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Developing and Characterization of Chemically Modified RNA Aptamers for Targeting Wild Type and Mutated c -KIT Receptor Tyrosine Kinases

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Abstract

The c-KIT is a transmembrane receptor tyrosine kinase that plays a crucial role in cancer progression. Deregulation of c-KIT has been detected in several human cancers. In particular, the two point mutations D816V and D816H in the kinase domains which induce ligand-independent activation of the kinase activity and acquired drug resistance. Therefore, c-KIT represents an attractive target for cancer therapy. Aptamers are emerging as a new promising and innovative class of nucleic acid therapeutic agents. In our study, a conventional SELEX approach was applied against the kinase domain of a group of c-KIT proteins (c-KIT WT, c-KIT D816V, and c-KIT D816H) to select RNA aptamers from a random RNA pool that can bind to the kinase domain of each c-KIT protein with high affinity and can selectively interfere with their kinase activities. Interestingly, our experimental data indicated that one of the candidate aptamers, called V15, can potently and specifically inhibit the in vitro kinase activity of mutant c-KIT D816V with an IC50 value that is 9 fold more potent than the FDA approved sunitinib drug tested under the same experimental conditions. Kinetic analysis revealed that V15 aptamer inhibits the kinase activity of the tested c-KIT kinases in a non-competitive manner. Another aptamer, named as H5/V36, showed the potential to functionally distinguish between the c-KIT WT, c-KIT D816H, and c-KIT D816V kinases by modulating the phosphorylation activity of each in a distinct mechanism of action and in a different potency. Finally, H5/V36 aptamer also revealed significant selectivity, since almost no inhibitory activity was detected after testing against two closely related kinases: PDGFRβ and JNK3 kinases. Taken together, our results suggest that these RNA aptamers may serve as a platform for the future development of novel aptamer-based targeted therapies for cancer.

Biography:

Dr. Ala'a S. Shraim is an Assistant Professor at the Faculty of Allied Medical Sciences, Al-Ahliyya Amman University in Jordan. She is working in aptamer technology, particularly in developing and characterization of aptamers against kinases. She has built her expertise after years of experience in research, evaluation, and teaching in academic institutions.

Speaker Publications:

1. Shraim, A. S., Hunaiti, A., Awidi, A., Alshaer, W., Ababneh, N. A., Abu-Irmaileh, B., Odeh, F., and Ismail, S. (2019). Developing and Characterization of Chemically Modified RNA Aptamers for Targeting Wild Type and Mutated c-KIT Receptor Tyrosine Kinases. Journal of Medicinal Chemistry. doi: 10.1021/acs.jmedchem.9b00868

2. Abbaspour Babaei, M.; Kamalidehghan, B.; Saleem, M.; Zaman Huri, H.; Ahmadipour, F. Receptor Tyrosine Kinase (c-Kit) Inhibitors: A Potential Therapeutic Target in Cancer Cells. Drug Des., Dev. Ther. 2016, 10, 2443−2459.

3. Jiang, H.; Shao, W.; Wang, Y.; Xu, R.; Zhou, L.; Mu, X. Molecular Mechanism of D816X Mutation-Induced c-Kit Activation and Mediated Inhibitor Resistance in

Gastrointestinal Stromal Tumor. J. Mol. Graphics Modell. 2018, 84, 189−196.
4. Klug, L. R.; Kent, J. D.; Heinrich, M. C. Structural and Clinical Consequences of Activation Loop Mutations in Class III Receptor Tyrosine Kinases. Pharmacol. Ther. 2018, 191, 123−134.
5. Tesmer, V.; Lennarz, S.; Mayer, G.; Tesmer, J. Molecular Mechanism for Inhibition of G Protein-Coupled Receptor Kinase 2 by a Selective RNA Aptamer. Structure 2012, 20 (8), 1300−1309.
6. Bjerregaard, N.; Andreasen, P. A.; Dupont, D. M. Expected and Unexpected Features of Protein-Binding RNA Aptamers. Wiley Interdisciplinary Reviews: RNA 2016, 7 (6), 744−757.

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