5 Mechanism of Action of Anti-Cancer Drugs

Introduction

Anti-cancer drugs are not easily classified into different groups. Our understanding of the precise mechanism of action of many anti-cancer drugs is incomplete, and the basis of their marginal anti-tumour selectivity is, in most cases, unknown. Several different classifications of anti-cancer drugs have been proposed and none is totally satisfactory. Thus, drugs have been grouped according to their chemical structure, presumed mechanism of action and cytotoxic activity in relationship to the cell cycle. Each classification has some merits, but the fact that there are so many different ways of grouping these compounds reflects the disparate origin of anti-cancer drugs and limited knowledge of their mechanisms of action and bases of tumour selectivity.

Classification Based on Chemical Structure

Chemical structure is a satisfactory basis for classifying only a small number of the present anti-cancer drugs. Common structural features exist for two groups of anti-cancer agents — the alkylating agents and nucleic acid antimetabolites — but the majority of drugs do not clearly fit into these two groups. Alkylating agents are characterised chemically by their ability to react covalently under physiological conditions with many cell constituents including enzymes, structural proteins and nucleic acids. Alkylation may be considered as the replacement of the hydrogen atom of an organic molecule by an alkyl group. Thus, classical alkylating agents have an alkyl (CH\textsubscript{2}) group which may interact with molecules that contain negatively charged centres. Alkylating agents react particularly with thiol (SH) groups (amino acids, enzymes and structural proteins), with ionised acidic groups (nucleic acids and proteins) and with amino groups (amino acids and proteins).

Classically, it is believed that the cytotoxicity (cell-killing effect) of alkylating agents is due to reaction with nucleic acids, in particular with DNA. The bifunctional alkylating agents are able to cross-link strands of DNA, and this can be...
demonstrated by careful biochemical analysis after drug treatment. However, it is not certain that reaction with nucleic acids is the determinant of alkylating agents' toxicity, and the mechanism of their selectivity for particular tumour types is unknown.

The second group of chemically defined anti-cancer drugs are the nucleic acid antimetabolites which have structural similarities to the nucleosides and bases that are the building blocks for RNA and DNA. Any compound that interferes with the utilisation of a natural metabolite by virtue of similarity of chemical structure may be termed an antimetabolite. But, at present, the only antimetabolites that are used in clinical cancer chemotherapy are structural analogues of nucleic acid precursors and folic acid. A few analogues of amino acids and vitamins have been prepared, but they do not at present have an established place as anti-tumour agents.

Classification Based on Presumed Mechanism of Action

A classification of anti-cancer drugs based on their mechanism of action has many attractions, but for many drugs the precise mechanism of action at a biochemical level remains obscure. Indeed, they may have several mechanisms. This classification groups drugs according to their effects on cell physiology. Thus,