TYPE I AND II BIR DOMAINS AS TARGETS FOR CANCER THERAPY

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Background: Inhibitors of Apoptosis Proteins (IAPs) are oncological targets whose over-expression enhances cell survival and resistance to anticancer agents. IAPs regulate NF-κB pathway acting as E3 ligases; furthermore, they sequester caspases to prevent apoptosis. Such IAPs functions are mediated by type I and II BIR (Baculovirus IAP repeat) domains, respectively. Methods and Results: Type II BIRs are validated targets for cancer therapy. The biophysical and structural analysis (crystallography, SAXS) of a specific cavity on type II BIRs allowed the rational design of Smac-mimetics, which we patented as potent anti-cancer agents; however, chemoresistance events depending on type I BIRs have been reported. We, thus, virtually screened libraries of commercial compounds (Chembridge, DrugBank, LOPAC) targeting type I BIRs, identifying candidates with promising in vitro profiles, both on isolated proteins and in cell-based assays. In particular, one candidate modulated NF-κB activation in breast adenocarcinoma, inducing cell death, both as single agent and in combination with Smac-mimetics.

Conclusions and Significance: Chemoresistance challenges the development of anti-cancer therapies. A deeper understanding of IAPs action at a molecular level and the use of high-resolution techniques represent the steps forward the development of precision treatments.

Keywords (max 5) - Drug discovery, Apoptosis, NF-κB, IAPs, Smac-mimetics

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Thematic Area:

New Computational Approaches in Drug Discovery/Targets identification in oncology

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