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Grant Title: NMR as tool to unveil molecular basis of NOD proteins-peptidoglycan interaction

Abstract:

This has been a multidisciplinary project aimed to establish the molecular basis of the interaction of NOD proteins and peptidoglycan fragments.

The innate immunity represents the first line of defense against attempted microbial invasions in mammals, plants and insects. All of them have acquired the ability to recognize, as non-self, invariant pathogen-associated molecular patterns (PAMPs), characteristic of microbial organisms and essential for their survival, but completely absent in the host. Several microbial glycans constitute important signatures for host immune activation. On the other hand, host receptor proteins serve as biochemical sensors implicated in the recognition of these PAMPs and in the regulation of immune and inflammatory responses against pathogens.

A large number of cytosolic proteins containing leucine-rich repeats, referred to as NOD-LRR proteins have been shown to play important roles in immune system as sensors of bacterial components. In detail, Nod1 and Nod2 are implicated in the signaling events triggered by host recognition of specific motifs in bacterial peptidoglycan and, upon activation, induce the production of proinflammatory mediators. Interaction between NOD proteins and their ligands has not been elucidated. The initial aim was to dissect the interaction of these proteins with muropeptide fragments by NMR spectroscopy. The muropeptides fragment have been ad hoc produced by organic synthesis producing in this way a plethora of differently functionalized muropeptides. The expression of the NOD proteins in vitro failed in several systems and is currently under achievement by other approaches.

So we have turned the project to looking at molecular modeling and docking of synthesized muropeptides in NOD proteins. In particular, we have focused on a 3D model of the NOD1 and NOD2 proteins by means of homology model techniques and have proposed a theoretical binding model of the different PGN fragments to the NOD1 and NOD2 proteins. In our docking studies, we have found differences in energy binding values for NOD1 ligand ie-Dap and its negative control ie-lys. However, in the case of NOD2, we did not find such differences between MDP positive and MDP negative control. These results point that MDP binding region either could not be located in LRR NOD2 domain or that it could require the participation of another domain like HD2.