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Drug Targeting And Cancer Therapy

Introduction

- Cancer is a disease which occurs when changes in a group of normal cells within the body, lead to uncontrolled growth causing a lump called a tumor
- Which can found in two major forms : benign and malignant
- Classification based on the tissue of origin of the malignancy to carcinoma, sarcoma, lymphoma ,lymphoma, germ cell tumor and blastoma
- Targeted cancer cancer therapies include drugs or other substances that block the growth and spread of cancer by interfering with specific molecules (molecular targets) that are involved in growth, progression and spread of cancer.

-Interfere with specific targeted molecules needed for carcinogenesis and tumor growth rather than by simply interfering with all rapidly dividing cells (e.g. with traditional chemotherapy).

-Drug targeting improves efficacy of the while by reducing side effect .

Drug targeting to tumor based on

-EPR (Enhanced Permeability and Retention)
-Nanoparticle properties and design
-Ligand-receptor interaction

Principles Of Drug Targeting To Tumors

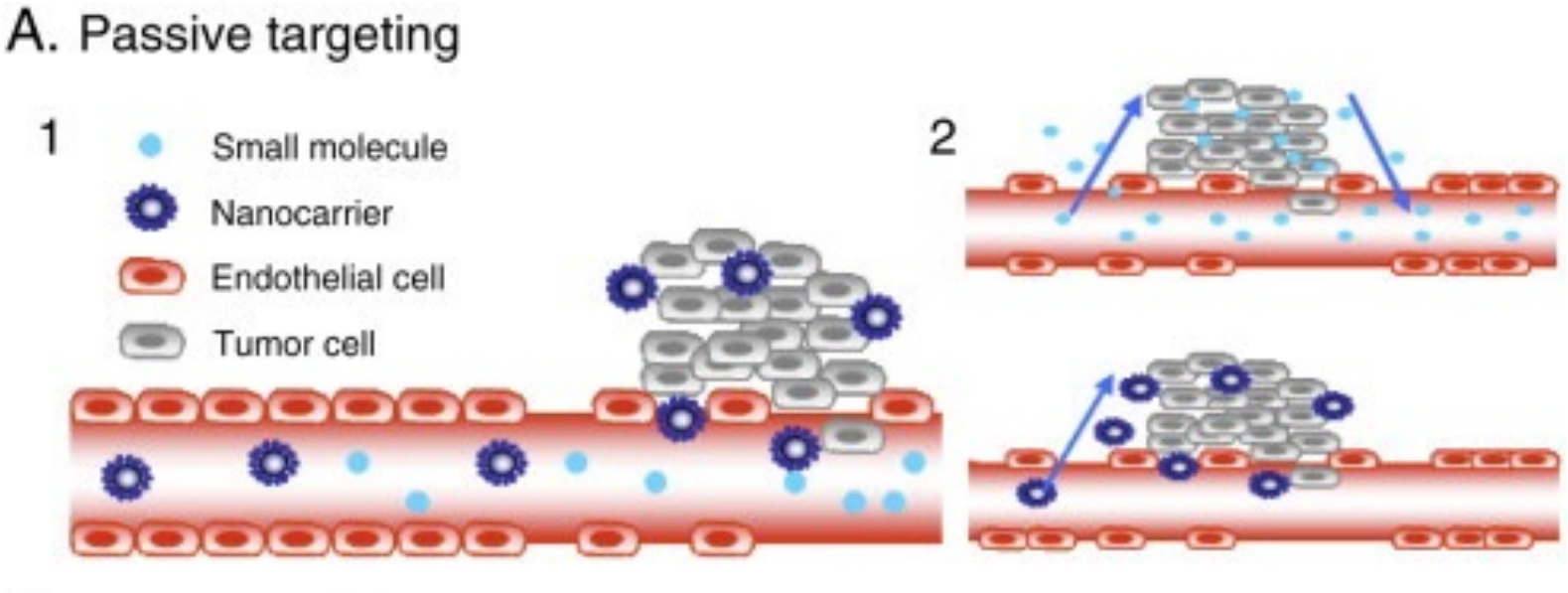
- Passive targeting.
- Active targeting to cancer cells
- Active targeting to endothelial cells
- Triggered drug delivery (using stimuli-responsive carrier materials)

- Site specific drug delivery requires localization of drug and carrier within the desired target organ.
- The role of carrier systems in providing site specificity can be evident from terms passive and active targeting approaches.

Passive Targeting

- Passive targeting involves therapeutic exploitation of the natural distribution pattern of the drug-carrier construct in vivo
- Passive targeting define the preferential accumulation of the drug in the area around tumor.
- Passive targeting is primarily relying on enhanced permeability and retention (EPR) effect, is unique phenomenon of solid tumors based on their anatomical and pathophysiological differences from normal tissues.
- EPR based chemotherapy is thus becoming an important strategy to improve the delivery of therapeutic agents to tumors for anticancer drug development.

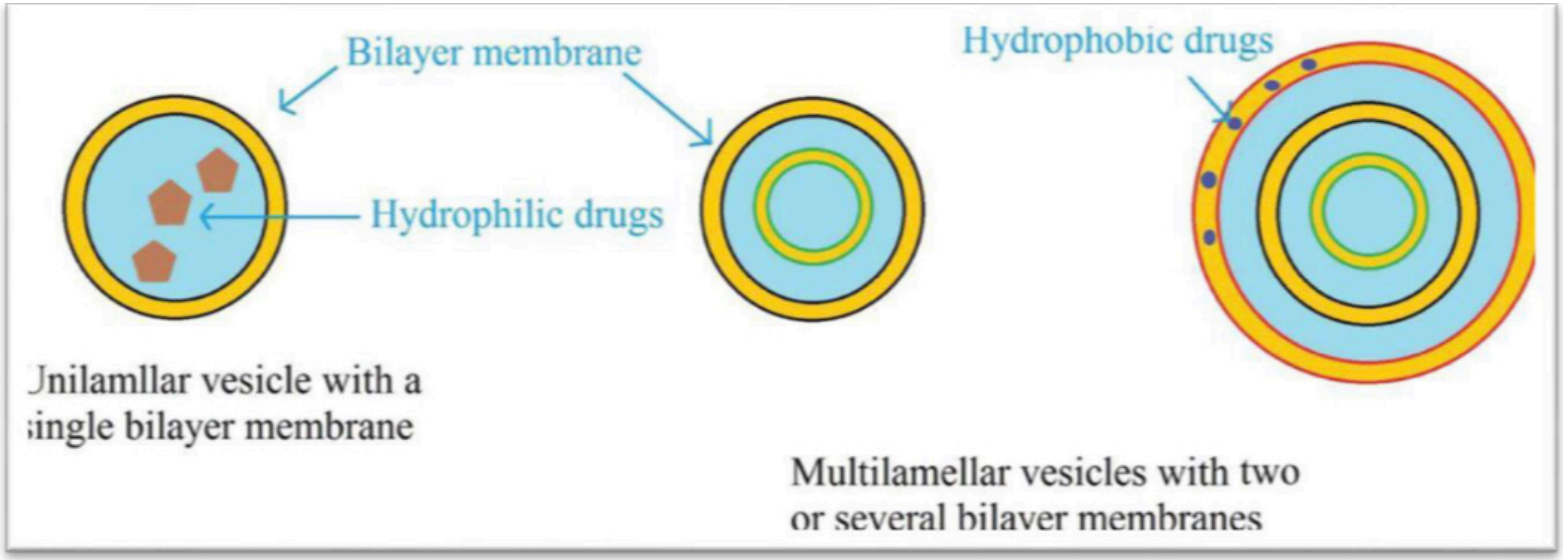
Passive Targeting



Liposomes

- Being one of the oldest while still promising drug carrier, liposomes are spherical structures made of a hydrophilic core surrounded by a bilayer made of some amphiphic lipid material, mainly phospholipids.
- The size of liposome be range of 25nm-2.5um with one of several bilayer membranes classification of liposomes is based on these two parameter, i.e. number of bilayer and size. In the case of bilayer number, there are unilamellar (with one phospholipid liposomes with unilamellar type type divided into two subtypes of small and large unilamellar type divided into two subtypes of small and large unilamellar liposomes (figure)

Liposomes


Bilayer membrane
Hydrophilic drugs
Hydrophobic drugs
Jnilamllar vesicle with a
;ingle bilayer membrane
Multilamellar vesicles with two
or several bilaver membranes

Liposomes

- These structures are important in encapsulating of various drugs with different size, shape and solubility in water. By modification of these vesicles, it may be possible to target specific tissue , organ and cells .Also based on the charge of the lipid constituents in the formation of liposomes, there are cationic and anionic liposomes.

Active Targeting

- The term of "active targeting" defines a specific ligand interaction which occurs at the target site after reaching via blood circulation and extravasation.
- Is generally implemented to improve target cell recognition and target cell uptake, and not to improve overall tumor accumulation.
- Active targeting of accomplished by coupling drugs or nanocarrier with cell-specific targeting moiety called ligand, with or without cross-linking agent.
- These targeting moieties have specific affinity for the cell surface antigens (receptor) and they can differentiate between normal and tumors cells based on the receptor or antigen expression level.

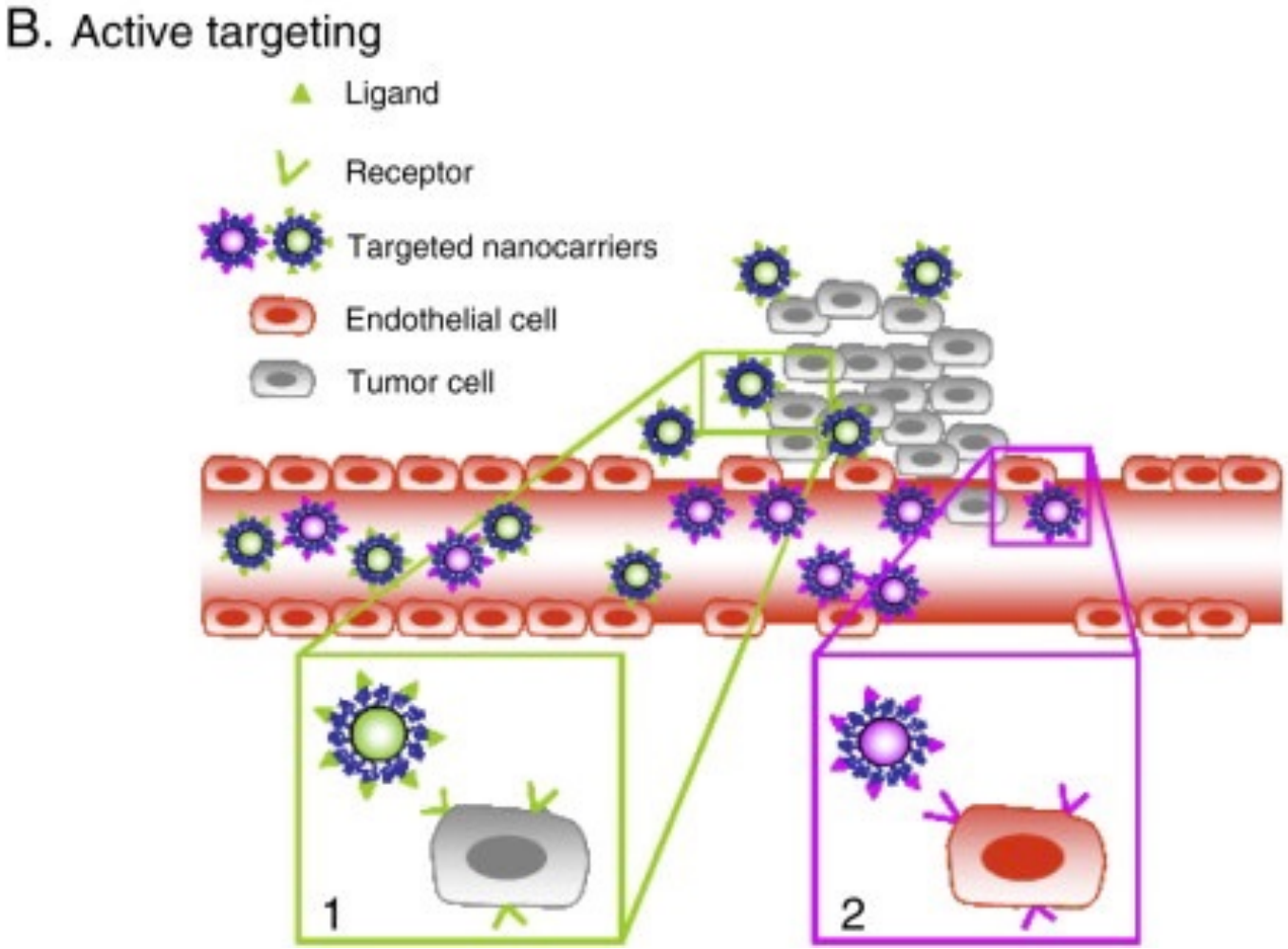
Active Targeting

- Ligand mediated targeting is the major approach that involves ligands developed against cell receptor or antigenic determinants expressed on tumor cells or vasculature.
- Examples of targeting ligands used for active targeting is folate, transferrin, galactosamine.
- These ligands mediate the effective transfer of anticancer drug to the early endosomes to inhibit cell signaling system. several anticancer therapies could target endosomes that have been internalized through receptor mediated endocytosis.
- Folic acid is a popular ligand that targets the folate receptor. Folate receptor overexpressed in solid tumors such as breast ovarian, lung, uterine head and neck cancers while normal tissue lack such abundance receptors. This could be an advantage for target ligands to seek out tumors cell.

Active Targeting

- Transferrin is a glycoprotein with the capacity of ion transportation in the body. Overexpression of transferrin receptors on cancer cells makes them an attractive target for its suitable ligand to deliver anticancer drugs into target cells.
- Monoclonal antibodies(mAb) have been already approved by FDA for targeted cancer treatment. Antibody fragments are also used as because they possess longer circulation time, smaller size and low immunogenicity as well as the ability to overcome the steric hindrance for binding compared to full antibody.

Active Targeting



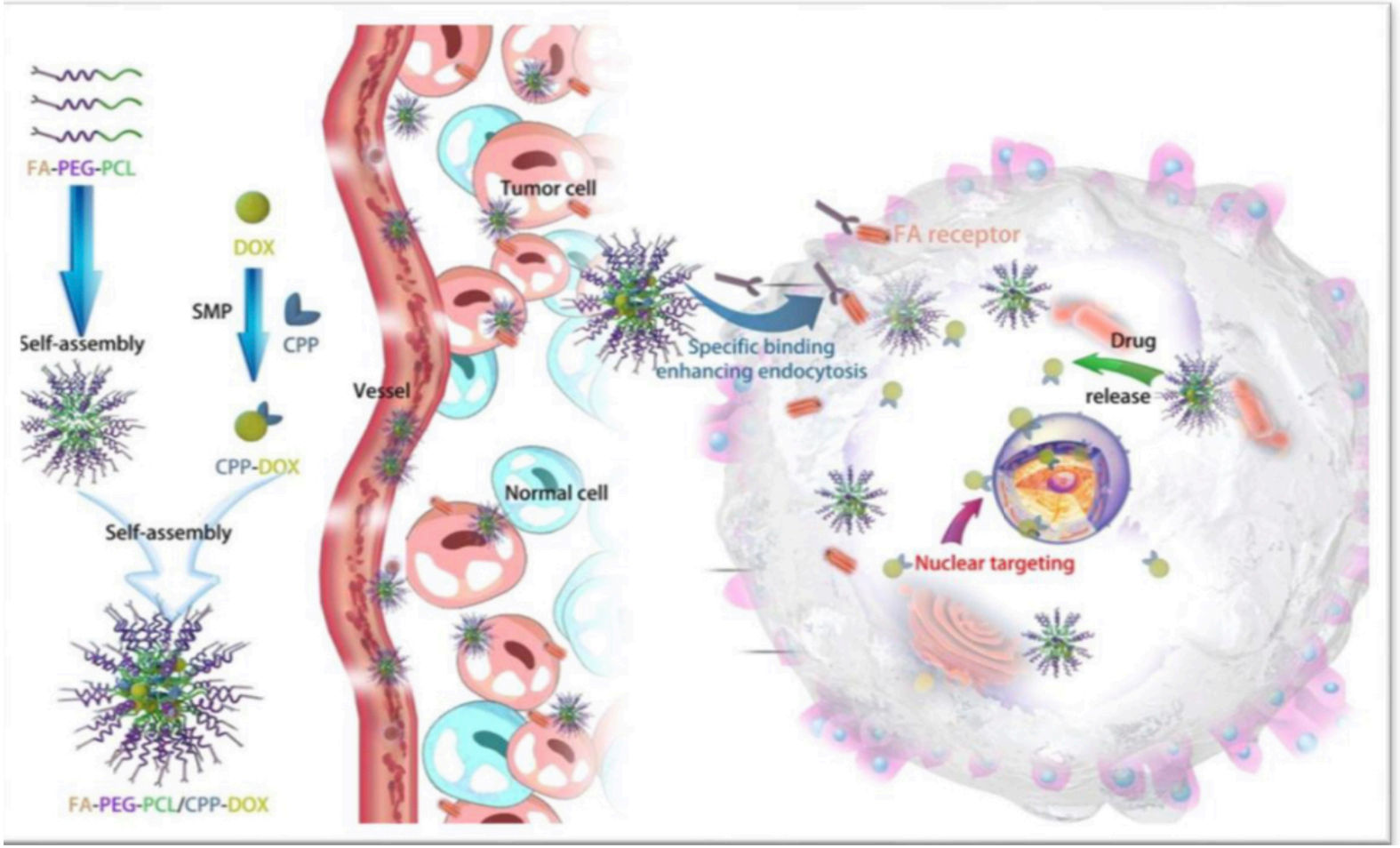
Polymeric Drug Delivery System With Actively Targeted

- Cell penetration and nuclear targeting for efficient cancer therapy. The nanocarriers were self-assembled from poly ethylene glycol-block-poly (caprolactone), decorated with folic acid (FA-PECL) for active targeting via amide reaction for selective delivery of drugs to tumors.
- A cell penetration peptide (CPP) was decorated with doxorubicin (DOX), and the conjugate (CPP-DOX) was encapsulated in the carrier system for efficient cell penetration and nuclear targeting of drugs.
- Multifunctional polymeric drug delivery system has been developed, combining conjugated folic acid for active targeting, efficient cell penetration, and nuclear targeting ability.

Count....

- In this study, we designed and fabricated multifunctional polymeric drug delivery system (named FA-PECL/CPP-DOX) with the capabilities of cell penetration and nucleus targeting .As shown in the scheme1, the poly ethylene glycol-block-poly(caprolactone) is self-assembled into active targeting micelles decorated by folic acid for specific targeting the tumor cells.
- CPPs were used to target the nucleus for delivering DOX, which significantly enhanced the intracellular efficiency of anticancer drug. Moreover, we also evaluated antitumor efficiency of the drug delivery system in vivo and in vitro.

count....


FA-PEG-PCL
Self-assembly
DOX
SMP
CPP
CPP-DOX
Self-assembly
FA-PEG-PCL/CPP-DOX
Vessel
Tumor cell
Normal cell
Specific binding
enhancing endocytosis
FA receptor
Drug
release
Nuclear targeting

Cell penetrating peptide (CPP)

- CPPs are promising to target the nanocarrier to specific cells and penetrate cells . CPPs can be attached to the nanocarrier surface conferring the potential to translocate across the membrane via micropinocytosis.
- The conjugation of paclitaxel and camptothecin to a cyclic CPP containing tryptophan and arginine residue. Results revealed that antiproliferative activities of the CPP-deug conjugates were less than that of the free hydrophobic drugs in the breast cancer cell line MCF-7 after 72-hr incubation.
- Considering the targeting of CD44recepter again, several peptide sharing homology with HA-binding domain of CD44 have been discovered for treatment and diagnosis of cancer.

conclusion

- The present review discusses recent advances in smart-targeted delivery system , including the use of NPs.
- Although stimulus-responsive strategies add tumor specific-city to DDS , it is important to note that only a nanosized carrier increases the chances of the drug reaching the tumor tissue.
- Both active targeting and stimulus-responsive strategies are more efficient if the drug accumulates in the tumor tissue and is not distributed evenly throughout the body and/or eliminated from bloodstream via renal or hepatic pathway.
- However , drug accumulation in the tumor tissue is not enough if the drug released before reaching the target site or cannot enter the tumor cells.

conclusion

- In summary, combining the use of passive targeting with additional passive strategies such as active targeting and employing stimuli-responsive chemistry can potentially enhance the DDS selectivity towards cancer tissues and improve the overall therapeutic index . Even through nanomedicine is a young science, it has demonstrated the potential to increase the therapeutic.

References

- 1-urruticoechea A, Alemany R, Balart j , et al. Recent advanced in cancer therapy: an overview. Curr pharm Des, 2010;16;3-10.
- 2-Burstein HJ, krilov L, Aragon-Ching JP , et al. Clinical cancer advances 2017:annual report on progressagainst cancer from American society of clinical Oncology.
- 3-Parkhill LA, Oral mucositis and stomatitis associated with conventional and targrted anticancer therapy 2013;1:2021
- 4-pastoreli D, solda C. chemotherapy –induced nausea and vomiting (CINV):the achiles heel of oncologists. Chemother.2015;10:1-10

References

- 5- Cree IA, Charlton p . Molecular Chess ? Hallmarks of anti-cancer drug resistances. BMS Cancer.2017;17:10
- 6-Friberg S, Nystrom AM. Nanomedicine : will it offer possibilities to overcome multiple drug resistances in cancer? J Nanobiotechnology. 2016;14:1-17
- 7-schroeder A, Heller DA winslow MM, et al Treating metastatic. Cancer with nanotechnology . Nat Rev cancer. 2012;12:14-50
- 8-Upreti M J youti A, sethi P. Tumor microenvironment and nanotherapeutic. Transl Cancer Res. 2013;2:309-319