-1-one sub-moiety was identified as a weak inhibitor of ATPase activity. The fragment was functionalized using other structural motifs present in derivative INF39, previously identified as able to bind to NLRP3 and to hamper ATPase activity[2]. Modulation of selected molecular moieties (Structure 1: A; B; X; W; Z; R1, R2) was performed using classical medicinal chemistry techniques such as bioisosteric replacement and refining of conformational flexibility.



Results / Conclusions

Newly synthesized compounds showed 5-10-fold improved NLRP3 ATPase inhibition with respect to starting fragments. INF97 elicits an interesting concentration-dependent ATPase inhibition (IC_{50}: 17.2 μM, 15.4 – 19.2 C.L. 95%) and inhibits LPS/ATP triggered pyroptosis. Using a fragment-based approach, new NLRP3 ATPase inhibitors were obtained, and a new non-covalent hit compound (INF97) has been identified and characterized.

References:

1. Groslambert M, Py BF, Spotlight on the NLRP3 inflammasome pathway, *Inflamm Res* (2018) 11:359-374
2. Cocco M et al., Development of an acrylate derivative targeting the NLRP3 inflammasome for the treatment of inflammatory bowel disease, *J Med Chem* (2017) 60:3656-3671