Impedance-based screening of novel heterocyclic molecules designed for apoptosis induction

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Pancreatic adenocarcinoma is one of the most aggressive tumor with poor prognosis, the five-year survival rate is 5% [1]. The resistance of pancreatic carcinoma to treatment regimens represents a major challenge, whereas pancreatic carcinoma cell resistance to apoptosis is well known and may contribute to treatment failure [2]. A potential drug selectively restoring the regulation of apoptosis or inducing apoptosis of the tumor cells may reduce the therapeutic failure.

Aims of our study were: (i) to design a new library of heterocyclic molecules for apoptosis induction; (ii) to screen the novel molecules on different tumor cell lines by HTS impedimetry; (iii) to identify the molecular target of the hit molecules; (iii) to check how the hit molecules act on the apoptotic pathway.

Methods: the drug-like library were developed upon non-flat 3-dimensional templates and libraries (Smart Diversity ApproachTM). Compounds with small molecular weight, more favorable physicochemical properties, higher sp3/sp2 atom ratio, and novel 3-dimensional shapes with various functionalities were selected and synthetized. Biological tests were performed on different tumor cell lines, PANC1(pancreatic adenocarcinoma), COLO 205 (colon cancer), A2058 (melanoma), EBC1 (lung cancer). Cytotoxicity was measured by impedance based technique in xCELLigence SP (ACEA) system. Flow cytometry were applied to detect the apoptotic effect of the molecules, caspase 3 or 7 activity were measured.

Results: In total 193 novel heterocyclic molecules containing linker connection functional groups with a relatively low molecular weight, below 600 Daltons were synthetized in high purity (> 95 %). 18 of the tested compounds were significantly cytotoxic on pancreatic tumor cells (PANC-1). These molecules were able to reduce the cell viability of other tumor cell lines (COLO 205, A2058 and EBC1) as well. Screening in databases based on structural similarities revealed that the potential target of several components is the XIAP (X-linked inhibitor of apoptosis). However, the apoptotic pathway analysis proved, that some of the hit molecules were able to induce caspase 3 and 7 activation in the model cells, further examination is required to test the interaction of the XIAP and the hit molecules.

Although XIAP is not expressed in normal pancreatic ductal cells, several clinical study recently proved that it is overexpressed in pancreatic carcinoma cells, associate with invasiveness and shortens the survival of pancreatic cancer patients [2]. Selective inhibition of XIAP may have a favorable therapeutic effect.

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