

TARGETED DELIVERY TO LYMPHOID CELLS OF IMMUNE NETWORK

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LYMPHATIC SYSTEM: Lymphatic system is a connective tissue scattered throughout the body. It consists of lymphoid organs with fluid lymph, a network of lymphatic vessels & specialized cells called lymphocytes.

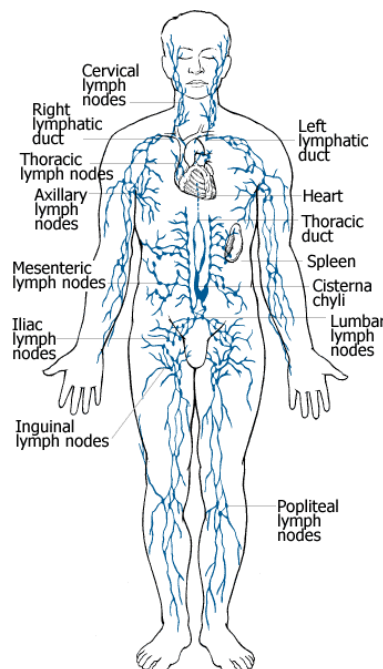
Lymphoid organs,

Primary: spleen & thymus.

Secondary: Peyer's patches.

Functions:

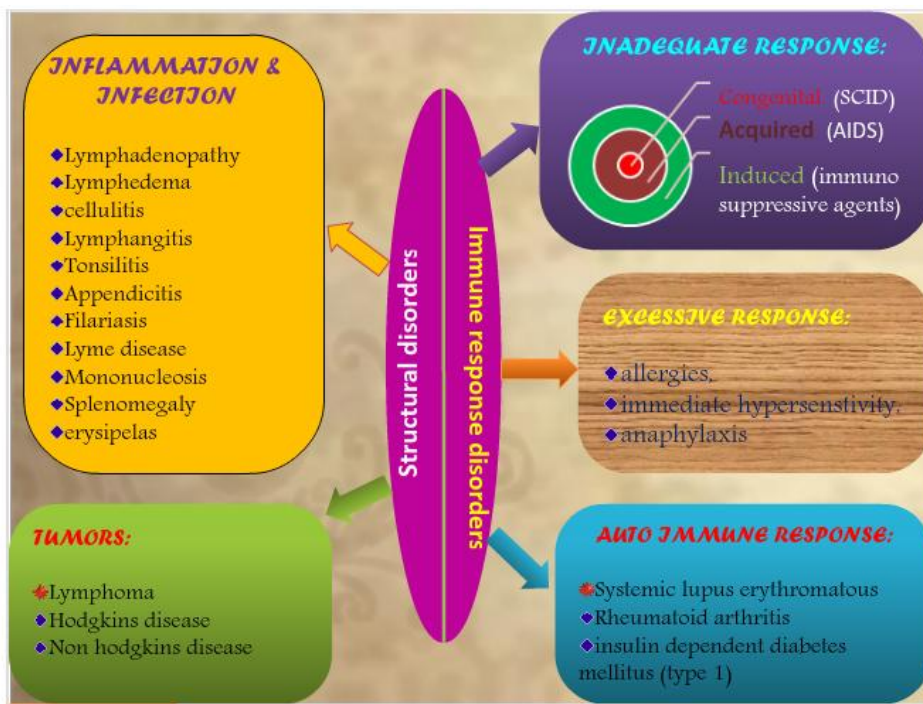
1. To protect the body through immune response.
2. Transport fluid from the interstitial fluid to the blood stream.
3. Helps in distribution of hormones, nutrients & transports waste.
4. They also involve in the activation & proliferation of B & T lymphocytes.



(Read Lymphocytes types and their introduction from Vyas and Khar text book)

DISORDERS: Disorders are observed in 2 ways,

- a) problem "affect the immune function".
- b) problem regarding to circulatory function of lymphatic system.



Lymphatic Drug Targeting:

Targeting of drugs & therapeutic agents into lymphatic system for drug action or transport of drug through lymph to specific tissues of interest.

Objectives:

- Targeting of anti cancer agents in lymphomas.
- Transport of anti inflammatory drugs to the site of inflammation.
- Transport of macromolecules by subcutaneous administration.
- To detect the tumors in lymph nodes using labeled liposomes.

LYMPHATIC DRUG TARGETING THROUGH ORAL ROUTE:

The GIT organs drained along the lymphatic & through nodes lying in mesenteries & omenta with the vessels supplying these organs. These nodes are finally drained into “cysterna chyli ” Some of the regions in GIT like a) Peyer’s patches b) gut associated lymphoid tissue (GALT). They involve in the transport of particulates from GIT to lymphatic system.

LYMPHATIC DRUG TARGETING THROUGH PARENTERAL ROUTE:

Lymphatic system is a major absorption route for compounds those impermeable to capillary membranes.

In SC & IM injections drug absorption occurred by diffusion, area of drug depot, drug conc., pH, biological factors effect the diffusion.

Molecular weight >16000 Daltons are absorbed mainly by lymphatic system due to: a) lack of basal lamina around lymphatic capillaries. b) Gap up to 20-100 nm b/w cells.

Strategies for Lymphatic drug delivery with particulate carriers:

Targeting delivery of drugs achieved by using carriers with a specified affinity to target tissue, There are 2 approaches.

Chemical modification: In this chemical approach representing PRODRUGS, the drug has to possess a suitable functional group in its molecular structure.

Pharmaceutical modification: It is utilizing particulate carriers. The technology once achieved it is principally applicable to any drugs, process also easy.

To achieve “active targeting” to target site utilizing specific physical forces such as magnetic force biochemical interaction such as receptor- ligands or Ag- Ab interactions.

E.g: liposomes, polymeric and solid lipid nanoparticles Self micro emulsifying drug delivery Nanospheres Microspheres.

POLYMERIC NANOPARTICLES:

- Their diameter up to 1µm.
- Natural polymers: proteins or polysaccharides
- Synthetic polymers: poly lactic acid, poly glycolic acid, & PLGA.
- Microspheres remain in Peyer’s patches, while nanoparticles are systemically disseminated.

E.g.:

- ✓ Mucoadhesive polymers (chitosan or carbopol) coated nanoparticles have shown prolonged action & more effective.
- ✓ Prolonged hypoglycemia is produced by PACA nanospheres entrapped with insulin, dispersed in an oily phase with a surfactant.
- ✓ PACA nanocapsules incorporated with a peptide, octeotide showed improved & prolonged therapeutic efficacy.

- ✓ Positively charged nanoparticles carrying cyclosporine A showed relative bioavailability of 20-35%.
- ✓ The oral administration of antigens incorporated in nanoparticles induces a stronger Ag specific immune response than Ag in water soluble form.
- ✓ Magnette-dextran nanoparticles have been investigated for diagnostic use.

SOLID LIPID NANOPARTICLES

These are submicron level particles composed of biocompatible & biodegradable materials such as triglycerides & fatty acids.

E.g.:

- ✓ Peroral administration of camptothecin loaded SLNs to rats showed in bioavailability.
- ✓ Clozapine SLNs administered by IV & intraduodenal routes showed bioavailability with in AUC.
- ✓ Tobramycin loaded SLNs after administration to rats into the duodenum showed 100 & 20 times higher AUC than IV administered tobramycin -SLM & tobramycin solution.
- ✓ Idarubicin SLNs administered by IV or oral route & effective in the treatment of tumours.

Preparation of nanocapsules by the interfacial deposition method:

Alcoholic solution of isobutylcyanoacrylate + oil containing drug



Poured into water



Alcohol diffused out from oil phase to produce fine oil droplets.



At oil/water interface polymer polymerizes to form POLYISOBUTYLCYANOACRYLATE. (PIBCA).

LIPOSOMES:

- Liposomes provides a simple & convenient formulation for oral drug administration.
- PEG coated liposomes containing recombinant human epidermal growth factor were administered orally, which has shown in AUC.
- Chitosan or carbopol coated liposomes containing calcitonin showed that pharmacological efficiency of the intestinal absorption in rats of coated liposomes was greater than twice of non coated liposomes.

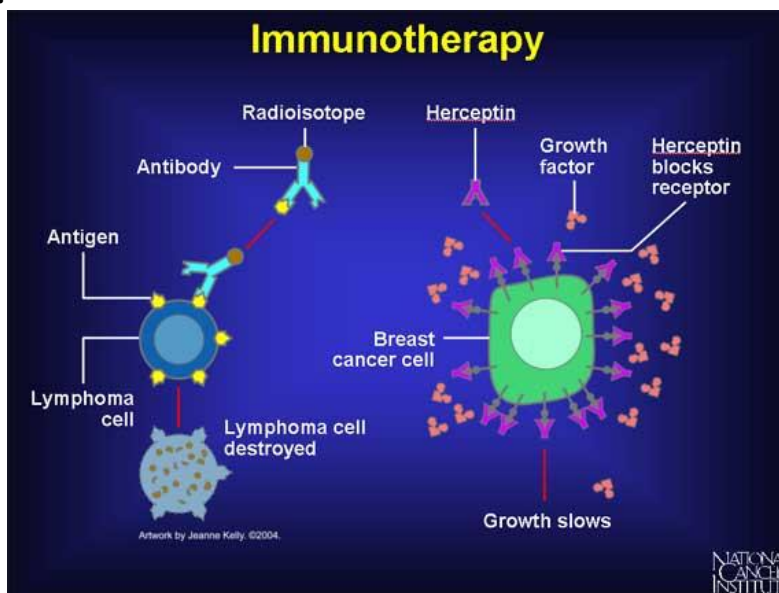
SELF (MICRO) EMULSIFYING DRUG DELIVERY SYSTEMS:

These are isotropic mixtures of oils, surfactants, solvents & cosolvents which is used for the improvement of oral absorption of highly lipophilic drugs.

E.g.:

- ✓ Paclitaxel supersaturable formulation with hydroxypropylcellulose as precipitation inhibitor showed a 5 fold increase in oral bioavailability.
- ✓ Coadministration of P-glycoprotein inhibitors (cyclosporin A) with paclitaxel S(M)EDDS to rats showed improved oral bioavailability than commercial taxol .

Immunotherapy:



APPLICATIONS OF LYMPHATIC DRUG TARGETTING:

1. Controlled Delivery of Vaccines:

- Oral immunization has great advantage if adsorption of the colloidal carriers for vaccines could be achieved in useful quantities.
- There is a chance to develop a single dose vaccines that would reduce the booster dosings.
- Eldrige et.al studied the controlled release of vaccines in GALT.
- They demonstrated that particle size of staphylococcal enterotoxin B toxoid has a significant impact on onset & intensity of Ab production.
- Increased lymph node delivery & immunogenicity of hepatitis B surface Ag was found when Ag entrapped in galactosylated liposomes was administered IM in rats as compared to nonliposomal Ag.

2. Treatment of Inflammation:

- A characteristic feature of inflammation is oedema.
- With infiltration of leucocytes from the vascular compartment into tissues.
- Exudates, leucocytes enter the synovial fluid through the gaps that open between epithelial cells in blood vessels under the influence of inflammatory mediators.
- Distribution of latex microspheres in vivo, as a potential passive targeted systems for the treatment of inflammation.

3. Detection of Tumor Metastasis:

- One of the major problems of neoplastic disease is the metastasizing of cancer cells.
- Metastasis is the spreading of cancer cells to different areas in body through blood circulation from the originating site.
- Lymphatic circulation is one of the major routes of movement for metastasis.
- Tc labeled liposomes used for lymph node imaging and that nodes involved in metastatic spread showed a suppression of uptake of labeled liposomes made from phosphatidyl choline and cholesterol.

4. Cancer Therapy:

- One of the major disadvantage of chemotherapy is non-specific action which leads to severe side effects and huge wastage of dose.
- To overcome this better to concentrate on their cytotoxicity at tumor site by changing the biological and pharmacokinetic properties. One possible approach is to alter the biopharmaceutical behaviour would be the derivitisation .
- E.g.: A macromolecule derivative of MMC, MMC-D conjugate and examined its pharmacodynamic properties:
 - MMC-D exhibited increased anti-tumor activity against Murine tumors and ehrlich ascites carcinoma.
 - Free MMC was detected for several days in plasma and urine of mice.
- Another approach is usage of endogenous proteins (biological response modifiers).
- rDNA technology facilitated identification and production of human proteins.
- Effective therapy of proteins depends on the distribution of the drug.
- **Endocrine molecules:** Released in to blood stream and then reaches to their target tissues
- **Paracrine Molecules:** They act only on limited regions & rapidly inactivated at another sites. They interact with mediators facilitates + ve or – ve feedback regulation
 - E.g.: Interferon and IL-2

5. Treatment of Infections:

- Lymphatic targeting used to treat infections of lymphatics and RES and parasitic diseases of liver.
- E.g.: Liposomal encapsulated anti- monial drugs for Leishmaniasis. Liposomal encapsulated immunomodulators to stimulate macrophages.

6. Peroral Delivery of Marcomolecules:

- Macromolecules such as peptides and proteins used extensively in therapeutics.
- Oral route is most preferred for this, but due to different pHs , enzymatic degradation and their size, low lipophilicity prevents to enter in to blood.
- To overcome this that drug should be targeted to regions where enzymatic activity is low and where macromolecules absorbed.
- E.g.: Colon specific delivery Cyclosporine is a lipophilic administered with oil vehicle majorly absorbed by lymphatic system.

CONCLUSION:

Lymphatic targeting aimed specifically in case of carriers for peptides to avoid first pass metabolism for tumor detection & treatment, treatment of inflammations.

Carrier systems like Microspheres and Nanoparticles used to target diabetes, rheumatic disorders.

A good deal work has been done from 1960, achieved success in some systems.

More research work is needed to develop practical systems, used clinically, especially for molecules prepared by rDNA technology.

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