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Drug Targeting

- Recently, new therapies have been proposed which attempt the localization of prodrug activation enzymes into specific cancer cells prior to prodrug administration.

- These new approaches are:
  1. *Anti-body directed enzyme prodrug therapy (ADEPT)*
  2. *Gene directed enzyme prodrug therapy (GDEPT)*

A. Anti-body directed enzyme prodrug therapy (ADEPT)

- Enzymes that activate prodrugs can be directed to human xenografts by conjugating them to tumor selective monoclonal antibodies.

- An antitumor antibody is conjugated to an enzyme not normally present in extracellular fluid or on cell membranes and then these conjugates are localized in the tumor via IV infusion.

- In ADEPT procedure after allowing for the conjugate to clear from the blood, a prodrug is administered that is normally inert but is activated by the enzyme delivered to the tumor.

B. Gene directed enzyme prodrug therapy (GDEPT)

- Tumours have also been targeted with genes encoding prodrug-activating enzymes.
- This approach uses a viral vector e.g. retroviral vector or adenoviral vector to carry a prodrug-activating enzyme gene into both tumour and normal cells.
- By linking the foreign gene downstream of tumour-specific transcription units, tumour-specific expression of the foreign enzyme gene can be achieved.

Targeted Prodrug Design to Optimize Drug Delivery

- Prodrug design can no longer be considered as just a chemical modification to solve problems associated with drugs. Explain.
- Prodrug design is becoming more elaborate in the development of efficient and selective drug delivery systems.
- The targeted prodrug approach is a promising strategy for precise and efficient drug delivery and the enhancement of therapeutic efficacy.

Targeted prodrug design

- ***Is based on the followings:***

1. Targeting specific enzymes.

2. Targeting specific membrane transporters.

Prodrug Design Based on Targeting Enzymes

- The enzyme-targeted prodrug approach has been used to:

1. improve oral drug absorption.
2. site-specific drug delivery.

Examples on prodrug design based on targeting enzymes:

- Glycoside derivatives are hydrophilic and poorly absorbed from the small intestine, but once they reach the colon, they can be effectively cleaved by bacterial glycosidases to release the free drug.
- delivery of Dopamine to kidney in the form of its prodrug L-glutamyl dopa. The prodrug is first cleaved by L-glutamyl transpeptidase producing L-dopa, which is converted to dopamine by L-amino acid decarboxylase.

Prodrug Design Targeting Membrane Transporters

This targeted prodrug approach uses transporters designed for facilitating membrane transport of polar nutrients such as amino acids and peptides.

Prodrugs are designed to resemble the intestinal nutrients structurally and to be absorbed by specific carrier proteins.

Peptide Transporter Associated Prodrug Therapy (PTAPT)

- A polar drug with low membrane permeability through passive diffusion is converted into a prodrug that is absorbed via the peptide transporter into the mucosal cell.

- Following membrane transport, enzymes in the mucosal cell, blood, or liver hydrolyze the prodrug to release the active drug.

Active targeting by Polymeric prodrug:

1. Monoclonal antibodies.
2. Lectins.
3. Angiogenic vessels of tumor cells.

Monoclonal antibodies

- The monoclonal antibodies can be used as targeting group for coupling with the drug to increase the specific targeting of the prodrug on the tumor cells.

Monoclonal antibodies

- Examples:

(a) Conjugate of plant toxins and antibodies, referred as immunotoxin is a very potent anti-tumor therapy

(b) Tumor selective monoclonal antibody is covalently attached to an enzyme which converts nontoxic prodrug into potent cytotoxic drug after specific targeting at the tumor site.

Lectins

- The sugar specific receptors present on the plasma membrane are called lectins and they have been characterized mainly on hepatocytes.
- Galactose specifically targets these lectins.
- This targeting seems to be an attractive approach for target specific drug delivery.

Lectins

- Applications of targeted lectins:
  - For treatment of liver diseases such as:
    - hepatitis.
    - parasitic infections, and
    - liver metastasis.
    - Drug delivery to macrophages (e.g. Kupffer cells) can be employed for targeted treatment of various malfunctions such as leishmaniasis.

Angiogenic vessels of tumor cells

- The endothelial cells in angiogenic vessels of tumors show increased expression of cell surface proteins.
- These proteins include receptors for vascular endothelial growth factor (VEGF) and integrin receptors.
- The peptides which specifically bind to these receptors can be used as targeting moiety for drug delivery such as RGD (arginine-glycine-aspartic acid) containing peptides that specifically bind with integrin receptors.
- The conjugation of RGD peptides and poly ethylene glycol (PEG) showed increased efficacy of drug against breast cancer.

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Any question?

Thank you