Phosphatidylserine Exposed by Cancer Cells Plays the Key Role in the Development of New Antitumor Drugs

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Every year millions of people are diagnosed with cancer. Chemotherapy is the standard treatment but chemotherapeutics can hardly discriminate between cancer and healthy cells consequently causing severe side effects. In the FWF project P20760-B11, we enforce a weapon derived from innate immune system against cancer cells in the form of small cationic peptides that will target specifically the cancer cell without binding to specific receptors or inner cell targets. LF11, a short peptide stretch derived from human Lactorferricin, exhibiting antibiotic, antifungal, antiviral and anti-tumor activity, is taken as a parent peptide and is further optimized in its activity and selectivity towards cancer cells. This is provided by the interaction of the cationic peptides with cancer cells that expose the negatively charged phospholipid phosphatidylserine (PS) in the outer leaflet of their plasma membranes, which in healthy cells only comprise neutral lipids.

Within *in vitro* studies plasma membranes of melanoma (different tumor development), prostate-, brain- (primary cell line) and kidney cancer cells and their healthy counterparts were characterized for presence or absence of PS exposure by flow cytometry and fluorescence microscopy. Selectivity of LF11 derived peptides for model membranes was improved by structure-activity relationship studies using Differential Scanning Calorimetry (DSC), Fluorescence spectroscopy and further techniques. These biophysical investigations on model membranes revealed that some peptides have specific impact on the lipid membrane of cancer cells. From the outcome of the first screening with model membranes 2 peptides (the most active non acylated and its N-acylated form) were chosen for cytotoxicity studies with cancer and non cancer cells. These experiments revealed that the N-acylated peptide induced lysis of cancer cells at a similar level as Melittin (bee venom), that is known to be toxic for cancer cells, as well as for non cancer cells, whereas the N-acylated derivative of Lactoferricin was shown to be less toxic for non cancer cells than Melittin.

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