



ORIGINAL ARTICLE

***In Silico* Activity of AS1411 Aptamer Against Nucleolin of Cancer Cells**

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ABSTRACT

Background: It has been expected that AS1411 aptamer could work against the cancer cells. Although the general information is available, there is still lack of details for the purpose. Therefore, activity of AS1411 aptamer against the nucleolin (NCL) target of cancer cells has been investigated in current work at the molecular scale. In addition, the same features have been also investigated for examining the activity of AT11, one of AS1411 derivatives.

Methods: This work has been done employing *in silico* Molecular Docking simulations. Ten starting 3D configurations have been considered for each aptamer to be docked against the NCL target. Conformational search processes of ligands against the target indicated that the starting configuration of ligand could play an important role in determining the final complex formation in both of quantitative and qualitative aspects.

Results: A04 and B01 are those starting configurations of AS1411 and AT11 making the strongest complexes with the NCL target among other ligands. The analyses indicated that the complexes of AT11 are slightly stronger than those of AS1411, in which the NCL target structure is more involved in the chelated complexes with the AT11 in comparison with the AS1411.

Conclusion: AS1411 and AT11 are specified for targeting the NCL of cancer cells for the diagnosis and therapeutic purposes. They have reasonable binding affinity and could work as possible inhibitors of NCL.

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Introduction

Cancer has been seen as one of the serious problems to the health quality of people all around the world for several years.¹ Although the conventional therapeutics such as chemotherapy and surgery have been improved for better treatments of patients, but the problem is still remained unsolved.² Besides, unwanted side effects could suffer the patients after using such treatments.³ Therefore, considerable efforts have been dedicated to find possible solutions for developing more efficient protocols of cancer therapy.⁴ To this aim, knowledge about details of mechanism of cancer growth prevention could help to reproduce novel therapeutics for this health problem.⁵

In the case of pharmacotherapy, conditions of ligand-target interactions in both quantitative and qualitative aspects are important to make a brighter decision about the efficacy of desired ligand for inhibiting of target activity.⁶ Such details could be very well recognized by employing the *in silico* methodologies on simulation of 3D structures of molecular counterparts of interacting systems using computer systems and softwares.⁷⁻¹⁴ The quantitative binding energy could reveal information about the strength of ligand-target complex formation whereas the spherical shape could show the corresponding molecular configurations of interacting counterparts.¹⁵ By the benefits of employing *in silico* methodologies,

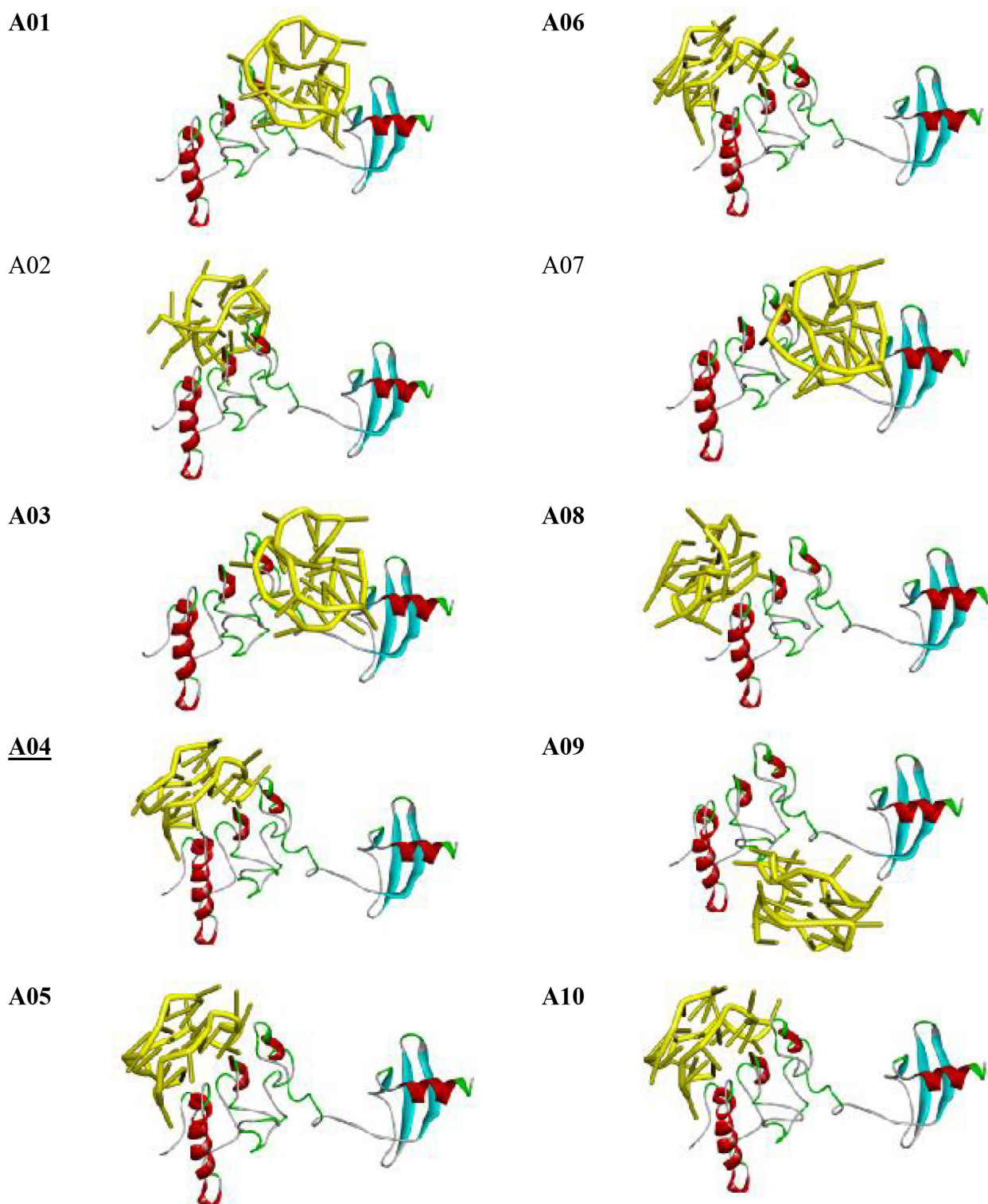


Figure 1: AS1411-NCL complexes regarding ten initial 3D configurations of AS1411. See Table 1 for more details.

differences for the obtained values of HDOCK scores, in which the score of A01 is only close to A04 and the strength orders for all complexes of different starting configurations are A04 > A01 > A08 A10 > A03 > A06 > A09 > A05 > A07 > A02. For showing molecular details of interactions in complexes, the NCL sequence could be divided into two left and right sites in Figure 1; the left site is [GSHMVEGSESTTPFNLFIGNLPNKS VAEKVAISELFAKNDLAVVDVRTGTNRKFGY VDFESAEDLEKALELTGLKVFGNEIKLEKPKG

RDSKKVRAARTLLAKNLSFNIT] and the right site is [EDELKEVFEDALEIRLVSQDGKSKGIAY IEFKSEADAENLEEKQGAIEDGRSVSLYYTGEK]. The results indicate that the ligands are mostly oriented to interact with the left site but with different binding strength. Very much interestingly, A04 interacts with NCL through its 5'-part (5'-GGTGGTGGTGGT) showing the highest strength but A02 interacts with NCL through its 3'-part (GTGGTGGTGGTGG-3') showing the lowest strength of complexes. By emphasizing again on the importance

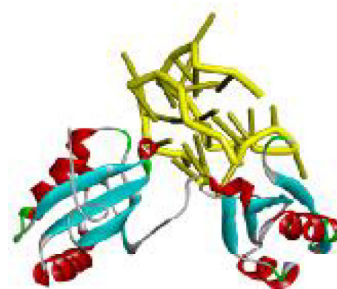
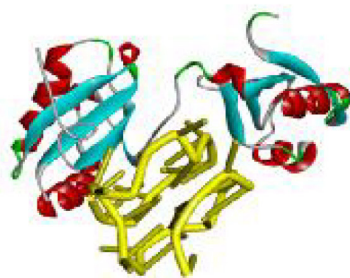
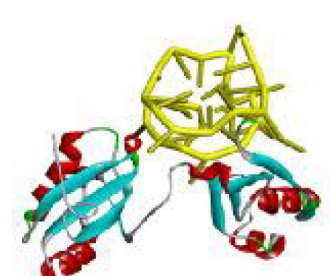
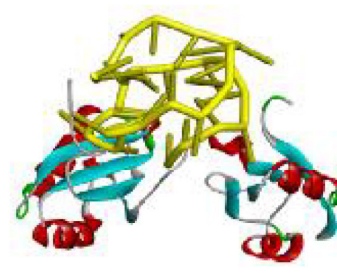
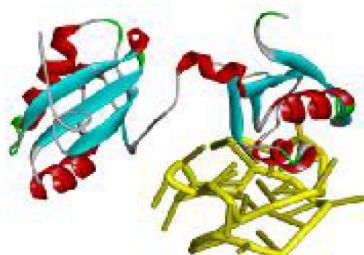
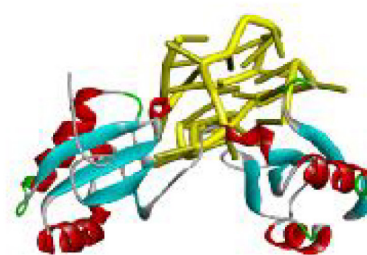
B01**B06****B02****B07****B03****B08****B04****B09****B05****B10**

Figure 2: AT11-NCL complexes regarding ten initial 3D configurations of AT11. See Table 1 for more details.

of starting configuration of ligand, the trend shows that it could orient the AS1411 how to relax at the target site, as could be clearly seen for A02 and A04 complexes. The same story has been seen for other A complexes, in which the 5'-part of AS1411 could make stronger complexes with NCL in comparison with the 3'-part.

AT11-NCL Complexes

For exploring efficacy of AS1411 derivative activity on interacting with the NCL target, the features of AT11

have been investigated and the resulted complexes have been compared with those of the original AS1411. Ten starting configurations have been employed in parallel with the configurations of the original AS1411, and the MD simulations with 100 numbers of conformational searching process have been performed to evaluate the formations of AT11-NCL complexes. The main difference between AS1411 and AT11 is additional of two T nucleotides; one T to beginning 5'-part and one T to ending 3'-part, besides replacement of one G of AS1411

by another T nucleotide (see Materials and Methods). The changes of aptamer building shows significant effects on the interactions of AT11 with the NCL target as presented in Figure 2 in comparison with Figure 1. Interestingly, the structural configuration of NCL also detects significant effects of AT11 presence in comparison with that of AS1411. By the obtained HDOCK scores, B01 shows the highest stability and B09 shows the lowest stability of AT11-NCL complexes, in which the stability order is $B01 > B07 > B06 > B02 > B08 > B03 > B10 > B05 > B04 > B09$. Comparing the average HDOCK scores indicates that the B complexes are slightly more stable than A complexes with the average score: -246 kcal/mol for B complexes and -244 kcal/mol for A complexes.

Discussion

Based on the importance of employing nucleic acid aptamers for cancer growth prevention, the activity of AS1411 against the NCL target has been investigated in this work employing the *in silico* MD simulations of interacting ligand-target complexes. Besides the original AS1411, AT11 has been also examined as one of derivatives with expected potency of interaction with the NCL target. Since the over-expression of NCL at the cell surface is a characteristic biomarker feature of cancer cells, aptamer binding with the NCL could have dual benefits of diagnosis and therapeutic for cancer problem. Therefore, knowing details of interacting aptamer-NCL complexes is important to be achieved *in silico*.

Since the performed MD simulation was flexible for both of ligand and target, slight changes of NCL structure could be observed for the complexes of the panels of Figure 1 for AS1411-NCL complexes. Avoiding the changes of each structural configuration, localization of AS1411 ligands at the NCL surface should be carefully considered for targeted drug deliver purposes and to improve the efficacy of employed treatment for the cancer diagnosis and therapeutic purposes. As an advantage of *in silico* investigations in comparison with experimental achievements, the localization of ligand at the target site could be recognized at the molecular scale in addition to its binding strength. Earlier investigations also indicated that the AS1411 is a proper ligand for binding with the NCL target but almost without details of importance of starting configuration and finalizing localization of ligand at the target site.³⁰ As a concluding remark of this part, it could be mentioned that the starting configurations of AS1411 is an important factor for assigning its activity against the NCL target with significant changes of binding energies of interacting complexes and the conformational localization of ligand at the target surface. The left site of NCL is a proper site for AS1411 to interact with, in which the 5'-part of aptamer is more proper for this purpose. And finally, such important configuration features should be considered for the targeted drug delivery purposes regarding the AS1411-NCL complexes.

The achievements of AT11-NCL complexes could mean that the activity of derivative has been slightly improve for more effective interaction with the NCL target, which is in agreement with the previous works introducing

AT11 as a proper ligand.¹⁴ Furthermore, Figure 2 represents that the AT11 is almost chelated by the NCL meaning that all structure of target is almost involved with the interacting ligand to make a chelated complex. Comparing with Figure 1, the target NCL structure was still free of influence of interacting AS1411 ligand in the complexes but this trend is more complicated for AT11 by re-configuration of the NCL sequence to make complexes. For drug delivery purposes, it could be mentioned that the dosage consumption of AT11 could be expected to be slightly lower than that of AS1411 based on the achievements in both of HDOCK scores and structural configurations. Molecular scale analyses show that in all cases the 5'-part of AT11 is involved in interactions with the NCL target in contrast with the obtained achievements about the 5'-part of AS1411 involving in strong and 3'-part involving in weak complex formations. As concluding remarks of this part, it could be mentioned that the AT11 derivative could work somehow better than the original AS1411 in both of quantitative and qualitative aspects regarding the achievements of AT11-NCL complexes.

Conclusion

Within this work, we have performed *in silico* MD simulations to investigate the activity of AS1411 aptamer against the NCL target of cancer cells. Besides, the same features have been also investigated for examining the activity of AT11, one of AS1411 derivatives. By the obtained results, some trends could be concluded. First, the starting configuration of aptamer is important for both of AS1411 and AT11 to make strong interactions with the NCL target. Second, overall strength of AT11 is slightly higher than AS1411 for complex formations with the NCL target. Third, 5'-part of AS1411 plays role of making stronger interactions with the NCL and 3'-part plays role of making weaker interactions whereas 5-part plays all roles in AT11 related complexes. Fourth, the NCL target is more involved in complexes with AT11 than AS1411. Fifth, the NCL target could be very well recognized by both of AT11 and AS1411 with higher overall efficacy for AT11. And finally, A04 and B01 are those aptamers specified for targeting the NCL of cancer cells for the diagnosis and therapeutic purposes.

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Conflict of Interest: None declared.

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