

P011 Structure-function analysis of caspase-1/CARD mediated NF- κ B activation

Kristof Kersse, Mohamed Lamkanfi, Tom Vanden Berghe and Peter Vandenabeele

Department of Molecular Biomedical Research, VIB, Ghent University, Technologiepark 927, B-9052 Zwijnaarde, Belgium.

Caspase-1 contributes through two independent pathways to an inflammatory response. On the one hand it mediates the maturation of pro-interleukin (IL)-1 β and pro-IL-18 through its proteolytic activity, while on the other the N-terminal caspase recruitment domain (CARD) is able to mediate NF- κ B activation. The latter is dependent on a homotypic interaction with the serine/threonine kinase Rip2. COP/Pseudo-ICE, INCA and ICEBERG are three CARD-only proteins that share a high degree of identity with the prodomain of caspase-1. All three proteins bind with caspase-1 and prevent the maturation of pro-IL-1 β and pro-IL-18. However, in contrast to INCA and ICEBERG, only COP interacts with Rip2 and gives rise to NF- κ B activation. Hence, we can divide these homologous CARD-proteins in two groups, the NF- κ B activators (caspase-1 CARD and COP) and the non-activators (INCA and ICEBERG). Potentially critical amino acids on the surface of caspase-1 CARD for interaction with Rip2 and subsequent NF- κ B activation were selected by comparing the sequences and the three-dimensional models of these two groups. Point mutation analysis of these differential amino acids in caspase-1 CARD resulted in the identification of two amino acids that are absolutely crucial for NF- κ B activation. Furthermore, reverting these mutations in INCA restores INCA-mediated NF- κ B activation.