Chapter I

Introduction

Deoxyribonucleic acid (DNA) is the genetic material of the cell, while ribonucleic acid (RNA) is the intermediary or messenger and proteins regulate cellular functions through proteins. DNA, RNA and proteins all play essential roles in the cell and are therefore potential targets for therapeutic intervention.\textsuperscript{1-4} Modern-day medicinal chemistry is focused on the modulation of protein function. During cell growth, all the three types of macromolecules are synthesized. DNA is replicated, leading to the synthesis of exact copies. The information in DNA is transcribed into complementary sequences of nucleotide bases in RNA; this RNA containing the information for amino acid sequence of the protein is called messenger RNA (mRNA). Messenger RNA is then translated using the specific protein-synthesizing machinery of ribosome and the translation product is protein. Nucleic acids have valid, yet potentially more challenging, therapeutic sites due to their early role in disease-related pathways and hence they considered as attractive drug targets.\textsuperscript{5-7} By designing drugs that alter processes at the nucleic acid level, the biosynthesis of harmful proteins can be modulated. Furthermore, since DNA is transcribed into larger quantities of RNA which is subsequently translated into an even greater abundance of a protein, a statistical advantage may be gained by targeting nucleic acids rather than proteins and their functional gene products.
1.1. Structure of DNA and RNA

Nucleic acids are chain-like macromolecules which are composed of pyrimidine and purine bases, sugars and phosphates. The four bases characteristic of deoxyribonucleotide units of DNA are the purine derivatives, adenine (A) and guanine (G) and the pyrimidine derivatives, cytosine (C) and thymine (T). Similarly, RNA too has four characteristic bases, adenine, guanine and cytosine and uracil instead of thymine. Also the pentose sugar in RNA is ribose whereas it is deoxyribose in DNA. The purine and pyrimidine nitrogenous bases are called nucleobases. A base linked to a sugar is called a nucleoside; when a phosphate group is added to the base-sugar unit it is called a nucleotide (Fig. 1.1). Nucleotides provide the building blocks from which nucleic acids are constructed. The nucleotides are linked into a polynucleotide chain by alternating sugar and phosphate residues, which form the backbone. The 5'-position of one pentose ring is connected to a 3'-position of the next pentose ring via a phosphate group. Thus the sugar-phosphate backbone consists of 5',3' phosphodiester linkages.
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Fig. 1.1. Structure of nucleobases, nucleoside and nucleotide in DNA and RNA
1.1.1. DNA

The DNA model proposed by Watson and Crick contains two polynucleotide chains wound into a right-handed helix wherein the phosphodiester bonds of the DNA chains run in opposite direction i.e., they are antiparallel. One strand runs in the 5'-3' direction while the other runs in the 3'-5' direction (Fig. 1.2). There is specificity of hydrogen bonds whereas between bases: adenine pairs with thymine with three hydrogen bonding and guanine pairs with cytosine with two hydrogen bonds. Such specificity in pairing is known as base pairing. The ability of DNA to form a double helix is of prime importance in considering its function in the cell. The double helical structure immediately suggests a mechanism for the accurate replication of genetic information.
Fig. 1.2. Polynucleotide chain and double helix structure of DNA
1.1.2. DNA conformation

The DNA double helix has three structurally characterized conformations, i.e., A, B and Z forms (Fig. 1.3). These three conformation structures are all double helical in nature and rely upon the Watson and Crick hydrogen bonding interactions between the two antiparallel strands of nucleic acid. However, the resulting shapes of the conformations are different.

The B form, considered to be the most common is a right-handed helix, with base pairs stacked in the centre of the helix and average base plane aligned normal to the helical axis. A remarkable and biologically important structural feature of B-DNA is the presence of the two grooves in the outer envelope of the double helix. The grooves, called the major and minor grooves, are of different width and depth, and are a consequence of the glycosyl bonds between the sugars and bases of a given base pair not being directly opposite to one another, i.e., the asymmetric attachment of the base pair to the backbone results in a groove becoming wider than the other thereby leading to the major and minor grooves.

The A conformation is also a right-handed helix, but it is distinctly different from B conformation with respect to the helical grooves. Due to the sugar puckering, the bases are pushed outward towards the minor groove and are tilted substantially with respect to the helix axis. Thus the helix has very a deep major groove and virtually no minor groove as it is pulled deeply into the interior of the structure thereby becoming inaccessible to the molecules in solution.

The Z-DNA is the third form and is characterized structurally by a double helical conformation. This conformation is distinctly different since it spirals into a
left-handed rotation. The repeating unit is a dinucleotide, resulting in a zigzag helix, because of the alteration in sugar pucker and disposition of the bases about the glycosidic bond.

The nucleotides alternate in syn and anti conformations of the bases. Since the syn conformation is more stable for purines than for pyrimidines. In B DNA, all of the nucleotides have the anti conformation and a c2' endo pucker of the deoxyribose ring. Z DNA displays a syn-anti alternation in base geometry and an alternation in base geometry and an alternating c2' endo, c3' endo sugar puckering, both of which lead to the overall zigzag geometry of the helix characteristic of the Z DNA. Also the helix is long and slender than the A or B DNA forms.

The conformation of DNA is dependent on humidity, salt content, and base pair composition. The most important biological form of DNA is B, which is present in aqueous solution and in cells but Z DNA has also been observed in the cell. The major finding is the formation and stabilization of Z DNA by negative super coiling. It has also been proposed that the energy necessary to form and stabilizing Z DNA in vivo can be generated during the transcription process.
Fig. 1.3. The structures of A, B and Z DNA
1.1.3. Modes of binding

Transition metal complexes/small molecules/drug can interact with DNA via different binding modes.\textsuperscript{8-11} (Fig. 1.4)

- Intercalation binding
- groove binding
  - Major groove binding
  - Minor groove binding
- Electrostatic/external binding

Fig. 1.4. Schematic diagram of different modes of binding in DNA
1.1.3.1. Intercalation binding

Intercalation binding results when a small molecule or the drug interacts into the non-polar interior of the DNA helix. Aromatic group is stacked between the base pairs in this type of binding. This happens when ligands of an appropriate size and chemical nature fit themselves in between base pairs of DNA. The ligands suitable for interaction are mostly polycyclic, aromatic, and planar and therefore often make good nucleic acid stains (Fig. 1.5). There is a current interest in designing and synthesizing the DNA strand, as these molecules might function as chemotherapeutic agents.

![Intercalation mode of binding of metal complex and organic molecules](Image)

**Fig. 1.5.** Intercalation mode of binding of metal complex and organic molecules

1.1.3.2. Groove binding

Groove binding involves direct interaction of the bound molecule with edges of base pairs in either of the major (G-C) or minor (A-T) grooves of the nucleic acids (Fig. 1.6). The antibiotic netropsin is a model groove binder in which methyl groups
prevents intercalation. Binding within the major grove of the double helix is rare for small molecules.\textsuperscript{13-15}

Fig. 1.6. Groove binding molecules and metal complexes

1.1.3.3. Electrostatic/external binding

This type of interaction happens in the case of positively charged molecules (Fig. 1.7) interacting with negatively charged phosphate backbone of DNA chain. Electrostatic interaction is generally weak under physiological conditions. Cations such as Mg\textsuperscript{2+} usually interact in this way.\textsuperscript{16}

Fig. 1.7. External/electrostatic interacting molecules of metal complexes and metal ions
1.1.4. Structure of tRNA

RNAs are typically single-stranded molecules. However, they may have complementary regions that interact by base-pairing to form short stretches of A-form helix. An example of this is the cloverleaf secondary structure model of tRNA (Fig. 1.8). The crystal structure of tRNA elucidates other important regions such as the D-loop, anticodon, variable loop, $\Psi$C loop and acceptor stem. Like proteins, RNAs have tertiary structure, and in tRNA, the interactions responsible for tertiary structure are made between residues far away from each other in the primary sequence.

In phylogenetic sequence comparisons, these residues have been identified as highly-conserved positions and are, virtually identical in all tRNAs. Phylogenetic comparisons have been made with small subunit-ribosomal RNAs and with large-subunit RNAs. These large, stable RNA molecules play a key role in protein synthesis, a fundamental cellular reaction.
Fig. 1.8. Secondary and tertiary structures of tRNA
1.1.5. RNA interaction mode

Ribonucleic acid (RNA) is an essential macromolecule that has diverse functions \textit{in vivo}. For example, RNA regulates transcription, translation, catalyzes protein synthesis and controls gene expression.\textsuperscript{17-19} Many of these functions have been uncovered, increasing the number of potential RNA targets for small molecule chemical genetics probes or therapeutics. Despite these discoveries, there are comparatively few compounds that target RNA with high affinity and specificity. This is in contrast to the large number of small molecules that target and modulate the biological function of DNA and protein.\textsuperscript{20} Although there are nearly 100 naturally occurring modified nucleotides in RNA,\textsuperscript{21} it is transcribed from only four nucleobases. In this regard, RNA is chemically similar to DNA and less complex than protein. There are far fewer examples of small molecules that target RNA grooves. This is likely due to the fact that the major groove of an A-form RNA helix is deeper and narrower than the major groove in B-form DNA, while the minor groove is shallower. The 3-dimensional structures that DNA and RNA adopt in vivo are very different. DNA is typically helical due to double stranded structure whereas RNA folds into diverse structures, adopting folds that are more similar to proteins. This is because RNA is single stranded and folds onto itself to minimize its energy. RNA structure often has unique binding pockets for small molecules and its structural diversity could be exploited to design small molecules that specifically target RNA of interest. To date, the most well described binding of small molecules to a highly structured RNA is the binding of antibiotics to the ribosome.\textsuperscript{22} Because RNA’s structural diversity should provide the potential for selective recognition by small molecules, targeting RNA could be a strategy for treating diseases. However, there is
a dearth of information about the chemical scaffolds that are privileged to bind RNA. The end result is that high-throughput screening campaigns for RNA targets are far less successful than protein targets because small molecule libraries employed in these efforts are biased for binding proteins.

### 1.2. Polyethyleneimine

Polyethyleneimine (PEI) is known to exist in two forms (Fig. 1.9), either as a linear structure (LPEI) or highly branched (BPEI). The structure generally depends on the synthetic procedure. BPEI is commercially available,\(^{23}\) whereas LPEI has to be synthesized by a quite lengthy process. It has been found that BPEI is, for most purposes, a more useful ligand than LPEI as the complexes of BPEI are usually more stable and also more soluble in aqueous solution. BPEI is therefore investigated more frequently than LPEI.\(^{24}\) The ratio of primary, secondary and tertiary amine groups in BPEI is \(ca. 1:2:1\). In contrast to LPEI, which shows a high degree of crystallinity, BPEI is amorphous because the high number of branches prevents crystallization. There is experimental evidence that branching sites are separated mainly by secondary amine groups, with about one branch for every three nitrogen atoms within a linear part of the chain, as depicted in Fig. 1.9.
In recent years, there has been growing interest in water-soluble polymers as ligands for metal ions because polymer metal complexes are not only excellent models for metalloenzymes, but they could also lead to the development of interesting new materials. Furthermore, the study of the interaction of metal ions or metal fragments with synthetic macromolecules can give much insight into the binding of metal ions to biomacromolecules and upon the role and activity played by metal ions in the treatment of diseases.25

PEI has a number of properties which makes it a noteworthy complexing agent,26 e.g.

- Good water solubility provided by the hydrophilic amine groups, and therefore its metal complexes are also water soluble;
- High capacity for metal uptake due to high local concentration of functional groups;
High molecular weight, which allows an easy separation, by the usual methods (e.g. membrane filtration) of polymer metal complexes from low molecular weight species present in solution;\textsuperscript{27-29}

- Good chemical and physical stability;
- Reversible complexation is easily achieved for labile metal ions with acids and stronger ligands;
- High flexibility of the molecular conformation enables it to achieve an optimum configuration for complex formation;
- The behaviour of aqueous solutions of the PEI molecule is largely determined by the combined action of the inert parts of the molecule causing hydrophobic interactions and of the polar amine groups causing hydrophilic interaction with the solvent.

1.3. Polymer-metal complexes

The first report of the metal-complex formation of a polymeric amine in the literature in 1963 concerned the binding of Cu\textsuperscript{2+} and Ni\textsuperscript{2+} by branched polyethyleneimine.\textsuperscript{30} Such complexes are highly water soluble and can, in principle, be investigated by conventional solution chemistry methods. It is therefore quite surprising that relatively few investigations of the interaction of metal ions with such polymeric ligands have been carried out, despite the fact that binding of a metal ion by a polymer has some very interesting aspects and even high potential for applications.\textsuperscript{31-42} There are many reports in which some kind of interaction between polymeric amines and metal ions was observed, yet rarely was this interaction investigated by methods generally used in coordination chemistry.
A polymer-metal complex is a coordination complex formed between a metal ion and a ligand function anchored on a polymer matrix (Fig. 1.10). These polymer-metal complexes can be obtained by the reaction between a polymer and a simple metal complex having coordinating ability. They show unique properties which are distinctly different from their low-molecular weight analogues. These unique properties generally originate from the properties of the polymer backbone.

![Diagram](image)

**Fig. 1.10.** General representation of polymer-metal complex

Usually the reaction of a polymeric ligand with a metal ion or a stable metal complex in which one coordination site remains vacant results in various coordination structures which can be divided into pendant and inter-and/or intra-molecular bridged complexes (Fig. 1.11).
a. Pendant Complexes

(i) Monodentate Pendant Complexes

(ii) Polydentate Pendant Complexes

b. Inter- and/or Intra-Molecularly Bridged Complexes

Fig. 1.11. Different types of polymer-metal ion/metal complexes
1.4. Surfactant-metal complexes

1.4.1. Surfactants

Surfactants or surface-active agents are organic substances which have the tendency to concentrate at the surface or any interface of a system at low concentration, thereby significantly reducing the amount of work required to expand the interface. (Detergents, a term which is often used interchangeably with surfactant, refer to a combination of surfactants and other substances, organic or inorganic, formulated to enhance functional performance, specifically cleaning). Surfactants are considered amphipathic solutes, with their typical head-to-head/tail-to-tail ordering observed at the surface and also in bulk of the solvent as a result of physical interactions among the molecules. These structures may mimic biological structures, such as enzymes and membranes, which have vital importance in biochemical reactions and play a role in a variety of functions in the life of the cell, respectively.\textsuperscript{43-45} A whole new field of mimetic chemistry has grown around this concept and colloidal structures formed by surfactants are at the centre of the entire subject.

1.4.2. Classification of surfactants

The classification of surfactants depends on the nature of their hydrophilic group, which can be anionic, cationic, neutral or zwitterionic (amphoteric) (Fig. 1.12).
Anionic surfactants include carboxylates, sulfonates, sulfates or phosphates as solubilizing group, cationic surfactants are solubilized by amine and ammonium groups. Ethylene oxide chains and hydroxyl groups are the solubilizing groups in non-ionic surfactants whereas zwitterionic surfactants are solubilized by combinations of anionic and cationic solubilizing groups. The hydrophobic part of a surfactant may consist of one or several hydrocarbon chains containing 8 to 20 carbon atoms; the chains may be saturated or unsaturated, linear or branched and they may contain hetero (oxygen) atoms, aromatic rings, amides, esters, or other functional groups. The molecular weight of surfactants may be as low as ca 200 up to several thousand for...
polymeric structures. A surfactant with a straight $C_{12}$ chain and a solubilizing group is generally an effective structure.

1.4.3. Surfactant-metal complexes

Surfactant-metal complexes can be defined as surfactant molecules that contain a metal complex ion as part of the head group. As such, they will form monolayers, micelles and liquid-crystal phases in the same way that purely organic systems do, but they offer certain extra dimensions to their properties such as colour, paramagnetism, multi-charged head groups, electron-transfer photochemistry and reactivity to name a few. The incorporation of transition metal centers into surfactant molecules provides a means of localizing many of the physicochemical properties of these ions at oil-water or water-air interfaces. Although such surfactants are comparatively rare, they have recently found important potential applications in diverse subject areas such as magnetic resonance imaging, the templating of mesoporous materials, vesicle formation, laser-induced fluorescence, thin-film optoelectronics, interfacial photophysics, homogeneous catalysis and as anthelmintic therapeutics.

1.5. Schiff base ligands

Schiff bases are imines and can be represented by the general formula $R_2C=NR'$, where R and R' are various aliphatic or aromatic substituents. These compounds contain the azomethine group ($\text{>C=N-}$). They are formed by the
condensation of primary amines with compounds containing active carbonyl group as indicated below:

\[ RR'CO + R'NH_2 \rightarrow RR'C=NR' + H_2O \]

The experimental conditions for the formation of Schiff bases depend on the nature of amine and carbonyl compounds. Usually, it is better to remove water formed during the reaction by distillation or by using an azeotrope-forming solvent. This is necessary in the case of diaryl or arylalkyl ketones. However, aldehydes and dialkyl ketones can usually be condensed with amines without the removal of water. Aromatic aldehydes react smoothly under mild conditions and at relatively low temperatures in suitable solvent. In the condensation of aromatic amines with aromatic aldehydes, electron withdrawing substituents in the para position of the amines decreases the rate of reaction. When such groups are on the para position of the aldehyde, the rate of reaction was found to be increased.\textsuperscript{55-60}

The stability of the Schiff base complexes depends on the strength of the C=N bond, basicity of the imino group and steric factors. The presence of a second functional group with a replaceable hydrogen atom, preferably a hydroxyl group very near to the imine group allows the ligand to form a fairly stable four, five, or six membered rings on chelation to the metal atom. The role of the metal ions in these complexes seems to involve both stabilization and trapping of the Schiff base, and in addition it also ensures the planarity of the system.
1.6. Surfactant-copper(II) Schiff base complexes

Metal complexes in which a single central metal atom or ion is surrounded by a set of ligands, play an important role in inorganic chemistry, especially for elements of the d-block. Interaction of metal ions with N, O and S containing organic moieties has attracted much attention in recent years.\(^61\) Such ligands and their complexes are important due to their biological activity and also because they provide a better understanding of metal protein binding.\(^{62,63}\) Schiff bases containing these groups could act as versatile model of metallic biosites.\(^64\) Catalytic oxidation of many organic compounds is also of fundamental and industrial significance. Several transition metal Schiff base complexes are reported to be effective homogeneous catalysts for such oxidation reactions.\(^{65,66}\)

The general methods of preparation of Schiff base complexes are given below:

(a) Complexation in the basic medium

(b) Condensation method

(c) Template reaction

(d) Mechano-chemical method

1.7. Role of metal complexes in biological systems

Metal ions are often classed as ‘toxic’ or ‘non-toxic’, however their biological activity depends very much on speciation and it is now widely accepted that, with carefully controlled coordination chemistry, even ‘toxic’ metals can exhibit therapeutic properties.\(^67\) It is also true that toxicity is concentration-dependent and elements considered to be biologically essential can be toxic at high doses. It is
therefore very important to investigate and understand the effects of varying the oxidation state, numbers and geometries of coordinated ligands on the biological properties of metal complexes to design metal-based drugs with therapeutic properties at desired doses successfully. A number of metallic elements play crucial roles in biology and it is clear that many organic compounds used in medicine require metal ions for activation or biotransformation in order to achieve their mode of action. For example, haemoglobin which binds and delivers oxygen to body tissues requires an iron atom to function and calcium minerals are required in order for our bones to exist and grow. Electron-deficient metal centres attract electron rich biomolecules, such as proteins or DNA, leading to a high tendency for metal ions to bind to and interact with important biological targets. It is this extensive use of metal ions by nature which prompted inorganic chemists to investigate the potential of utilizing metal complexes in medicinal applications.68,69

Copper exhibits considerable biochemical action either as an essential trace metal or as a constituent of various exogenously administered compounds in humans. In its former role it is bound to ceruloplasmin, albumin and other proteins, while in its latter it is bound to ligands of various types forming complexes that interact with biomolecules, mainly proteins and nucleic acids. The multifaceted role of copper in biological systems is demonstrated by several studies. In particular the involvement of copper in human diseases has been described from a medicinal-chemical70 and a biochemical view71 focusing on the molecular physiology of Cu transport.72 Much of the current research effort is cited on copper homeostasis73 and its relation to ironmetabolism74 as well as the role of copper in biological processes related to human physiology and pathology.75,76 While a lot of the functions that have been
proposed to account for the homeostasis of inorganic noncomplex copper in humans have been described, only a limited number of review studies have focused on the multiple biochemical events which could be directly implicated in the use of copper complexes in medicine. Current interest in copper complexes is stemming from their potential use as antimicrobial, antiviral, antiinflammatory, antitumor agents, enzyme inhibitors or chemical nucleases. Markedly, the biochemical action of Cu complexes with non-steroidal antiinflammatory drugs (NSAIDs) has been studied. Numerous Cu(II) complexes of NSAIDs showing enhanced antiinflammatory and antiulcerogenic activity as well as reduced gastrointestinal toxicity compared to the uncomplexed drug, have been prepared and structurally characterized. They comprises a class of potential antiinflammatory drugs with reduced side effects and their mode of action is attributed to their marked superoxidizedismutase- (SOD-) mimetic activity. Other studies have concentrated on the potential chemotherapeutic properties of copper-based compounds. Moreover, several authors have brought to attention the antiviral and antibacterial activity of Cu(II) complexes. For instance, it was shown that the infectivity of influenza virus is reduced after exposure on copper surfaces. The mechanism of this process is only partly understood, but it has been speculated the degradation of the viral nucleic acid takes place after the intervention of copper ions. In addition, the study and development of Cu complexes could be helpful in the design and production of antiviral and antibacterial materials, able to deactivate HIV or H1N1 viruses and antibioticresistant bacteria, respectively. Towards this direction, a method of producing copper-impregnated materials that possess broad-spectrum antimicrobial properties has been reported.
1.8. Interaction of transition metal complexes with DNA and RNA

A large number of transition metal complexes have been used as probes of DNA structure in solution, as agents for mediation of strand scission of duplex DNA and as chemotherapeutic agents.82-86 A great diversity exists in the design of nucleic acid probes based upon transition metal chemistry in part because of different binding mode of interactions to nucleic acids.

Spectroscopic and redox characterization of the metal complexes offer a range of methods to assay these probe interactions. The spectroscopic perturbations in the metal complex on binding to its target serve as a reporter for binding and a means to examine characteristics of that binding interaction. The electronic structure of a metal centre can provide a sensitive spectroscopic handle to examine the region to which the metal complex is bound. This same spectroscopic sensitivity can be utilized in studies of nucleic acids. The redox reactions of the metal complexes bound to the nucleic acids also provide sensitive chemical reporters that mark specifically the sites of binding on the polymer.

In transition metal complexes cisplatin is widely used and well known metal based drug for chemotherapy. Next to Ru(II) complexes, Cu(II) complexes are regarded as the most promising alternatives to cisplatin as anticancer substances. Cu(II) is known to play a significant role in biological systems and also pharmacological agents.87 Synthetic Cu(II) complexes have been reported to act as potential anticancer agents and a number of copper complexes have been found to be active both in vitro and in vivo.88 Recently, Reedijk and coworkers have found that the complex [Cu(pyrimol)Cl] brings about efficient self-activated DNA cleavage and cytotoxic effects towards leukemia and human ovarian carcinoma cell lines.89 Sadler
and coworkers have observed the mixed ligand bis(salicylato) copper(II) complexes with diimines as coligands exhibits cytotoxic and antiviral activities.\textsuperscript{90} Also Ng and coworkers have prepared Cu(II) complexes of EDTA and 1,10-phenathroline, which strongly bind to DNA and also regulate apoptosis.\textsuperscript{91} Also there are some mixed ligands copper(II) complexes of diimines, which bind and cleave DNA and also exhibit anticancer activity that is more efficient than that of cis-platin. Recently there are some spectroscopic investigation on the RNA interaction with Ru(II) complexes of porphyrin ligands and \([\text{Ru(phen)(MHPIP)}]^2^+\) and some organic dye molecules are emerged.\textsuperscript{91-94}

As a modulator of gene expression at multiple levels, RNA is an important potential drug target.\textsuperscript{95} In addition to the well defined functions of mRNA, tRNA and rRNA, novel regulatory roles are continuously being defined in both transcription and translation.\textsuperscript{96} Such findings include the discovery of siRNA, microRNA, pi-RNA and long noncoding RNAs. Moreover, RNA damage and RNA-protein interactions have been linked to early events in disease and to programmed cell death.\textsuperscript{97-100} RNA targeting by small molecule interactions has the potential to influence these cellular pathways through both specific and nonspecific mechanisms. While drug-RNA interactions have the potential to impact cell fate by disrupting RNA regulatory pathways, a challenging aspect for this field is assessing RNA-drug interactions and RNA accessibility in vivo. For this purpose, a covalent RNA-drug adducts is of value in quantifying target binding and following the fate of the targeted RNA. The inertness of metal-RNA adducts formed following treatment with Pt(II) anticancer drugs provides one method of monitoring small molecule distribution on cellular RNA.
1.9. Cancer

Cancer known medically to numerous distinct diseases and each is an end product of a multistep process characterized by unregulated (abnormal) cell growth and differentiation (Fig. 1.13). When cancer occurs, cell growth becomes uncontrolled. Often, but not always, these cancer cells form into a solid mass called a tumor. Not all tumors are cancerous, however: cancerous tumors are called “malignant,” while non-cancerous tumors are known as “benign.” If the cancerous cells are blood cells, as in leukemia, there is no solid tumor. Early detection and treatment are very important to increasing the patient’s chances of recovery.

Fig. 1.13. Normal and cancer cell division
Cancer can occur in many parts of the body and can take many different forms. The various forms can behave very differently from one another; they may grow at differing rates and respond to treatments inconsistently. Cancer can also spread to other parts of the body through the bloodstream or lymphatic system (this is called metastasis), but the original site of the cancerous cells determines the cancer type.

1.9.1. Apoptosis

Apoptosis is a form of programmed cell death and it involves a series of biochemical events which leads to a variety of morphological changes, including blebbing, changes to the cell membrane such as loss of membrane asymmetry and attachment, cell shrinking, nuclear fragmentation, chromatin condensation and chromosomal DNA fragmentation. Kerr, Wyllie and Currie first created the term apoptosis. Apoptotic process is executed in such a way as to safely dispose of cellular debris. In contrast to necrosis, which is a form of traumatic cell death that results from acute cellular injury, apoptosis is carried out in an orderly process that generally confers advantages during an organism’s life cycle.

Apoptosis is triggered through 2 signaling pathways: Intrinsic pathway and extrinsic pathway. Intrinsic pathway: As its name suggests, the intrinsic, or mitochondrial, pathway is initiated from within the cell. This pathway is often activated in response to signals resulting from DNA damage, loss of cell-survival factors or other types of severe cell stress. Normally, pro-apoptotic proteins are released from the mitochondria to activate caspase proteases and trigger apoptosis.
Currently, the intrinsic pathway is more widely implicated as a blockade to tumorigenesis. Extrinsic pathway: The extrinsic pathway begins outside the cell through activation of pro-apoptotic receptors on the cell surface. These are activated by molecules known as pro-apoptotic ligands.

1.9.2. Necrosis

Necrosis is the name given to accidental death of cells and living tissue. Necrosis is less orderly than apoptosis, which is part of programmed cell death. In contrast to apoptosis, cleanup of cell debris by phagocytes of the immune system is generally more difficult, as the disorderly death generally does not send cell signals which tell nearby phagocytes to engulf the dying cell. This lack of signaling makes it harder for the immune system to locate and recycle dead cells which have died through necrosis than if the cell had undergone apoptosis. The release of intracellular content after cellular membrane damage is the cause of inflammation in necrosis.

1.9.3. Causes of cancer

The unusual cell growth that brings about cancer is the result of damage to DNA - the substance inside all cells that directs cell behavior. Damaged DNA can be caused by genetics, by behavior (such as smoking or diet) or by things in the environment (such as air pollutants, radiation or occupational exposure to certain chemicals). Usually, the body can repair damaged DNA, but cancer cells evade this natural process.
1.9.4. Treatment of cancer

The choice on which type of treatment is the most appropriate depends on the type and location of cancer, genetic patterns and epidemiological factors. The major types of treatment are surgery, radiation, chemotherapy, immunotherapy, hormone therapy and bone-marrow transplantation. As of now, emerging field combinatorial or target-based chemotherapy is considered the best.

1.9.5. Cancer treatment by chemotherapy

The term ‘chemotherapy’ refers to the use of drugs to kill or inhibit the growth of cancer cells. Most chemotherapy drugs cause damage to deoxyribonucleic acid (DNA) or prevent chromosomal replication, which leads to programmed cell death (apoptosis). The field has been stimulated by the success of cisplatin, the world’s best selling anticancer drug and platinum complexes with reduced toxicity, oral activity and activity against resistant tumors are currently on clinical trial.\textsuperscript{101,102} It is now increasingly accepted that part of the efficacy of anti-cancer drugs is due to their ability to activate apoptosis. Moreover, the resistance of tumor cells to drug-induced apoptosis is promising as major category of cancer the resistance of treatment failure. Therefore, amongst cancer biologists, there is increasing attention in understanding the regulatory mechanisms of apoptosis. The recent efforts in this field are focused on uncovering the cellular factors that determine the fate of the cell through their ability to control the balance between life and death. Understanding the biological role of these factors will enable the design of more efficient and selective drugs in order to overcome resistance to apoptosis.
References


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