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Antitumor activity of cationic peptides is maintained in acquired multidrug-resistant tumors

Abstract

Background: One of the reasons for the increase in cancer incidence is tumor multidrug resistance , associated with their polyclonality and the appearance of resistant tumor cells (RTC) in response to therapy. The development of drugs to solve this problem is an urgent matter of molecular oncology.[1] Biodegradation-resistant cationic peptides (CPs) with a dendrimer structure and with immunomodulatory, antiviral, antibacterial activities are perspective for this purpose. Earlier, we have investigated a selective cytotoxicity of Arg/Lys-enriched CPs on sensitive and resistant tumor cell sublines.[2] We have revealed that multidrug resistance can be overcame through the interaction of CPs with specific molecular targets, including VEGFR2, FGFR, EGFR/ErB1, AQPs and glycosylated NCL, expressed by RTC on their surface in addition to t nucleus and cytoplasm. As multifunctional chaperone protein with kinase activity, NCL can regulate proliferation, transcription, translation, chromatin remodeling , ribosome biogenesis and other important cell functions , including tumor and stem tumor cells.

Objective: Study of antitumor activity of Arg/Lys-enriched dendrimer-structured CPs *in vivo* .Development of approaches to model molecular interactions and search for cellular targets of CPs that induce tumor cell death, including RTC.

Results: Some Arg/Lys-enriched CPs under our design and study induce apoptosis through inactivation their cell targets – chaperone proteins nucleolin/NCL and nucleophosmin/NPM both in sensitive and resistant tumor cells. The results obtained on murine subcutaneous xenografts of human melanoma mel IS ,hepatocarcinoma Huh-7, ductal pancreatic carcinoma AsPC1, clear cell renal cancer Rpoch1-KK. as well as breast cancer RTC HBL 100/ID 120, confirm wide antitumor activity of these CPs including tumors with acquired drug-resistance.

Keywords: tumor drug resistance, NCL/NPM expression, cationic peptides, apoptosis induction, ligand- cell targets molecular interactions.

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Abbreviations: CPs, cationic peptides; Dox, doxorubicin; BC, breast cancer; NCL, NPM chaperone proteins as a targets for CPs.

Introduction

Drug resistance in tumor cells is one of the obstacles for effective cancer therapy. Polyvalent cationic peptides (CPs) are currently considered as selective antitumor agents capable of selectively targeting both sensitive and resistant tumor cells due to interaction with specific cell surface target proteins. Unlike normal cells with a neutral surface charge, a number of functionally important negatively charged molecules are intercalated into the membrane of tumor cells, for example, gangliosides, anionic phosphatidylserine, glycosylated mucins, proteoglycans, etc. Differential overexpression of glycosylated chaperone protein NCL, VEGFR, EGFR, FGFR2, aquaporins (AQPs), tyrosine kinases (KIT), etc. on the surface of tumor cells is also characteristic. Inhibition of these proteins suppresses hyperactivated signaling, cell proliferation, ribosome biogenesis, activates caspases 3, 8 and 9, triggering apoptosis by nucleolar stress (Figure 1).

Cytosolic fractions of NCL and NPM binds with p53 and down regulate its activity. Moreover, NCL is involved in stabilization of BCL2 mRNA by binding of 3'UTR AU-rich elements (ARE) resulting in increase of anti-apoptotic protein BCL2. Overexpressed NCL has been shown to mediate the antiangiogenic and antitumor activity of endostatin. So, both NCL and NPM play an important role in malignant tumor progression and carcinogenesis. Cell surface nucleolin is characterized as a target for cancer therapy with antibody-related agents[3] Earlier we have also found that some cationic peptides are perspective as a ligands for NCL and NPM overexpressed in tumor cells[4] Here, activity of two CPs in relation to tumor xenografts in immune-deficient nude mice is described and its possible application in anticancer therapy is discussed.

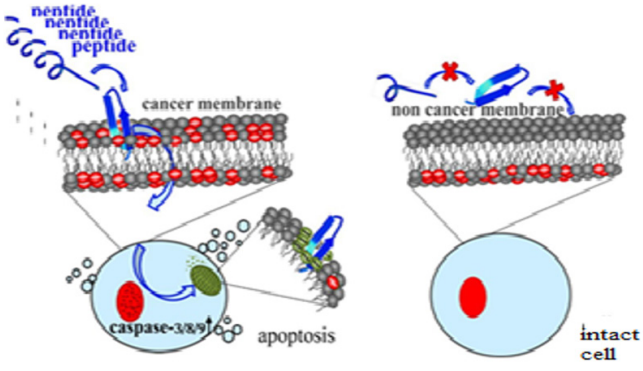

Figure 1 Cationic peptides interact with cancer cell surface followed by apoptosis triggering.

Materials and methods

Subcutaneous murine xenografts (MX) of Huh-7 hepatocarcinomas, Mel IS / Mel Cher cutaneous melanomas. Rpoch1-KK clear cell renal carcinoma, ductal pancreatic carcinoma and BC RTC HBL 100/ID 120 .

Two CPs NC-783 and AM-2 (Figure 2) were injected intraperitoneally, 150 µl, 2 µg/ml of saline, a total of 2.1 µg/mouse (n = 15), 7 injections, control mice - 0.9% NaCL, Cyanine-labeled Cy5-NC811 was injected on day 14, 2 hours before the end of the experiments (150µl, 2 µg.ml) to follow CP affinity to tumor nodes. Tumor growth inhibition TGI (%) was evaluated, measuring the volume of tumor nodes before the next injection, as well as the histological characteristics of CP, liver and kidneys, assessing the cellular structure, glycogen accumulation, cell morphology in histological sections of paraffin embedded tissues.. Cellular targets of CPs were assessed by immunohistochemistry assay, immunoblotting, and molecular docking of CPs to cell target proteins using Maestro, ZDOCK, and Rosette server programs . Cationic peptides with different charge and molecular mass ~2kDa were synthesized by solid phase method using the Fmoc-protective strategy. Cell viability was earlier evaluated by standard MTT-assay using control – human fibroblast line H1036. Standard deviations were calculated for the results obtained from all the experiments. Immunoblot analysis was used with proteins resolved from the cell lysates after SDS-PAGE followed by transfer to nitrocellulose membrane. The primary monoclonal antibodies against NCL, p53 and actin or GAPDH were obtained from Lab Biotech, (Dia-M, Russia). Anti-actin rabbit polyclonal antibody (Dia-M/ Abcam, Russia), HRP-conjugatedanti-rabbit immunoglobulin's from goat antiserum, HRP-conjugated anti-mouse immunoglobulin's from goat antiserum (Dia-M/ Abcam,Russia) were also used. Pair molecular docking was performed using program Maestro 11 to confirm the specific interaction between peptides and NCL/NPM.[4]

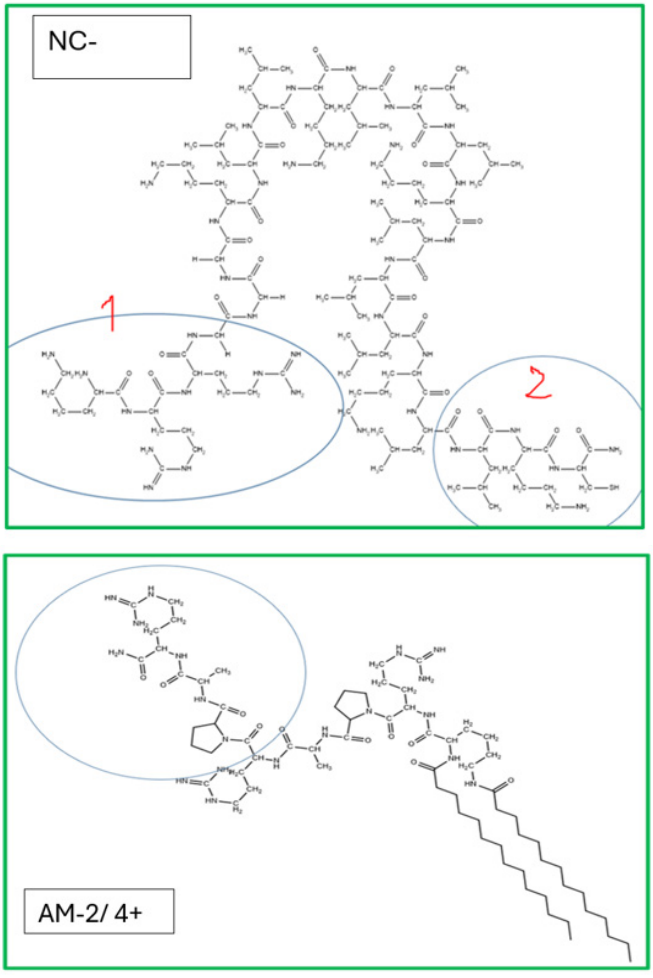

Figure 2 Molecular structures of CPs under study as ligands for docking.

Results

Selective cytotoxicity and antitumor activity of CPs have been confirmed.by cyanine labelled Cy5-NC811, which is localized mainly within tumor nodes in MXs, while tumor growth delay was recorded from 72% to 86% in comparison with continued PC growth and death of mice in control (n =15),for example, in AsPC1 aggressive pancreatic carcinoma MXs (Figure 3).

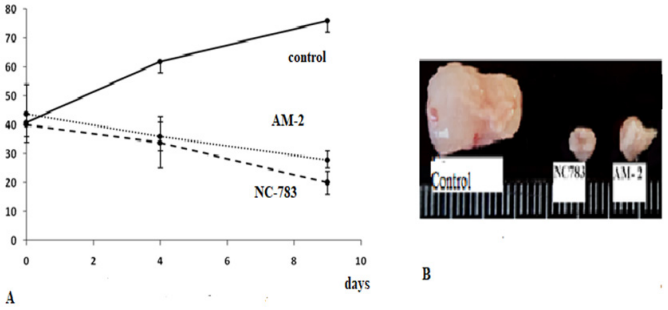

Figure 3 Reduction of subcutaneous pancreatic adenocarcinoma AsPC1 xenograft volumes (from 0 to 80 mm3) after intraperitoneal injections of CP NC-783 and CP AM-2 for 14 days with interval of 48 hours, 150 µL, 4 µg/mL

Finally, average tumor growth inhibition (TGI) after 14 days of CP injection with 48 h interval was amounted in % for AM-2 as 66.5 (mel IS), 74.6 (Huh-7), 68.0 (AsPC1), 70.2 (Rpoch-10; for CP NC-783 : 85.3 (mel IS), 82.3 (Huh-7, 86.3 (AsPC1), 78.3(Rpoch1).

The main mechanism of effective TGI is associated with the interaction of CP (ligands) with specific receptors, overexpressed on the surface of tumor cells (FGFR2, VEGFR 2, Erb 2, etc) and their subsequent inactivation, inhibition of Akt, CDK1/2 and activation of Fas, TP53 after NPM1 dislocation from the nucleus, activation of cas 3.8 and 9 with the induction of apoptosis by nucleolar stress, partially autophagy and mitoptosis. Moreover, significant changes in expression of apoptosis associated proteins are registered (Figure 4).

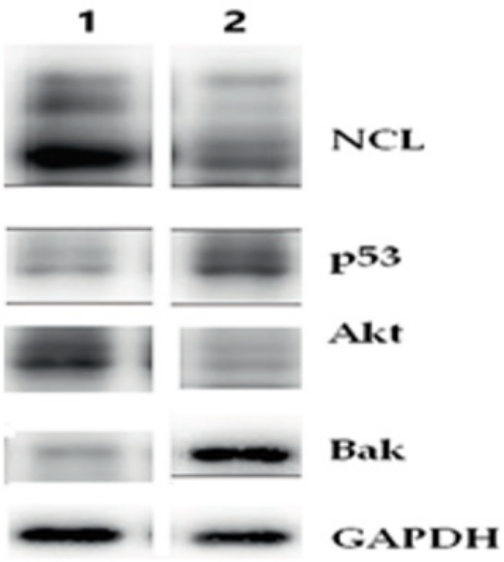

Figure 4 Changes in expression levels of NCL, p53, Akt, Bak and GAPDH (control) in Huh-7 cells before (1) and after (2) 3 days of incubation in presence of NC-783.

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These observations were interpreted using modeling of interactions of the each CP with cell targets by molecular docking (Figure 5 & 6).

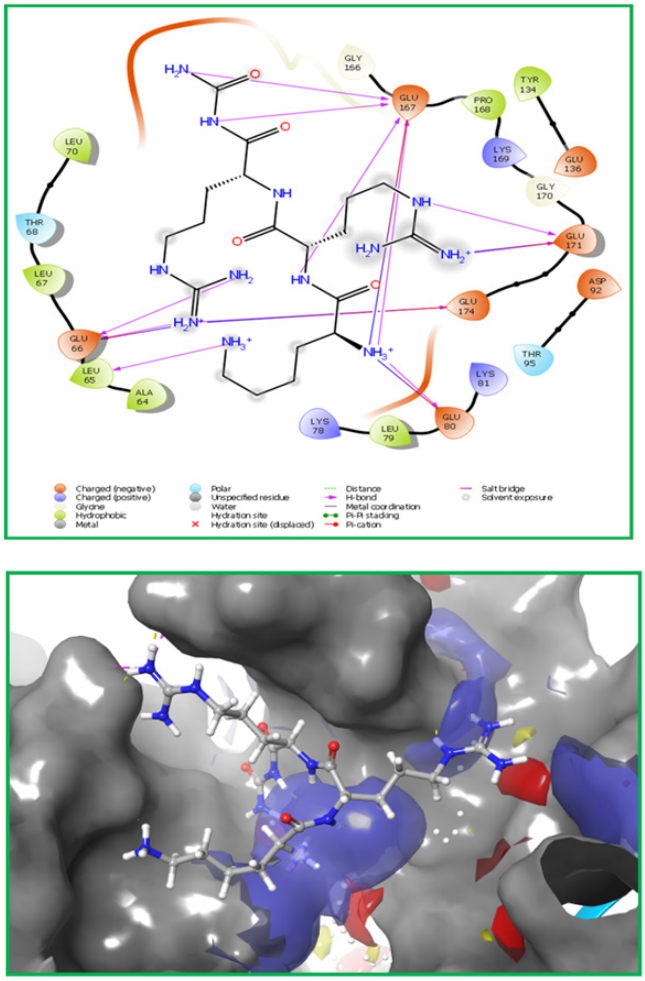

Figure 5 CP docking into target protein NCL produces high scores up to 10.5 modulo by hydrogen bonds and solt bridges. These interactions in active center of NCL molecule results to suppression of NCL activity and cell signal reduction or blocking.

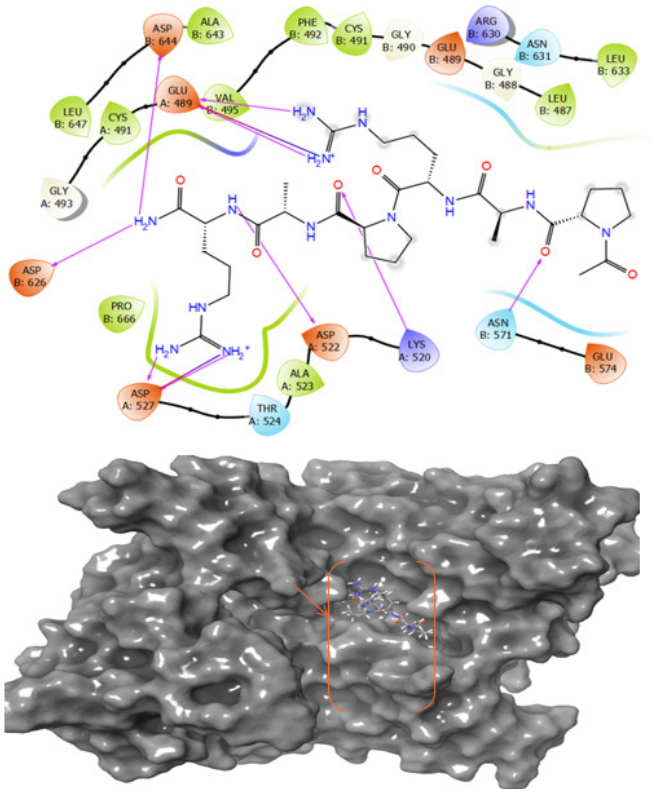

Figure 6 2D and 3D interactions between CP AM-2 and FEGFR2 receptor *Glide score* = – 10,415.

The results of molecular docking confirmed that the CPs bind strongly enough to the active sites of most target proteins with relatively low energy scores for their formation and can serve as potential inhibitors of the selected proteins.

The binding energy between the selected peptides and potential target proteins exceeds 7 kcal/mol in almost every case relative to references (REF) – standard drugs (Table 1).

Table 1 Estimation of " Ligand-Target " interaction by pair molecular docking using Maestro 11.0 (Schrödinger Inc

Target	Am-2	N G -783_1 (NH2 RICH)	NC -783_2 (SH_RICH)	NC810t	REF
NCL (2KRR)	8,7	8.7	8.7	9.3	
NPM (2P1B)	8	8.9	8.7	9.3	5.6
αGP (6QEX)	9,2	7.8	8.7	8,3	10.4
VEGFR2 (1Y6A)	8.4	7.3	6.4	9.5	8.6
FGFR2(6LVK)	10.4	10	8,4	8,3	6.3
KIT(6KLA)	6.9	7.6	7.2	8.4	5.4
KIT (6GQKcmyt)	8.1	6.5	8.3	8.8	11.9
ERK1(4QTB)	9.1	7,3	8.5	8.5	5.5
ERK2 (1TVO)	9	6.8	5.9	8.9	6.7
EGFR (1M17)	6.7	6.3	5.4	8.4	6.6

On the surface of tumor cells receptor proteins are expressed differentially and selectively interact with CPs , resulting in the suppression of the corresponding signaling pathways. The inactivation of NCL receptor molecules disrupts the key processes regulated by it, inducing nucleolar stress and apoptosis.

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Conclusion

The interaction of CPs with functionally important proteins that are overexpressed in tumors and their inactivation leads to the death of the most tumor cells that are both susceptible and resistant to drugs (such as doxorubicin, imatinib, and bortezomib).

CP can also be used as transporters for standard drugs (such as doxorubicin, imatinib) and microRNAs. Thus, universal mechanisms of PC activity, their relatively low toxicity in vivo, suppression of regulatory proteins and signaling pathways activated in tumor cells, including drug-resistant ones, induction of selective cell death in malignant tumors create the basis for the development of low-toxic anticancer drugs using CPs which have several advantages over other peptides.[5]

Acknowledgments

None.

Conflicts of interest

The author declares that there are no conflicts of interest.

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