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Editorial

Nanotechnology- A Promising Approach for Suicide Gene Therapy

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Editorial

Cancer is one of the world's most dreadful diseases and the battle against cancer continues till date [1]. Suicide gene therapy for cancer is one of the best approaches for annihilation of cancer [2]. In brief, suicide gene codes for an enzyme which converts a nontoxic prodrug into toxic metabolites and subsequently mediates death of host cells itself on account of which it is named "suicide" gene therapy [3]. These suicide gene when constitutively expressed by the cells not only mediates death of host cells but also inflicts strong bystander effects on neighboring cells by predisposing them to toxic downstream metabolites. Due to such advantages, they manifest minimal systemic toxicity and are also effective against many drug resistance cancer cells. Among all existing suicide genes, Cytosine Deaminase (CD) and Herpes Simplex Virus-thymidine kinase (HSVtk) have shown promising results initially and has been investigated extensively since long. The HSVtk enzyme initially phosphorylates the prodrug Ganciclovir (GCV) to its monophosphate form, which is subsequently phosphorylated again by endogenous cellular kinase to generate nucleotide analogs (di- and triphosphate forms of GVC). Triphosphate form of GCV is then readily incorporated into DNA during the course of DNA synthesis and acts as a chain terminator to prevent further DNA synthesis, which ultimately induces cell death [4].

The therapeutic efficacy of HSVtk suicide gene therapy is often limited by cell-to-cell contact which is a prerequisite for transport of downstream metabolic byproducts of ganciclovir to neighboring cells so as to attain bystander-killing effect. As an outcome of such drawbacks, HSVtk suicide gene does not seem to be effective against different cell types [5]. In contrary to this, Cytosine Deaminase (CD) efficiently converts prodrug 5-Fluorocytosine (5-FC) into therapeutically active anticancer agent 5-Fluorouracil (5-FU), which subsequently permeates across the cell membrane to mediate bystander killing effects on adjacent neighboring cells [6]. Thus, 5-FC/CD system attains suicide gene therapy much more efficiently as compared to other counterparts. Although 5-FC/CD system attains better therapeutic outcomes, it is ineffective against 5-FC resistant cancer cells and thus its anticancer potential could not be generalized for all cancer types. In order to overcome such drawback, Gopinath et al. have designed Cytosine Deaminase-Uracil Phosphoribosyltransferase (CD-UPRT) bifunctional suicide gene construct in which Uracil Phosphoribosyltransferase (UPRT) acts upon product of CD i.e. 5-FU and converts it further into other toxic metabolites [7].

The therapeutic effect of suicide genes can be enhanced by combinatorial approaches. In combination therapy, two or more drugs with similar or different mode of action are employed to realize synergistic anticancer therapeutic potentials. Such synergistic anticancer potential of combination of radiation therapy and 5-FC/CD plus UPRT gene therapy was demonstrated by Kambara et al. against malignant gliomas [8]. Apart from this, the combination therapy also provides scope for exploiting radio sensitizing properties of 5-FU and by stander effects during the course of treatment [9-11]. Many research groups have reported the use of suicide gene in combination with chemotherapy and radiation to enhance the therapeutic effect and to overcome the drug resistance. Gopinath et al. were the first to report the applications of silver nanoparticles for synergizing the therapeutic effect of suicide gene [12]. They have also reported the synergistic therapeutic effect of suicide gene with anticancer drug curcumin. One of the major challenging tasks in suicide gene therapy is lack of suitable vectors for targeted delivery of suicide gene to cancer cells. The application of such DNA-based therapeutics is largely limited due to poor cellular uptake, degradation by serum nucleases and rapid renal clearance following systemic administration. In addition to these, organ specific targeted DNA therapy has been a major challenge to overcome off-target gene therapy. In order to circumvent these limitations, numerous organ specific targeted nanocarriers have been developed recently for systemic administration.

With the advent of nanotechnology, numerous nanomaterials have found promising application in health care industry [13,14]. Such nanomaterials have revolutionized cancer diagnosis and therapy and tissue engineering etc. In the recent past, several researchers developed variety of nanomaterials with high gene transfection efficiency and low toxicity (Figure 1). These nanoparticles can be targeted to cancer by passive targeting and active targeting. Passive targeting can be achieved by using polymeric nanoparticles which are known to accumulate at tumor site due to Enhanced Permeation and Retention (EPR) effect, which results in passive accumulation in solid tumor tissues. Other major advantages of polymeric nanoparticles are biodegradability and biocompatibility, and prolonged circulation time in the bloodstream. Active targeting can be achieved by incorporating tumor specific antibodies or peptides.

Only few studies have been carried out till date for delivering suicide genes using nanoparticles. Aoi et al. transduced HSVtk gene in to cancer cells using nanobubbles and ultra sound [15]. Hattori and Maitani developed a folate-linked nanoparticle for

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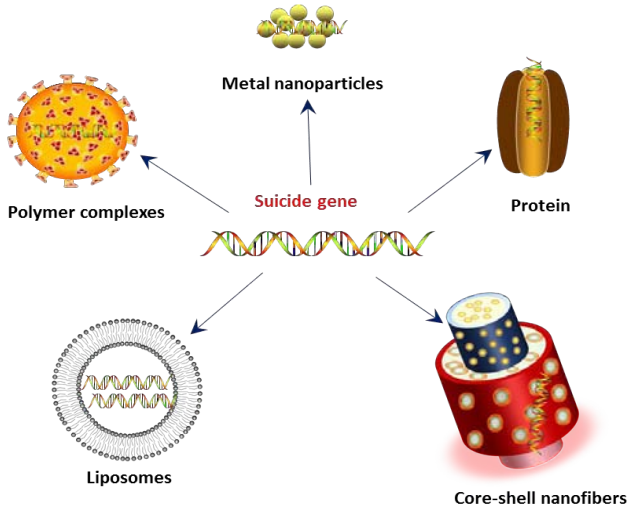

Figure 1: Different nano-carriers used for suicide gene therapy.

targeted delivery of HSVtk gene in to human prostate cancer and nasopharyngeal cancer cells for *in vitro* and *in vivo* suicide gene therapy [16]. Yu et al. developed poly(ethylene-glycol)-poly(γ-benzyl-L-glutamate) (PEG-PBLG) based nanocarrier for delivering HSVtk gene to Oral Squamous Cell Carcinoma (OSCC) cells and studied the therapeutic effect both *in vitro* and *in vivo* [17]. Recently, Yuan et al. used magnetic nanoparticles for the targeted delivery of suicide genes to cancer cells [18]. They have combined suicide gene therapy and magnetic hyperthermia methodology to treat cancer. Multifunctional nanoparticles hold great promise for suicide gene therapy as it can deliver suicide gene along with imaging probe for simultaneous diagnosis and therapy of cancer. Nanoparticles with such dual functions are named as theranostic nanoparticles. Sanpui et al. synthesized chitosan stabilized ZnS: Mn^{2+} QDs as a nanocarrier for delivery of CD-UPRT suicide gene which could be a promising approach for real-time monitoring of gene delivery [19]. Jaiswal et al. synthesized folic acid conjugated chitosan based theranostic nanocarriers for simultaneous delivery of ZnS QDs and CD-UPRT suicide gene for imaging and therapy, respectively [20]. Sahoo et al. synthesised multicolor fluorescent emitting gold nanoclusters for CD-UPRT suicide gene delivery [21]. As these metal nanoparticles are often associated with cytotoxicity, their long term application is very limited. Recently, Chen et al. transfected HSVtk gene in to prostate cancer cells using generation 5 poly (amidoamine) dendrimers as a polymeric nanocarrier [22]. The use of biofriendly polymeric nano carriers for targeted delivery of suicide gene and imaging agents could also be a promising approach for suicide gene therapy. Development of such nanomaterials has enormous potential applications and implications in cancer theranostics (diagnosis and therapy).

Serum albumin has become a promising carrier for diverse therapeutic molecules due to its biocompatibility and low immunogenicity [23,24]. In this quest, cationized albumin has been used as non-viral vector for gene delivery. The presence of cations over albumin enables stable polyplex formation with plasmid DNA by spontaneous self-assembly process and which subsequently attains efficient transfection when supplemented with chloroquine mediated endosomal escape [25]. Similarly, Faneca et al. reported use of albumin associated cationic liposomes for delivery of HSVtk/GCV suicide gene and consequently reported their synergistic antitumoral effect with vinblastine [26]. As an alternative approach, Orson et al. have synthesized PEI-albumin conjugates for improved gene delivery [27]. In the recent past, apart from PEI, dendrimer with similar functional groups is also been sought as carriers for gene delivery [28]. The Generation 5 Poly (Amidoamine) Dendrimers (G5-PAMAM-D) was observed to double the efficiency of suicide gene therapy (HSVtk /GCV fused with Cx43) against human prostate cancer cells both *in vitro* and *in vivo* [29].

Apart from these carriers, polymeric scaffolds like electrospun nanofibers and gels are also explored for controlled and sustained gene therapy [30-34]. Although nanofibers versatility for gene therapy has been studied since long, their role in suicide gene delivery was not explored until recently [35]. In pursuit of this, Sukumar et al. have fabricated core-shell bPEI-PEO nanofibers for efficient transfection of suicide gene (Cytosine Deaminase-Uracil Phosphoribosyltransferase (CD::UPRT)) and also manifested subsequent time resolved delivery of prodrug(5-Fluorocytosine (5-FC)) [36]. Such composite scaffold for simultaneous delivery for suicide gene and prodrug could efficiently manifest by-stander effects of suicide gene and attained improved anticancer therapeutic potential. As an outcome of rapid development of such diverse nano-carriers for gene delivery, anticancer efficacy of suicide gene therapy has improved drastically.

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