Selective Induction of Cancer Cell Death by VDAC1-Based Peptides

The voltage-dependent anion channel (VDAC) has been identified as an attractive potential target for modulating cellular energy and apoptosis. VDAC1, located at the outer mitochondrial membrane, mediates the cross-talk between the mitochondria and other parts of the cell by transporting anions, cations, ATP, Ca^{2+} and metabolites. Substantial evidence points to VDAC1 as being a key player in apoptosis, regulating the release of apoptogenic proteins, such as cytochrome *c*, from the mitochondria and interacting with anti-apoptotic proteins. Even in the presence of oxygen, most cancer cells rely on glycolysis as the main pathway for generating energy (Warburg effect) and as a source of products for generating proteins, nucleotides and lipids. Such metabolic re-programming in cancer cells also includes a marked over-expression of VDAC1. Most tumor cells have also developed apoptosis escape mechanism involving upregulation of hexokinase (HK), the Bcl-2 family, as well as VDAC, which serves as the anchoring site for several anti-apoptotic proteins, including HK, Bcl-xL and Bcl-2. Mitochondrial-bound HK and Bcl2 are over-expressed in many cancer cells including breast, lung, pancreas, esophagus, renal and liver cancer while Bcl2 is overexpressed in colon, breast, prostate, lymphoma, glioma, leukemia cells and their over-expression in tumors is coupled with resistance to chemotherapy-induced apoptosis. Thus, complexes between VDAC1 and HK, Bcl-2 or Bcl-xL represent attractive targets for apoptosis-inducing anti-cancer therapy.

The Technology

We have developed several VDAC1-based peptides that directly interact with HK, Bcl2 and Bcl-xL and interfere with their anti-apoptotic activity. These “decoy” peptides compete with VDAC1 for the Bcl2-, Bcl-xL- and HK-VDAC1 interaction sites and consequently interrupt their anti-apoptotic activity. Moreover, due to the peptides mode of action, involving both disrupted energy and metabolic homeostasis and inducing apoptotic cell death, the peptides selectively promote cancer cell death in a panel of cancer types regardless of the mutations and acquired survival mechanisms. Thus, VDAC1-based peptides provide the opportunity for the development of new anti-cancer therapies allowing overcoming the chemo-resistance of cancer cells.

Applications

Treatment of various types of cancers, and specifically of apoptosis resistant cancer cells including CLL.

Advantages:

- VDAC1-based peptides induced cell death in many cancers affecting both cell energy production and inducing apoptosis and thus have a pronounced therapeutic potential in various cancers, particularly those in which traditional therapies are ineffective
- Based on their modes of action, VDAC1-based peptides represent potentially “universal” anti-cancer agents. This is because their desired bioactivities can be demonstrated on a variety of cancer types regardless of mutations and acquired survival mechanisms.
- Our VDAC1-based “decoy” peptides eliminate the advantages gained by cancer cells in over-expressing VDAC1 and anti-apoptotic peptides.
- Strong IP position: A patent has already been issued in the US. Patent applications have been filed in Europe, and Israel.

Patent Status

US Granted
EU and IL Pending

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