Sažetak predavanja:

Ciljano aktiviranje apoptoze u tumorima: Istraživački put od gusjenica do klinike

Evasion of cell death is a characteristic feature of human cancers and represents a key cause of resistance to current treatment approaches. Therefore, reactivation of cell death programs in cancer cells is a promising strategy to overcome treatment resistance, one of the major unsolved problems in clinical oncology. In principle, cell death pathways can be blocked by abnormal expression of antiapoptotic molecules in cancer cells. Inhibitor of Apoptosis (IAP) proteins comprise a family of antiapoptotic proteins that promote survival signaling pathways and prevent the activation of the effector phase of apoptosis by interfering with the activation of caspases. Since overexpression of IAP proteins frequently occurs in various human cancers and has been linked to tumor progression, treatment failure and poor prognosis, they are considered as promising targets for therapeutic intervention.

We have designed small-molecule IAP antagonists that bind with high affinities to select baculovirus IAP repeat (BIR) domains of IAPs and induce cell death as single-agents or in combination with chemotherapeutics or death receptor agonists. In addition, IAP antagonists trigger dramatic induction of c-IAP auto-ubiquitination activity and rapid proteasomal degradation. Our biochemical and structural studies reveal that the un-liganded, multi-domain c-IAP1 protein sequesters the RING domain within a compact, monomeric structure that prevents RING dimerization. Antagonist binding induces conformational rearrangements that enable RING dimerization and formation of the active ubiquitin ligase. This is in contrast to TNF family ligand (e.g. TWEAK, CD40) signaling where aggregation of receptor-associated complex recruits c-IAP proteins via TRAF2 interaction, which promotes dimerization of c-IAP RING domains to activate c-IAP1 ubiquitin ligase activity. Neutralization of c-IAPs through knockdown or small-molecule IAP antagonists blunts TNF stimulated NF-kB activation and greatly sensitizes cells to TNF induced cell death. Our IAP antagonists inhibit tumor growth *in vivo* as single agents and in combination with a number of anti-tumor agents. While TNF is critical for the single-agent activity of IAP antagonist, the role of TNF signaling in combinations with other anti-tumor agents is not yet clear.

Understanding the significance of IAP ubiquitin ligase activity and TNF signaling is important for the design of potent IAP-directed therapeutics. These compounds can be used in the treatment of malignancies in which IAP expression contributes to tumor progression and resistance to conventional chemotherapeutic agents.