

Preclinical approach to study the biological activity of stilbenoids against lung cancer (LuCa).

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Research Theme/Topic: Cellular and molecular mechanisms of resveratrol derivatives against cancer development.

Background. Lung cancer (LuCa) is one of the most clinically relevant tumours, and its eradication remains an elusive clinical goal, largely because of the heterogeneous and peculiar nature of individual cancers, the onset of metastasis, and the inability to target therapies to neoplastic cells without damaging normal tissues. Growing evidence demonstrates that natural or synthetic derived compounds represent a fundamental source to reduce or delay the occurrence of malignancy or to synergise with traditional chemotherapeutic agents. In the last few decades, stilbene-based compounds have been widely investigated due to their multiple biological properties, and among these, the most studied has been resveratrol (3,4',5-trihydroxy-*trans*-stilbene), especially for its cancer chemoprevention activity. We have previously demonstrated that the 4' phenolic hydroxyl group, *trans* conformation and double bond of the molecule are specific structural determinants required for the inhibition of cell proliferation. These functional groups provide resveratrol with great potential to be modified into derivatives with more therapeutic efficacies. We have synthesized and studied the anticancer activity of new hydroxylated and methoxylated resveratrol analogues, and in particular 4,4'-dihydroxy-*trans*-stilbene, which has shown a stronger inhibition of LuCa proliferation than resveratrol.

Aim of this PhD project is to investigate 1) the molecular mechanisms underlying the antitumor activity of 4,4'-dihydroxy-*trans*-stilbene, which appear to involve different signalling pathways from those activated by resveratrol; 2) the potential influence in epigenetic regulation involving sirtuin family members; 3) the effect on inflammatory and immune responses cancer-associated; 4) the impact on subpopulation of cancer stem cells (CSCs). Combined treatment approaches with the most bioactive derivatives together with traditional chemotherapeutic agents will also be explored.

Techniques: Human and mouse cell cultures, Immunofluorescence, Western Blotting, Flow Cytometry, Elisa, Immunohistochemistry, qPCR, siRNA, Comet Assay, Adhesion and Migration assay (Boyden chamber), Animal models

