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Review

siRNA-nanoparticle conjugate in gene silencing: A future cure to deadly diseases?

Rituparna Acharya [a], Suman Saha [b], Sayantan Ray [b], Sugata Hazra [a], Manoj K Mitra [a], Jui Chakraborty [b,*]

[a] Jadavpur University, 188, Raja S.C.Mullick Road, Kolkata 700 032, India
[b] CSIR, Central Glass & Ceramic Research Institute, 196, Raja S.C.Mullick Road, Kolkata 700 032, India

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ABSTRACT

Alzheimers, cancer, acquired immune deficiency syndrome (AIDS) are considered to be some of the most deadly diseases of the 21st century on account of their severity and rapid increase in the number of affected population and with scarce cases of recovery, they still remain a troubling paradox. Specifically, with millions of cancer patients worldwide and lack of proper cure for the same, understanding the deadly disease at the molecular level and planning a therapeutic strategy in the same line is the need of the hour. Further, the potential threat of prevalence and escalation of Alzheimer's and HIV (human immunodeficiency virus) infection by more than three times as of recent past, needs a medical breakthrough to arrive at a meaningful solution to tackle the present day scenario.

It is evident that these diseases initiate and propagate based on certain genes and their expression which needs to be silenced by the help of small interfering RNA (siRNA) by at least 70%. For short term silencing of the protein coding genes, siRNA is the most appropriate tool. Hence, the present communication explores the possibility for treatment and cure of a plethora of deadly diseases, *e.g.*, cancer, including Alzheimer's and AIDS to some extent, emphatically at the molecular level, using the current trend of RNAi (RNA interference) delivery *via* a wide variety of nanoparticles.

Contents

* Corresponding author.
E-mail address: jui@cgcri.res.in (J. Chakraborty).

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1. Introduction

In a chronic neurodegenerative disorder like Alzheimer's disease that accounts for millions of people worldwide having both early (4 to 5% in the age group of 30 to 60 years) and late onset, is believed to be primarily of genetic origin involving a number of genes [1]. In the early age group, different single gene mutation on chromosomes 21, 14 and 1 takes place resulting in abnormal amyloid precursor protein (APP), while at late onset, a single genetic risk factor, *e.g.*, apolipoprotein E gene on chromosome 19 has the primary role to play [2–4]. Importantly, no drug treatments are available that can cure Alzheimer's disease, except for some medications that can alleviate symptoms or slow down its progression, *e.g.*, cholinesterase inhibitors (*e.g.*, donepezil, rivastigmine and galantamine) curb the breakdown of acetylcholine in the brain, and thereby aid in the treatment regimen of Alzheimer's disease [5–7], although all of them are associated with a number of side effects. Similar are the cases of deadly diseases like AIDS or cancer, where the ailing population is treated with a large number of drugs, leading to *in situ* toxicity and enveloping multiple drug resistance (MDR). A popular example is of human immunodeficiency virus (HIV) that develops MDR against antivirals, as it mutates rapidly under monotherapy. Cancer is another well known area where combination chemotherapy using neurotoxic drugs are the usual practice to avoid MDR [8].

In the above scenario, while relentless medical research is not only looking for possible treatment measures of some of the most widespread, deadly diseases of the current century, but also exerting a high level effort to eradicate the same by approaching and understanding its molecular mechanism. Interestingly, herewith we observe that in each of the above diseases the root cause is the genes and their expression [9,10]. In this context, gene silencing is a procedure that refers to the ability of a cell for preventing the expression of specific genes as above at transcriptional or translational level [11,12]. As it is evident, it is a molecular level strategy to selectively turn off specific genes in diseased tissues and hence, inhibit the progress of the same. It is the same as gene knock down, as, when silenced, its expression is not completely eliminated but reduced, by at least 70%. Hence, this approach provides a more complete view on the development of diseases, based on the genetic expression [13–15].

There are three major categories of gene silencing, a.) transcriptional b.) post transcriptional and c.) meiotic. Of these, transcriptional gene silencing (TGS) involves sequence-specific RNA degradation by post transcriptional gene silencing (PTGS) or decreased RNA synthesis by promoter methylation [16]. Meiosis refers to gene silencing by unpaired DNA, this in turn that DNA unpaired in meiosis causes silencing of all DNA homologues including genes that are themselves paired. Of the above, the post transcriptional gene silencing is the most widely adapted category of the process involving RNA interference (RNAi), which is a biological process encompassing the RNA molecules that inhibit gene expression, destroying the specific mRNA (messenger RNA) molecules *in vitro* [17,18].

RNA interference therapy is primarily carried out using two types of small ribonucleic acid molecules, *e.g.*, microRNA (miRNA) and siRNAs. In this, siRNAs and oligonucleotides are one the most powerful tools to combat against several diseases like cancer, acquired immune deficiency syndrome (AIDS), Alzheimer's *etc.* By binding with mRNA, the RNA fragments can suppress the expression of the protein sequence specifically [19–22]. siRNAs produce RNA-induced silencing complex (RISC) after which the mRNA/siRNA duplex is degraded (Fig 1) [23,24].

siRNA forms tight complexes with the cationic nanoparticles *via* attractive electrostatic interactions [25]. During circulation and cellular internalization the siRNA must be dissociated from its cationic carrier before they are loaded into RNA-induced silencing complex (RISC) in the cytoplasm and initiate gene silencing. The physicochemical properties of the nanoparticle that dictates their molecular affinity to siRNA, can be altered by intracellular stimuli, such as change in pH in the endosome and cytosolic reducers, as a result the siRNA/polymer polyplex to disassemble. The specific changes which include the reduction of the cationic density and the molecular weight, and changes in the hydrophilicity/hydrophobicity of the nanoparticle siRNA complexes help in the dissociation of the polyplex. The protonation process and acid-responsive degradation within the endosome and glutathione (GSH)-mediated reduction in the cytoplasm, is the combination of the gradual stimuli-independent hydrolysis [25].

In last few years a number of research groups have focused on the utilization of this specific gene silencing mechanism [22,26,27] and in this regard, nanoparticles (NP) have further progressed largely. The half-life of the bare siRNAs in the systemic circulation is <5 min but when it is modified, *e.g.*, being encapsulated in liposome or tagged with cholesterol, its biological half-life enhances approximately by six times, *e.g.*, to 30 min. However, once inserted in the cell, the intracellular half-life of the siRNA is 24 h, which is enough for gene silencing [28]. Among the other hurdles of siRNA therapy, the passage of the same through the blood brain barrier for treatment of Parkinson's or Alzheimer's diseases becomes the biggest challenge [29,30], which can be readily taken care of by encapsulation of the siRNA within a nanocarrier. This serves a dual purpose of aiding a safe delivery of the encapsulated siRNAs to the target site in physiological condition, as, its bare counterpart readily degrades in the blood due to their fragile configuration [31,32].

siRNA based gene silencing mechanism is a promising area of research as it aids in a novel treatment procedure by which it can selectively reduce the expression of the disease producing genes that lead to several incurable diseases including cancer, AIDS, Parkinson's, Alzheimer's *etc.*, where the ordinary pharmaceutical formulations have normally failed (Fig. 2). Hence, herewith, the significance of the siRNAs is utmost, although, major challenges remain w.r.t siRNA stability and its delivery *in vivo*, including the need for their modification and