Institut Européen de Chimie et Biologie

I E C B

Warburg effect and prodrug activation: superoxide anion dependent prodrug activation inhibits tumour angiogenesis and tumour growth

Pascal Collin
UMR 8601, LCBPT, CNRS-Paris Descartes and University Paris Diderot, Dental University, Hospital Rothschild (AP-HP), Paris, France

The aim of our project is to develop an innovative concept in chemotherapy for cancer treatment, by targeting simultaneously the 3 main compartments of solid tumors, namely normoxia, hypoxia and angiogenesis, through a common Warburg restricted prodrug activation system. The prodrug activation mecanism is based on the reactivity with superoxide anion produced at the plasma membrane (PM) by the transplasma membrane electron transfert (TPMET) (Coenzyme Q metabolism), directly linked to the Warburg effect for NAD+ recycling. Production of this superoxide anion at the PM, as well as in the mitochondria is known to represent a real Achille's heel for these cells.
Robotic chemical library screening (CNRS-ICSN) against $O2^{\cdot}$- identify one compound among 7500, having such properties in vitro and in cellulo. Furthermore, after activation through an oxidative coupling mecanism, chemical structure of the activated drug was in agreement with the reductive metabolism specific to the hypoxic area.
The value of this prodrug was confirmed by proof-of-concept studies at the chemical, biological, biochemical and cellular levels. We identify the Thioredoxin Reductase enzyme (TRXR) and its selenocysteine residue as one possible cellular target for the active drug, in agreement with the cytosolic and mitochondrial oxidative stress observed after treatment. Cellular cytotoxicity involved a main Radical Oxygen Species (ROS) associated mitochondria dependent apoptotic process, which pathway remains to be clearly determined. Moreover, this prodrug inhibits « in ovo » tumoral angiogenesis and reduces « in vivo » tumor growth in a mice xenograft model.

Institut Européen de Chimie et Biologie
2, rue Robert Escarpit - 33607 Pessac, France
Tél. : +33(0)5 40 00 30 38 - Fax. : +33(0)5 40 00 22 15
www.iecb.u-bordeaux.fr