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Searching drugs for NF-κB pathway regulation: BIR1 domains of IAPs as promising new targets

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Inhibitor of apoptosis proteins are target of extensive research in the field of cancer therapy since they control apoptosis and cell survival. The most studied IAPs, namely XIAP, cIAP1 and cIAP2, were investigated for their ability to bind and inhibit caspases, thus blocking apoptosis. However, IAPs interaction network is much more complicated as they interact with multiple cellular partners to regulate the NF-kB signaling pathway, which is pivotal for cell survival. So far, the development of highly active Smac-mimetics (SM) targeting type II BIR domains of IAPs was pursued by many research groups. Nevertheless, in some cases, SM-mediated cIAP1 degradation leads to non-canonical NF-κB activation, by inducing $cIAP_2$ gene expression, which overcomes cIAP1 absence and suppresses TNFα-mediated cell death. We propose to explore alternative mechanisms that can be exploited to interfere with IAP-involving signaling cascades in NF-κB regulation. We focused our attention on IAPs' type I BIR domains (BIR1), that lack the N-terminal peptide-binding groove necessary for SM-binding in type II BIR domains. The BIR1 domains of cIAP2 and of XIAP interact with a TRAF1:$(TRAF2)_2$ heterotrimer and with TAB1, an upstream adaptor for TAK1 kinase activation, respectively, to regulate the canonical NF-κB signaling. We investigated the protein-protein interaction surfaces of IAPs' BIR1 domains finding that, in the crystal structures of $cIAP_2$-BIR1/TRAFs and XIAP-BIR1/TAB1, they display an identical interaction surface. This observation points out remarkable common features in IAPs-BIR1 domains that can be exploited to identify a new class of molecules able to specifically inhibit type I BIR domains. In this context, we identified the compound NF023 and solved the crystal structures of human XIAP-BIR1 domain in the absence and presence of the inhibitor or of its analog cmp247. Furthermore, we identified several new molecules that could possibly inhibit XIAP-BIR1 homodimerization and that are currently under study.

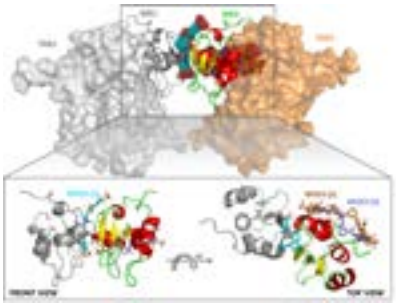

Figure1: *NF023 potentially impairs XIAP-BIR1 homodimerization. Crystal structure of XIAP-BIR1 (colored cartoons) in the presence of NF023 (in sticks), as superimposed with the crystal structure of BIR1 in complex with TAB1 (colored surfaces, PDB code: 2POP). The compound impairs XIAP-BIR1 homodimerization, possibly destabilizing its interaction with TAB1.*

Biography

Luca Sorrentino has always been interested in the study of proteins involved in the regulation of cell death or cell survival, two pivotal processes at the base of cancer development. During his education and PhD program, he gained expertise in cloning, production and purification of recombinant proteins followed by their thorough biochemical and structural characterization. Moreover, he also performed several experiments at the ESRF synchrotron in Grenoble. During the last years, he participated in international conferences and was supervisor of several graduate students. He is currently post-doc in the laboratory of Dr. Eloise Mastrangelo and Dr. Mario Milano (IBF-CNR, Milan, Italy), working on a project aimed at the structure-based design of a new class of compounds active in the regulation of the NF-κB pathway.

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