**Targeting BIR-mediated onco-PPIs: rational design of NF-*κ*B modulators**

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**Sessione Tematica:** Molecular Biophysics

Over-expression of inhibitors of apoptosis proteins (IAPs) family enhances cell survival and resistance to chemotherapics. IAPs-mediated complexes ubiquitylate substrates regulating NF-κB pathway. Type I BIR (Baculovirus IAP repeat) domains of IAPs are pivotal for the assembly of such complexes. IAPs’ Type-II BIRs interact with caspases to inhibit cell-death, or with SmacDIABLO for apoptosis restoration. Type II BIRs-directed therapies, Smac-mimetics (SMs), relieve caspases from inhibition by X-linked IAP and induce cIAPs (cellular IAP1 and 2) auto-ubiquitination and degradation. Despite IAPs-directed therapies target pockets or hotspots on isolated, globularly structured BIR domains, their relative positioning within the entire IAP molecule is the key for various pro-survival roles. Since SMs treatment produces divergent effects, such as cIAP2 upregulation leading to cell survival, full length IAPs structural information is necessary.

Our aim is to target BIR-mediated onco PPIs to (i) develop/improve IAPs-targeting therapies and (ii) unravel the molecular determinants of the action of IAPs or IAPs-inhibitors. We have already identified compounds binding BIR1-mediated PPI surfaces and we characterized a library of more than 50 novel putative anti-cancer molecules *in vitro*, analysing the ability to bind target proteins and to induce cell death in a panel of four tumor cell lines (prostate cancer, triple negative adenocarcinoma, non-small cell lung cancer). We selected 2-3 candidates with best profiles to elucidate pro-death mechanisms. We are currently producing the recombinant form of different FL-IAP homologues and protein partners as TRAF2 and TAB1, for biophysical and biochemical investigations. The modulation of pro-survival complexes regulating the NF-κB pathway, as the ones mediated by IAPs, can be the strategy to overcome cases of resistance to current IAPs-targeting chemotherapics.

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