Chapter II

Scope of the investigation

There is a great interest in understanding the factors that control the binding of metal ions to nucleic acids. This has been fuelled to a great extent by the success of several platinum complexes that exert anticancer activity by forming covalent adducts with the purine bases of DNA. In addition, metal complexes that can bind to DNA via non-covalent interactions, such as intercalation, groove binding and electrostatic binding have also attracted interest as antitumor agents. Ribonucleic acid once considered basically as intermediary between genomic information and the primary sequences of proteins has been now found essential for transcriptional and translational regulation and also proteins synthesis. This recent explosion in RNA biology underscores the importance of RNA and highlights the potential of targeting RNA for the treatment of a multitude of disease states. Metal complexes that can bind selectively to RNA may provide novel points of therapeutic intervention. RNA targets may be the best and only option due to the intractability of targeting certain segments of proteome and the inherent difficulty of targeting DNA.

Copper and ruthenium complexes are considered as promising alternatives to platinum complexes as anticancer drugs. Copper is an essential transition element that plays a fundamental role in the biochemistry of all aerobic organisms and, therefore, it is involved in many biological pathways. Also, serum copper levels correlate with tumor incidence, tumor weight, malignant progression and recurrence in a variety of
human cancers: Hodgkin’s lymphoma, sarcoma, leukemia and cancer of the cervix, breast, liver, lung as well as brain tumors, supporting the idea that copper could be used as a potential tumor-specific target. Several copper complexes have been now projected as potential anticancer substances and cancer chemopreventive agents, as they demonstrate remarkable anticancer activity and show general toxicity lower than platinum compounds. Recently, copper(II) complexes having amino acids and their derivatives as ligands have been shown to serve as bioinorganic model compounds to illustrate DNA binding and DNA cleavage abilities.\textsuperscript{18} Most of these complexes have monopositive charge due to the presence of amino acid ligand.\textsuperscript{19-21} These monopositively charged complexes are expected to be more lipophilic than the corresponding dicationic complexes, thereby providing for greater uptake by cells and enhanced cytotoxicity.

Recently there are reports on the high efficiency of binuclear and trinuclear copper(II) complexes in binding to and cleave DNA compared to their corresponding monomeric complexes.\textsuperscript{22-24} In the case of binuclear copper(II) complexes it has been proposed that while one part of the complex binds to DNA by partial intercalation, the other one makes favorable contacts in the minor groove. Pendant type polymer-metal complexes are compounds containing many units of metal complexes attached to a single polymer back-bone and the bonding between polymer and the metal complex part is through coordination mode. These attachments of complex units on the polymer are expected to exert more binding strength into the metal complex part for DNA binding because of the possibility of the co-operative effects between complexes units to bind to DNA. Recently there are some reports on such kind of
binding between polymer-metal complexes not much work is available in the literature on these studies.\textsuperscript{25-28}

Polyethyleneimine (PEI) and other polycations are good vehicles for transferring genes into the cells. The metal complexes represent a prodrug, from which the active agent is hydrolytically or enzymatically released into the predestined biological environment, which, for anticancer action are the cytoplasmic lysosomes and cell nuclei. Among various polymers, polyethyleneimine (PEI) has different molecular weights associated with different transfection efficiencies.\textsuperscript{29} The ability of DNA condensing properties and proton-sponge effect of PEI are important factors for gene delivery,\textsuperscript{30} whether genes may be delivered into cytoplasm \textit{via} endocytosis or targeted to the nucleus.\textsuperscript{31} Only the PEIs larger than 10 kDa have been used successfully in transfection efficiency and the branched PEI of 25 kDa are the most effective transfection reagents used \textit{in vitro} and \textit{in vivo}.\textsuperscript{32}

The interaction between DNA and cationic surfactants has attracted immense interest in the separation and purification of DNA. Recently, there are several reports on the interaction of surfactants with DNA. These interactions have been proposed to be similar to surfactant-polymer interactions.\textsuperscript{33-37} Interest in the mechanisms of the interaction of cationic surfactants with nucleic acids is associated with the fact that the cationic surfactant-DNA complexes can be used for translocation of DNA across cell membranes for the gene therapy.\textsuperscript{38} Surfactant-metal complexes are considered as a new class of materials with hydrophilic head part with metal centre and hydrophobic tail part. The incorporation of metal complexes into amphiphilic structure is attracted due to their application in magnetic and catalytic and biological activities. While a
large number of studies have been dedicated to interaction between DNA and conventional surfactants, not much work has been done on the interaction of these surfactant-metal complexes with nucleic acids.

Therefore, a study on “Polyethyleneimine-anchored copper(II) amino acid complexes and surfactant-copper(II) Schiff base complexes: synthesis, DNA/RNA binding, cytotoxic and antimicrobial studies” is undertaken.

References
2. Y. Wang and J.-F. Chiu, Metal-Based Drugs, 2008, 1


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