Aptamer mediated selective and modulable siRNA delivery

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Résumé

Active targeting delivery, the combination of a biomolecule with a targeting ligand (Paunovska et al., 2022), is a promising strategy to deliver different kinds of drugs, in particular small interfering RNAs (siRNAs). Indeed, one major issue about siRNAs is their poor cell penetration when they are unassisted due to their negative charge, their size and their hydrophilicity (Alshaer et al., 2021). Therefore, conjugating this biomolecule with a targeting ligand would make it possible to overcome these barriers. Aptamers appear to be interesting candidates since they are single stranded DNA or RNA with a high affinity and selectivity to a specific target (Zhou et al., 2016), that can be a cell-surface receptor (Cruz Da Silva et al., 2022; Fechter et al., 2019; Mercier et al., 2017). In this study, we aim to develop selective and modulable structures associating a siRNA with one or more aptamers: an Aptamer-siRNA chimera (AsiC) and a nanotrain, to improve siRNA delivery.
First, we would like to create an AsiC combining one RNA or DNA aptamer with a siRNA. In our previous studies, we used an AsiC composed of a siRNA and an RNA aptamer, linked thanks to an RNA/RNA sticky bridge. In this study, we compared the hybridization of this AsiC with a novel one composed of the same siRNA, and the same RNA aptamer, but extended with a DNA sequence complementary to that of the siRNA to form an AsiC with an RNA/DNA sticky bridge. Our results show that the RNA/DNA binding is as efficient as the RNA/RNA sticky bridge. Second, we designed an innovative multifunctional and modulable nanotrain, inspired by the works of Cao and his team (Cao et al., 2023). Our nanotrain will be composed of one siRNA (the locomotive, also called the 'therapeutic part'), associated with one to three homo- or hetero-valent aptamers (the boxcars, also called the 'targeting parts'). The various elements will have hybridization sequences that will enable controlled self-assembly. Thanks to their versatile nature, the number, position and type of aptamers (DNA or RNA) could be easily changed. So far, we have designed RNA boxcar sequences and predicted their secondary structures using prediction softwares.

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Our preliminary results of RNA/RNA and RNA/DNA AsiC are encouraging and confirm the feasibility to combine DNA et RNA aptamers in nanotrains, new siRNA active delivery tools with great potential thanks to their selectivity and versatility. As perspectives, we wish (1) to deepen the characterization of RNA/DNA AsiC (stability and functional cell assays), and (2) characterize their intracellular traffic by bioimaging thanks to environment-sensitive fluorescent probes developed by our collaborators.

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Mots-Clés: siRNA, Aptamer, Aptamer, siRNA chimeras, Nanotrain, Active delivery strategy