Editorial

Nano-Enabled Approaches for Lung Cancer Therapy

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Editorial

According to the GLOBOCAN estimates lung cancer is the most frequently diagnosed cancer (13% of total diagnosed cancers) and the leading cause of cancer-related deaths worldwide [1]. Lung cancer is classified into Non-Small-Cell Lung Carcinoma (NSCLC), which attributes to the 85% of the diagnosed cancer, while remaining 15 % cases are assigned as Small-Cell Lung Carcinoma (SCLC). Existing strategies relies on the type and stage of malignancy and often comprise a combination of conventional therapies. Since the late 1990s, chemotherapy regimens including the platinum-based drugs such as carboplatin and cisplatin either alone or in combination with other anticancer drugs emerged as a first-line treatment option for advanced-stage lung cancer. Due to the hydrophobic nature of the existing cancer chemotherapeutics, high doses have been administrated which results in severe side effects [2,3]. To mitigate many of these untoward effects, various strategies have been employed, which includes the tumor-targeted delivery of therapeutic molecules that enhanced the drug efficacy and reduced toxicity to normal tissues [4]. Moreover, various experimental therapies such as immunotherapy, gene therapy and Photodynamic Therapy (PDT) either alone or in combination with conventional therapy or surgery emerged as a potential tool to fight lung cancer. Photosensitizer, like porfimer sodium has been employed in the treatment of early as well as advanced lung carcinomas. However, the poor water solubility of these photosensitizers restricts their intravenous administration [5]. Moreover, the immunologically active agents harnessed in immunotherapy, either trigger the immune system or hinder the immune suppressing activities of the tumor by interrupting the tumorigenic cascades [6]. In recent past large number of cancer suppressing genes has been identified for gene therapy. However, the delivery of these therapeutic genes still remains a major challenge among the scientific community. Previously, viral vectors have been exploited to deliver gene-based therapeutics [7]; but viral vector induced host immune responses restrict their future implications [8,9]. In concern, to develop a safe and effective delivery system, nanotechnology provides a potential platform by overcoming the various limitations associated with traditional delivery systems. The nano-scale delivery systems revolutionized the cancer treatment by enhancing the therapeutic efficacy of anticancer agents [10]. Moreover, the possibilities of functional modifications of these nanoparticles enhance their therapeutic efficacy by attenuating their non-specific bio distribution. In addition, these nano-sized particles also offers several advantages when compared to the standard solvent based drug formulations, such as enhanced payload, protect therapeutic cargo molecules from biodegradation, prolonged circulation time, enhanced solubility and chemical stability, enhanced intratumoral accumulation and diminished side effects.

To date, many nano-enabled technologies have been developed for lung cancer therapy and few of them have been proved to be a clinical breakthrough [11]. Among them the most prominent ones are: liposomes, polymer and protein based nano-approaches as shown in Figure 1.

Liposomes based nano-approaches

Liposome is one of the most successful delivery system with several FDA-approved nanoformulations in the market. Liposomes are closed spherical structures composed of one or more lipid bilayers made up of amphiphilic phospholipids and cholesterol that allows the storage of hydrophobic drugs, while the aqueous core are responsible for holding hydrophilic drugs [12]. The liposome enhanced the solubility of hydrophobic anticancer agents, extends their circulation time and enhanced their chance of intratumoral uptake.

Stealth [TM]PEGylated liposomal doxorubicin (Doxil or Caelyx), was among the FDA approved nanoparticles for cancer therapy. In phase I/ II study, Doxil in combination with other conventional therapy and supportive growth factors revealed significant results in Small Cell Lung Cancer (SCLC) and NSCLC patients [13-17]. Similarly, PEGylated liposomal formulation of irinotecan (PEP02, or MM-398) offer higher drug load, prolonged circulation and stability as compared to standard irinotecan [18]. In preclinical models, compared to standard irinotecan, MM-398 exhibited higher antitumor efficacy and lower toxicity in squamous cell lung cancer and small cell lung cancer models [19]. PEGylated liposomal cisplatin (Lipoplatin[TM]), originally designed by Regulon, Inc. Mountain View, CA, USA has been extensively examined in NSCLC treatment in Europe. Lipoplatin[TM] exhibited higher antitumor efficacy, higher intratumoral concentrations and lesser toxicity as compared to standard cisplatin [20]. Apart from it, the liposomal aerosolized formulations have been extensively explored for lung cancer therapy. The liposomal formulation of 9-nitrocamptothecin shows higher efficacy, negligible side effects compared to free drug [21]. Similarly, liposomal aerosolized formulation of anticancer drug, cisplatin (Sustained Release Lipid Inhalation Targeting, SLIT) showed higher accumulation in lungs and comparable cytotoxicity to free cisplatin both in human tumor cell line (NCI-H460) and Sprague-Dawley rats, respectively [22].

Polymers based nano-approaches

Polymeric nanoparticles are solid colloidal systems consists of polymer matrix made up of natural polymers such as chitosan, heparin etc. or synthetic polymers such as Polyethylene Oxide (PEO),
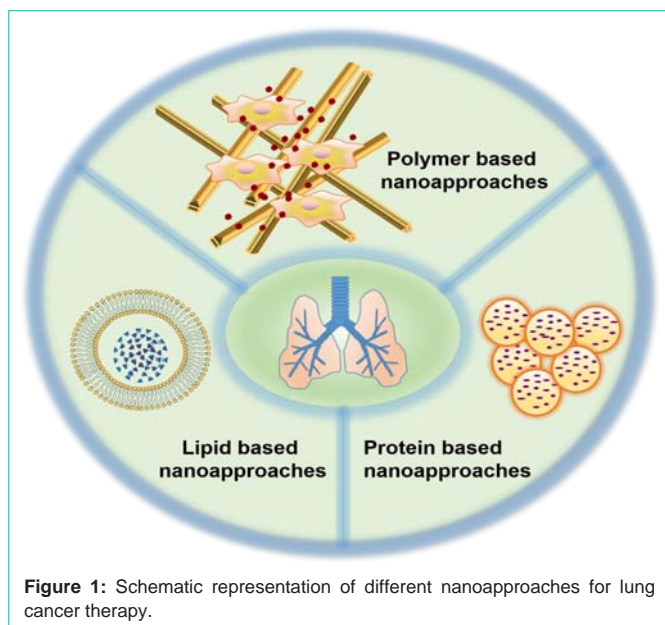

Figure 1: Schematic representation of different nanoapproaches for lung cancer therapy.

Polycaprolactam (PCL), poly (D,L-lactide-co-glycolic) acid (PLGA) etc. to which various therapeutic, imaging and targeting moieties are either covalently linked or encapsulated within [11].

Genexol-PM (Cynviloq) is a paclitaxel loaded polymeric micelle formulation consist of a monomethoxy polyethylene glycol-poly (D, L-lactic acid (mPEG-PDLLA) amphiphilic dib lock copolymer, originally designed by Sam yang Co, Seoul, Korea. Preclinical studies showed that the Genexol-PM either alone and in combination with other therapeutic drugs have higher antitumor efficacy, enhanced biodistribution, higher maximum tolerated dose and lesser toxicity issues as compared to other standard solvents based paclitaxel formulations and has been approved for NSCLC treatment in South Korea [23-25]. NC-6004 is another polymer based nano-approach comprised of hydrophilic PEG outer shell and contains a coordinate complex of polyglutamate [P(Glu)] with cisplatin in the inner core [26]. This polymeric nanoformulation offers extreme stability in distilled water, prolonged plasma circulation, lesser toxicity, enhanced intratumoral accumulation and has higher drug holding capacity as compared to standard cisplatin and other cisplatin-containing polymeric micelles [27,28].

Recently, polymeric nanofiber based scaffolds have been extensively exploited for the controlled and sustained delivery of various therapeutic molecules either alone or in combination with other bioactive molecules [29,30]. Moreover, an alternative approach has been investigated by developing a composite core shell nanofibrous scaffold that can efficiently transfect suicide gene in nonsmall lung cancer cells (A549) and simultaneously deliver prodrug, 5-Fluorocytosine (5-FC), which has been metabolically converted into toxic intermediates by the Cytosine Deaminase-Uracil Phosphoribosyltransferase (CD::UPRT) suicide gene expressing A549 cells [31].

Protein based nano-approaches

Proteins have numerous unique features that make them an ideal drug delivery vehicle. The major advantages associated with protein nanoparticles includes their biocompatibility, biodegradability, ability to interact with large number of hydrophobic molecules and enhance the solubility and bioavailability by their controlled release.

Among various protein nanoparticles, albumin nanoparticles based approaches have been widely explored [32,33]. The albumin bound nano-formulation of anticancer drug paclitaxel also known as Abraxane was the first FDA approved nanomedicine for treatment of advanced/metastatic NSCLC. In preclinical trials, the Abraxane either alone or in combination with other therapeutic agents shows higher therapeutic efficiency and lesser side effects as compared to the organic solvent based paclitaxel due to higher drug loading capacity and enhanced bioavailability [34-36]. Recently, a self assembled inhalable albumin nanoparticles conjugated with doxorubicin and octyl aldehyde and adsorbed with apoptotic TRAIL (Tumor Necrosis Factor (TNF)-related apoptosis-inducing ligand) protein has been fabricated for treating drug-resistance lung cancer [37]. Similarly, a biotinylated-EGF-modified cisplatin-loaded –Gelatin Nanoparticles (GNP) has been developed that exhibit enhanced anti-tumor activity and was less toxic than free cisplatin, *in vivo*. Moreover, aerosol delivery of these targeted nanodrug carrier leads to enhanced cisplatin accumulation in cancerous lungs [38]. Moreover, the gelatin nanoparticles have been extensively exploited for the delivery of hydrophilic and hydrophobic anti-cancer drugs such as resveratrol [39], curcumin [40] etc. for lung cancer therapy. In sum, these exciting nano-enabled approaches will serve as a foundation for the future lung cancer therapy.

Acknowledgement

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