Abstract

Design and synthesis of cationic polymers and evaluation of their in vitro anticancer activity

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Cancer is one of the leading causes of death worldwide. As the cancer burden continues to increase globally, it exerts tremendous physical, emotional, and financial strain on individuals, families, communities, and health care systems. Cancer can affect any part of the body and is characterized by its uncontrollable growth. Numerous treatments, such as radiation therapy and chemotherapy which utilize various drugs, are currently in use; however, their harmful side effects and the development of drug resistance have resulted in major roadblocks when treating cancer. With advancements in synthetic and polymer chemistry, the use of nanoparticle-based drug delivery systems and chemotherapeutic macromolecules have garnered increasing attention in the previous decade. Unfortunately, nanoparticle drug delivery systems are based on the activity of the drug itself and hence suffer from inherent limitations of the drug along with cellular barriers, burst release, significant off-target toxicity and resistance development. So, better therapeutic strategies are sought in clinics, which will help improve overall survival, reduce treatment side effects, increase patient compliance, and improve disease management and outcome. With the known limitations of small-molecule drugs and conventional drug delivery systems, the potential use of polymeric molecules as anticancer agents could be a game-changer in the field of polymer-based biopharmaceuticals. In this research I was focusing on these cationic polymers and evaluation of their biological activity against various cancer cell lines.

To resolve the issue related to the limitations of the small molecule drugs and the nanotechnology-based drug-delivery systems, the primary aim of this thesis is to develop anticancer cationic polymers. To this end I synthesized the cationic polymers containing the hydrophobic groups in them. We describe the design and synthesis of novel anticancer polymers containing hydrophobic groups. I established the fact that the cationic homopolymer of (3-acrylamidopropyl)trimethylammonium chloride does not show any anticancer activity on its own; however, the insertion of hydrophobic moieties (n-butyl methacrylate, n-hexyl methacrylate, n-octyl methacrylate) in copolymers enhances their anticancer activity with very low IC_{50} value. Also, I carried out the mechanistic investigation of the interaction between the cationic homopolymers and the copolymers with the cancer cell membrane and proved that the hydrophobicity enhanced the interaction along with enhanced cytotoxicity.

Further, I designed and developed systems comprising both a cationic charge and hydrophobic moieties with a focus on selectivity toward normal cells. A series of poly-L-lysine and nicotinic acid-based polymers with varying amount of dodecylsuccinic anhydride was synthesized. To obtain the selectivity, the cationic charge of polymers was concealed by coordination with the Zn^{2+} ions. The Zn-bound polymers were found to be highly selective and effective against the cancer cell lines use. Also, they exhibited potent anticancer activity against the drug resistance cell line (COR-L23/R). The obtained polymers were found to be effective when compared with the small molecule drug like doxorubicin and prevents the further tumour metastasis. Considering the easy synthetic route, availability and biodegradability of these polymers could proves to be a promising approach towards cancer treatment.

Next, I convert the bioactive anticancer compound methyl jasmonate a small molecule into the cationic polymer or to copolymerize it with the cationic monomers. For this purpose modified methyl jasmonate to the monomer and then further copolymerised it with (3-acrylamidopropyl)trimethylammonium chloride. The obtained copolymers showed the enhanced cytotoxicity towards the cancer cell lines when compared to the MJ alone. In order to obtained the selectivity the PEG-based copolymers of methyl jasmonate and the (3-acrylamidopropyl)trimethylammonium chloride were synthesised. The PEG-based copolymers showed enhanced selectivity and the better anticancer activity.

Lastly, I summarised the findings of each chapter. Also, I gave and outlook for each chapter for the further utilization of the research worked performed during this PhD.

Keywords: Anticancer agents, Cationic polymers, Membrane-polymer interaction, Hydrophobicity, Metal-coordinated polymers