Cancer Chemoprevention and Molecular Targeting Drug Delivery for Cancer

Dr.K. Umasankar.,M.Pharm.,Ph.D
professor
Krishna Teja Pharmacy College
Tirupathi

Introduction

- Chemoprevention as first defined in 1976 by **Sporn**, is the use of natural, synthetic or biological agents to reverse, suppress or prevent either the initial phases of carcinogenesis or the progression of premalignant cells to invasive disease .
- Chemoprevention may involve perturbation of a variety of steps in tumor initiation, promotion and progression.
- The aim of cancer chemoprevention is disruption or delay of the molecular pathways that lead to carcinogenesis.
    - Chemopreventive blocking and/or suppressing agents disrupt the molecular mechanisms that drive carcinogenesis such as DNA damage by reactive oxygen species, increased signal transduction to NFκB, epigenomic deregulation that leads to metastatic progression.
- It simply means prevention of cancer by administering chemical compounds. It is a process by which specific natural or synthetic substances are used for preventing, interrupting or reversing carcinogenesis.

Chemoprevention and Chemo-preventive agents

Carcinogenesis or oncogenesis is a process by which healthy cells are transformed into cancerous cells. This process is as a result of genomic injury in gene elucidation which is the basic cause of all cancers. This damage occurs by abnormal changes in the genetic makeup of healthy cells through mutations.

These changes may occur as a result of hereditary or environmental factors such as chemical carcinogens and ionizing radiation.

Cancer development involves three different but closely related stages of carcinogenesis;

- Initiation,
- promotion, and
- progression.

Initiation results from direct contact of the DNA with cancer causing agents which occurs as a result of fast and incurable attack on the cell.

Promotion leads to premalignancy which is irreversible and involves epigenetic mechanisms.

Progression is irreversible owing to genetic mechanisms; it is the span between transformations of initiated cells to cancer cells. Additional changes allow the outgrowth of the clone with metastatic potential. Each of these events is likely to make the cell more unstable and causes an increase in the risk of subsequent changes

Chemoprevention provides a novel promise which is realistic in lowering the occurrence of carcinogenesis.

It is aimed at identifying the most efficient agents that can be able to delay the proliferation of cancer but not to cure already established cancer in the body.

Chemo-preventive agents are substances that have potent **antigenic, anti-proliferative, anti-hormonal and anti- apoptotic effects** and are classified by the way they exert protective actions on the specific stages of multistep carcinogenesis.

These blocking, suppressing of other agents decrease tissue vulnerability to carcinogenesis.

Blocking agents are compounds that inhibit cancer initiation and prevent carcinogenic agents from reaching the targeted site. They are agents that decrease tissue vulnerability, preventing targeted tissues from receiving carcinogenic stimuli, while suppressing agents stop malignant proliferation of initiated cells in both promotion and progression stages of cancer transformation

Chemopreventive agents act by two ways

Blocking agents

Are compounds that inhibit cancer initiation are traditionally termed.
They may act by preventing the interaction between chemical carcinogens or endogenous free radicals and DNA, which stops cancer causing agents from accomplishing their effects on the normal cells, inhibit their metabolic stimulation, and also enhance their detoxification.

Chemicals or biomolecules that inhibit the initiation stage are important for the preservation of DNA in its native state and are referred to as "blocking agents" since they "block" mutagenic interactions with DNA.
Blocking agents may circumvent the permanent, irreparable DNA damage that occurs during initiation by inactivating or metabolizing carcinogens directly, acting as free - radical scavengers, or physiologically inducing antioxidative enzyme activity and triggering mechanisms of DNA repair.

Suppressing agents

Compounds that affect later stages of carcinogenesis (promotion and progression) are termed "suppressing agents" for their ability to decrease the proliferative capacity of initiated cells.

They interfere with the promotion and progression of carcinogenesis through their effect on cell proliferation, integration and programmed cell death(apoptosis) which inhibits translation of initiated cells to form cancerous cells.

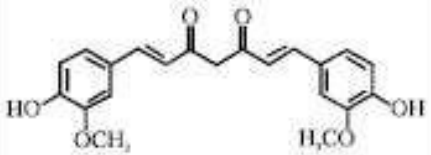
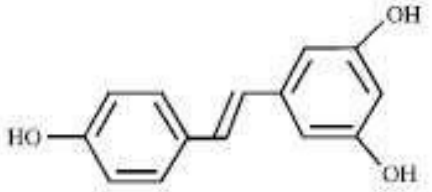
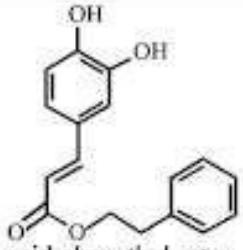
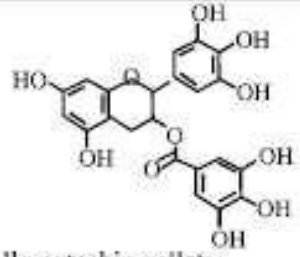
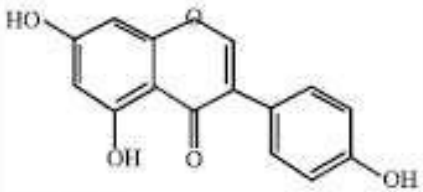
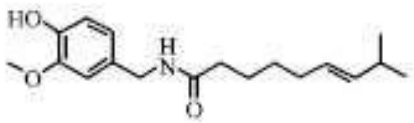
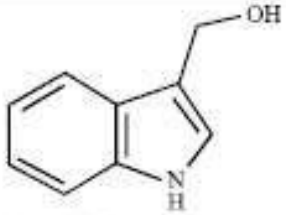
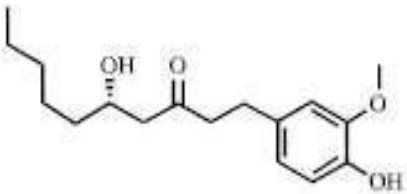
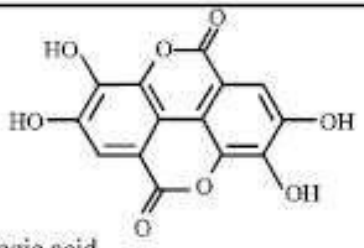
Additionally, suppressing agents are likely to reduce or delay the ability of cancer cells to evolve metastatic properties by promoting pathways leading to apoptosis and inhibiting pathways leading to angiogenesis, epithelial mesenchymal transition (EMT), invasion, and dissemination.

Phytochemicals in chemoprevention

Phytochemicals are biologically active non-nutritive chemical compounds that occur naturally in plants. They are found as a substance responsible for the health promoting properties of varieties of natural and functional foods due to their ability to **alter cell communication, and DNA repair and influence cell processes** that can cause development of cancer and other diseases.
These compounds are divided into two main groups as earlier stated:

The **Blocking agents** such as
- ellagic acid,
- indole-3-carbinol,
- sulphoraphane and
- flavonoids

The **Suppressing agents** like
- beta-carotene,
- genistein,
- capsaicin,
- Curcumin and
- gingerol

Natural source	Chemopreventive phytochemicals	Natural source	Chemopreventive phytochemicals
Turmeric 	 Curcumin	Grapes 	 Resveratrol
Honey 	 Caffeic acid phenethyl ester	Green tea 	 Epigallo-catechin gallate
Soybean 	 Genistein	Chilli pepper 	 Capsaicin
Broccoli 	 Sulphoraphane	Cabbage 	 Indole-3-carbinol
Ginger 	 [6]-Gingerol	Strawberry 	 Ellagic acid

Benefits of phytochemicals over synthetic drugs

The conventional radiotherapy and chemotherapy with synthetic drugs used in treating cancer evoke severe side effects such as immunosuppression, organ failure.

Infectious diseases which causes the death of patient after recovery from cancer.

Phytochemicals in cancer chemoprevention are considered as the cheapest option in cancer treatment.

Molecular Targeting and Drug Delivery for Cancer

Introduction

- Targeted drug delivery system is a special form of drug delivery system where the medicament is selectively targeted or delivered only to its site of action or absorption and not to the non-target organs or tissues or cells.

- It is a method of delivering medication to a patient in a manner that increases the concentration of the medication in some parts of the body relative to others.

- Targeted drug delivery seeks to concentrate the medication in the tissues of interest while reducing the relative concentration of the medication in the remaining tissues.
    - This improves efficacy and reduce side effects.

The drug may be delivered to:

- The capillary bed of the active sites,
- To the specific type of cell (or) even an intracellular region; Ex: Tumors cells but not to normal cells,
- To a specific organ (or) tissues by complexion with the carrier that recognizes the target.

REASON FOR DRUG TARGETING:

- Drug may arrive at a non-target organ.
- Drug concentrations could be diluted to the point where it has no effect.
- Pharmaceutical drug instability in conventional dosage form
  - ✓ solubility,
  - ✓ biopharmaceutical low absorption,
  - ✓ high-membrane bounding,
  - ✓ biological instability,
  - ✓ pharmacokinetic / pharmacodynamics short half-life,
  - ✓ large volume of distribution,
  - ✓ low specificity,
  - ✓ Low therapeutic index.

IDEAL CHARACTERISTICS of DRUGS:

1. It should be nontoxic, biocompatible, biodegradable, and physicochemical stable in vivo and in vitro.
2. It should restrict drug distribution to target cells or tissues or organs and should have uniform capillary distribution.
3. There should be controllable and predicate rate of drug release.
4. Drug release should not affect the drug action.
5. There should be therapeutic amount of drug release.
6. There should be minimal drug leakage during transit.
7. Carriers used must be bio-degradable or readily eliminated from the body without any problem and no carrier induced modulation of diseased state.
8. The preparation of the delivery system should be easy or reasonably simple, reproductive and cost effective.

CARRIER OR MARKERS:

Targeted drug delivery can be achieved by using carrier system. Carrier is one of the special molecules or system essentially required for effective transportation of loaded drug up to the pre-selected sites. They are engineered vectors, which retain drug inside or onto them either via encapsulation and/ or via spacer moiety and transport or deliver it into vicinity of target cell. Pharmaceutical carriers:

1. Polymers
2. Liposomes
3. Micelles
4. Dendrimers
5. Nanoparticle

STRATEGIES OF DRUG TARGETING

➢ Passive Targeting:

- Drug delivery systems which are targeted to systemic circulation are characterized as Passive delivery systems.
- In this technique drug targeting occurs because of the body's natural response to physicochemical characteristics of the drug or drug carrier system.

➢ Inverse Targeting:

- In this type of targeting attempts are made to avoid passive uptake of colloidal carrier by RES (Reticulo Endothelial Systems) and hence the process is referred to as inverse targeting. To achieve inverse targeting, RES normal function is suppressed by pre injecting large amount of blank colloidal carriers or macromolecules like dextran sulphate. This approach leads to saturation of RES and suppression of defense mechanism. This type of targeting is an effective approach to target drug(s) to non-RES organs.

➢ Active Targeting:

- In this approach carrier system bearing drug reaches to specific site on the basis of modification made on its surface rather than natural uptake by RES. Surface modification technique include coating of surface with either a bio adhesive, nonionic surfactant or specific cell or tissue antibodies (i.e. monoclonal antibodies) or by albumin protein. 3 Types:

  a)First order targeting (organ compartmentalization).

  b)Second order targeting (cellular targeting).

  c)Third order targeting (intracellular targeting).

➢ Ligand Mediated Targeting:

- It is achieved using specific mechanisms such as receptor dependent uptake of natural LDL particles and synthetic lipid microemulsions of partially reconstituted LDL particles coated with the apoproteins.

➢ Physical Targeting:

- In this type of targeting some characteristics of environment changes like pH, temperature, light intensity, electric field, and ionic strength small and even specific stimuli like glucose concentration are used to localize the drug carrier to predetermined site. This approach was found exceptional for tumor targeting as well as cytosolic delivery of entrapped drug or genetic material.

➢ Dual Targeting:

- In this targeting approach carrier molecule itself have its own therapeutic activity and thus increase the therapeutic effect of drug. For example, a carrier molecule having its own antiviral activity can be loaded with antiviral drug and the net synergistic effect of drug conjugate was observed.

TYPES OF TARGETED DRUG DELIVERY SYSTEM

- **Nanoparticle:**

✓ **Nano Tubes:** They are hollow cylinder made of carbon, atoms which can be filled and sealed for potential drug delivery.

Application: Cellular scale needle for attaching drug molecule to cancer cells as an electrode in thermo cells.

✓ **Nano wires:** The nanowire pinpoint damage from injury and stroke, localize the cause of seizures, and detect the presence of tumors and other brain abnormalities.

Application: Technique has potential as a treatment for Parkinson's and similar diseases.

✓ **Nanoshells:** Nanoshells are hollow silica spheres covered with gold. Scientists can attach antibodies to their surfaces, enabling the shells to target certain shells such as cancer cells.

Application: Technique has potential for targeting cancerous drug.

- **Dendrimers:**

Dendrimers precisely defined, synthetic nanoparticles that are approximately 510 nm in diameter. They are made up of layers of polymer surrounding a control core. The dendrimers surface contains many different sites to which drugs may be attached.

Application: In gene transfection, medical imaging

- **Liposomes:**

Liposomes are small artificially designed vesicles composed of phospholipid bilayers surrounding with the size ranging from 20 to 10 000 nm.

Many liposome formulations are rapidly taken up by macrophages and this can be exploited either for macrophage-specific delivery of drugs or for passive drug targeting which allow slow release of the drug over time from these cells into the general circulation.

The drug molecules can either be encapsulated in aqueous space or intercalated into the lipid bilayers.

The extent of location of drug will depend upon its physico-chemical characteristics and composition of lipids. Cationic liposomes and lipoplexes have been extensively researched for their application in non -viral vector mediated gene therapy.

ADVANTAGES

- Drug administration protocols may be simplified.
- Toxicity is reduced by delivering a drug to its target site, thereby reducing harmful systemic effects.
- Drug can be administered in a smaller dose to produce the desire effect.
- Avoidance of hepatic first pass metabolism.
- Enhancement of the absorption of target molecules such as peptides and particulates.
- Dose is less compared to conventional drug delivery system.
- No peak and valley plasma concentration.
- Selective targeting to infections cells that compare to normal cells.

DISADVANTAGES

- Rapid clearance of targeted systems.
- Immune reactions against intravenous administered carrier systems.
- Insufficient localization of targeted systems into tumor cells.
- Diffusion and redistribution of released drugs.
- Requires highly sophisticated technology for the formulation.
- Requires skill for manufacturing storage, administration.
- Drug deposition at the target site may produce toxicity symptoms.
- Difficult to maintain stability of dosage form. E.g.: Resealed erythrocytes have to be stored at 40 C.
- Drug loading is usually law. E.g. As in micelles. Therefore it is difficult to predict /fix the dosage regimen.

Targeted therapies that have been approved by FDA

Agent	Mechanism of Action	Cancer
Cetuximab	Epidermal growth factor receptor (EGFR) antibody	Colorectal cancer, squamous cell cancer of the head and neck
Panitumumab	EGFR antibody	Colorectal cancer
Gefitinib	EGFR, tyrosin kinase inhibitor (TKI)	Nonsmall cell lung cancer
Eriotinib	EGFR	Nonsmall cell lung cancer, pancreatic cancer
Trastuzumab	Human epidermal growth factor (HER)-2 antibody	Breast cancer
Lapatinib	HER-2/EGFR, TKI	Breast cancer
Bevacizumab	Vascular endothelial growth factor (VEGF) antibody	Colorectal cancer, Nonsmall cell lung cancer, Breast cancer, renal cell cancer
Vatalanib	VEGF receptor, platelet-derived growth factor receptor (PDGFR)	Colorectal cancer
Imatinib	C-KIT/PDGFR	Gastrointestinal (GI) stromal tumors
Sunitinib	Multikinase inhibitor	GI stromal tumors
Sorafenib	Multikinase inhibitor	Renal cell, hepatocellular carcinoma, melanoma


Thank You!