

MOLECULAR MECHANISM UNDERLYING THE ANTICANCER ACTIVITY OF NATURAL OR SYNTHETIC COMPOUNDS.

Since many years the main research of the laboratory has focused on biological activity of natural or synthetic derived compounds with a potential role in the prevention of human pathological processes, such as cancer. Our work has clarified the mechanism of action, through the identification of protein targets, of the antiproliferative and/or antioxidant effect of some natural agents, such as beta-carotene, anthocyanins and, more recently, stilbenes. In particular, in experiments with different synthetic derivatives of resveratrol (3,4',5-trihydroxy-*trans*-stilbene, a natural phytoalexin known for its wide spectrum of biological functions, and especially for its cancer chemoprevention activity), we have demonstrated that the 4'-hydroxystyryl moiety of the molecule is the specific structural determinant required for the inhibition of cell proliferation, but not for antioxidant activity, which is dependent on the three-hydroxyl groups in the molecule. A potential mechanism underlying this antiproliferative activity seems to be related to its ability to block DNA synthesis, through the inhibition of DNA polymerase. We have synthesized and studied the biological activity of new resveratrol analogues, and in particular 4,4'-dihydroxy-*trans*-stilbene, containing two 4-hydroxystyryl moieties, which showed a stronger inhibition of tumour proliferation than resveratrol, confirming the importance of this structural determinant, in addition to a potential pharmacological interest. Currently, we are focusing on i) the molecular mechanisms underlying the antitumor activity of 4,4'-dihydroxy-*trans*-stilbene, which appear to involve signalling pathways different from those activated by resveratrol, ii) a potential influence in epigenetic regulation and iii) a possible role in interfering with inflammatory and immune responses, usually unsuitable, associated to the presence of cancer.

STUDY OF PROTEINS INVOLVED IN CELL CYCLE REGULATION AND DNA REPLICATION AND REPAIR.

The DNA must be replicated and transmitted properly to avoid genomic instability, pathogenetic basis of several human diseases, such as cancer; to this end, cells have developed a complex system to monitor and signal DNA damage (checkpoints), and DNA repair systems. For many years the research of the laboratory has been directed to some proteins that regulate the cell cycle and appear also to be involved in the processes of DNA repair. Among these proteins, the cyclin-dependent kinase inhibitors p21^{CDKN1A} plays a very important role in cell cycle control, mainly in the "checkpoint" of G1 phase and in the inhibition of DNA synthesis by associating with PCNA, a cofactor necessary for the activity of many enzymes involved in the DNA metabolism. Recently, our research has demonstrated that p21, in cooperation with p27, an important member of CDK-inhibitor family, is involved in the induction in controlling the entry / exit from the temporary cell cycle (quiescence). In addition, p21 appear to promote the efficiency of DNA repair processes, like the Nucleotide Excision Repair (NER). In fact, p21 seems to be required to regulate the acetylation of some factors involved in NER. Among these, we are studying the protein that binds to damaged DNA (DDB2), which, combined with DDB1 in complex DDB plays a role in the recognition of DNA damage induced by UV in the Global Genome Repair (GGR-NER). In addition to its role in the repair of DNA damage, we are investigating a new and further activity of DDB2 concerning his involvement in cell cycle regulation and growth and invasiveness of cancer cells.