Design and synthesis of INF195, a new NLRP3 Inflammasome Inhibitor with ex vivo cardioprotective effect

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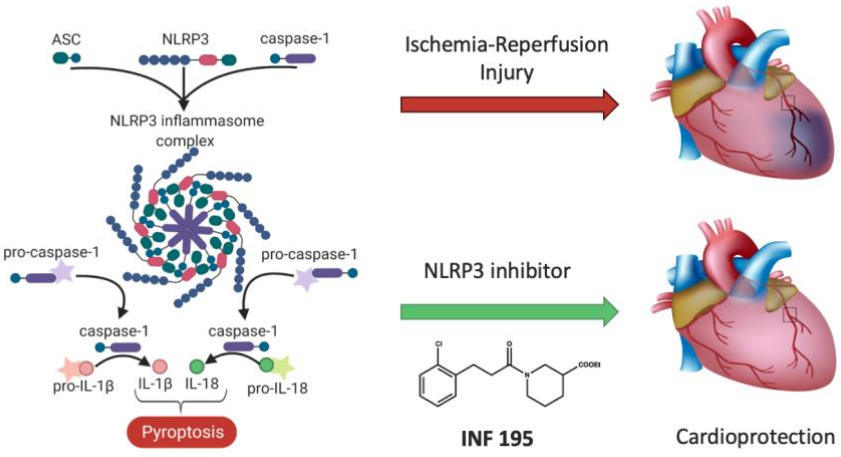
The NLRP3 inflammasome, a cytosolic multi protein complex involved in inflammatory processes, is emerging in the myocardial ischemia-reperfusion injury (IRI) framework, being engaged in both cell survival and damage [1-3].

In the search for novel NLRP3 inhibitors, we designed a series of compounds with the help of molecular docking techniques. The activity of the compounds was evaluated *in vitro* in human macrophages. One compound, INF195, was selected to investigate the cardioprotective properties [4]. We measured infarct size (IS) in isolated mouse hearts exposed to 30-minute global ischemia and then one-hour reperfusion, either in the absence or presence of different doses of INF195 (5, 10 or 20 µM). We also evaluated the production of the markers of NLRP3 activation, caspase-1 and IL-1β, measuring their concentrations in cardiac tissue homogenates. The results infer that heart pre-treatment with low doses of INF195, 5 and 10 µM, considerably reduce IS and IL-1β production, suggesting therefore that the activation of NLRP3 expressed in myocardial cells plays a role in IRI. Moreover, INF195 at low doses significantly reduced the infarcted area (the infusion at 5µM reduced IS from 64.8±1.9% to 38.1±1.3%). Overall, INF195 showed a promising cardioprotective effect worth of further studies.



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