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PASSIVE AND ACTIVE TUMOR TARGETING OF NANO CARRIERS FOR ANTI-CANCER DRUG DELIVERY- A REVIEW

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Abstract:

Because of the particular characteristics of the tumor microenvironment and tumor angiogenesis, it is possible to design drug delivery systems that specifically target anti-cancer drugs to tumors. Most of the conventional chemotherapeutic agents have poor pharmacokinetics profiles and are distributed non-specifically in the body leading to systemic toxicity associated with serious side effects. Therefore, the development of drug delivery systems able to target the tumor site is becoming a real challenge that is currently addressed. Nanomedicine can reach tumor passively through the leaky vasculature surrounding the tumors by the Enhanced Permeability and Retention effect whereas ligands grafted at the surface of nanocarriers allow active targeting by binding to the receptors overexpressed by cancer cells or angiogenic endothelial cells.

This review is divided into two parts: the first one describes the tumor microenvironment and the second one focuses on the exploitation and the understanding of these characteristics to design new drug delivery systems targeting the tumor. Delivery of conventional chemotherapeutic anti-cancer drugs is mainly discussed.

Keywords: *Active targeting, Passive targeting, Enhanced Permeability and Retention effect,Nanocarriers*

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INTRODUCTION:

Cancer is a leading cause of death around the world. The World Health Organization estimates that 84 million people will die of cancer between 2005 and 2015. For effective cancer therapy, it is necessary to improve our knowledge of cancer physiopathology, discover new anti-cancer drugs and develop novel biomedical technologies. Currently, the cancer therapy has become a multidisciplinary challenge requiring close collaboration among clinicians, biological and materials scientists, and biomedical engineers. Conventional chemotherapeutic agents are distributed non-specifically in the body affecting both normal and tumor cells. Given the potency of modern pharmacological agents, tissue selectivity is a major issue. Hence, the dose achievable within the solid tumor is limited resulting in suboptimal treatment due to excessive toxicities. The ultimate goal of cancer therapeutics is to increase the survival time and the quality of life of the patient by reducing the systemic toxicity of chemotherapy [1] the idea of exploiting vascular abnormalities of tumors, avoiding penetration into normal tissue interstitial while allowing access to tumors becomes particularly attractive. In this context, the tumor targeting of nanomedicine-based therapeutics has emerged as one approach to overcome the lack of specificity of conventional chemotherapeutic agents. This concept dates back to 1906 when Ehrlich first imagined the "magic bullet" [2] The challenge of the targeting is triple: (i) to find the proper target for a particular disease; (ii) to find the drug the effectively treats this disease and (iii) to find how to carry the drug .The specific tumor targeting of nano carriers leads to better profiles of pharmacokinetics and Parma co dynamics, controlled and sustained release of drugs, an improved specificity, an increased internalization and intracellular delivery and, more importantly, a lower systemic toxicity. The tumor targeting consists in "passive targeting" and "active targeting"; however, the active targeting process cannot be separated from the passive because it occurs only after passive accumulation in tumors [3]. Alternatively, existing anti-cancer agents can be more effective by using nanomedicines (the medical application of nanotechnology). The European Science Foundation's Forward Look on Nanomedicine defined nanomedicines as «nanometer size scale complex systems, consisting of at least two components, one of which being the active ingredient». Protecting drug from the degradation, nano carriers have to be able to target a drug to the tumor site, reducing damage to normal tissue. The development of nano carriers for poorly soluble drugs is very interesting because a large proportion of new drug candidate emerging from high throughput screening are poorly-water soluble drugs which are also poorly absorbed and which present a low bioavailability. The representations of the most currently used in preclinical and clinical tumor-targeted nanomedicines are illustrated in .Nanoparticles are solid and spherical structures, ranging around 100 nm in size, in which drugs are encapsulated within the polymeric matrix. We distinguish "nano spheres" in which the drug is dispersed throughout the particles and "nano capsules" in which the drug is entrapped in a cavity surrounded by a polymer membrane [4]. They can be PEG plated and grafted with targeting ligands (Polymeric micelles are arranged in a spherical structure with hydrophobic core which increases the solubility of poorly-water soluble drugs, and the hydrophilic corona which allows a long circulation time of the drug by preventing the interactions between the core and the blood components. These systems are dynamic and have a size usually below 50 nm [5]. Liposomes are closed spherical vesicles formed by one or several phospholipid bilayers surrounding an aqueous core in which drugs can be entrapped. They can be also PEGylated and grafted with targeting ligands [6]. Dendrimers are highly branched macromolecules with controlled three-dimensional architecture. Polymers grow from a central core by a series of polymerization reactions Fig 1. Drugs are attached to surface groups by chemical modifications [7]. They can be grafted with targeting ligands [8].. To contribute to the "stealth" characteristics of PEGylated nanoparticles, there are three important factors, (i) the molecular weight of the PEG chain, (ii) the surface chain density and (iii) the conformation. The coating of PEG chains to the surface of nanoparticles results in an increase in the blood circulation half-life by several orders of magnitude. By creating a hydrophilic protective layer around the nanoparticles, steric repulsion forces repel the absorption of opsonin proteins, thereby blocking and delaying the opsonization process [9].

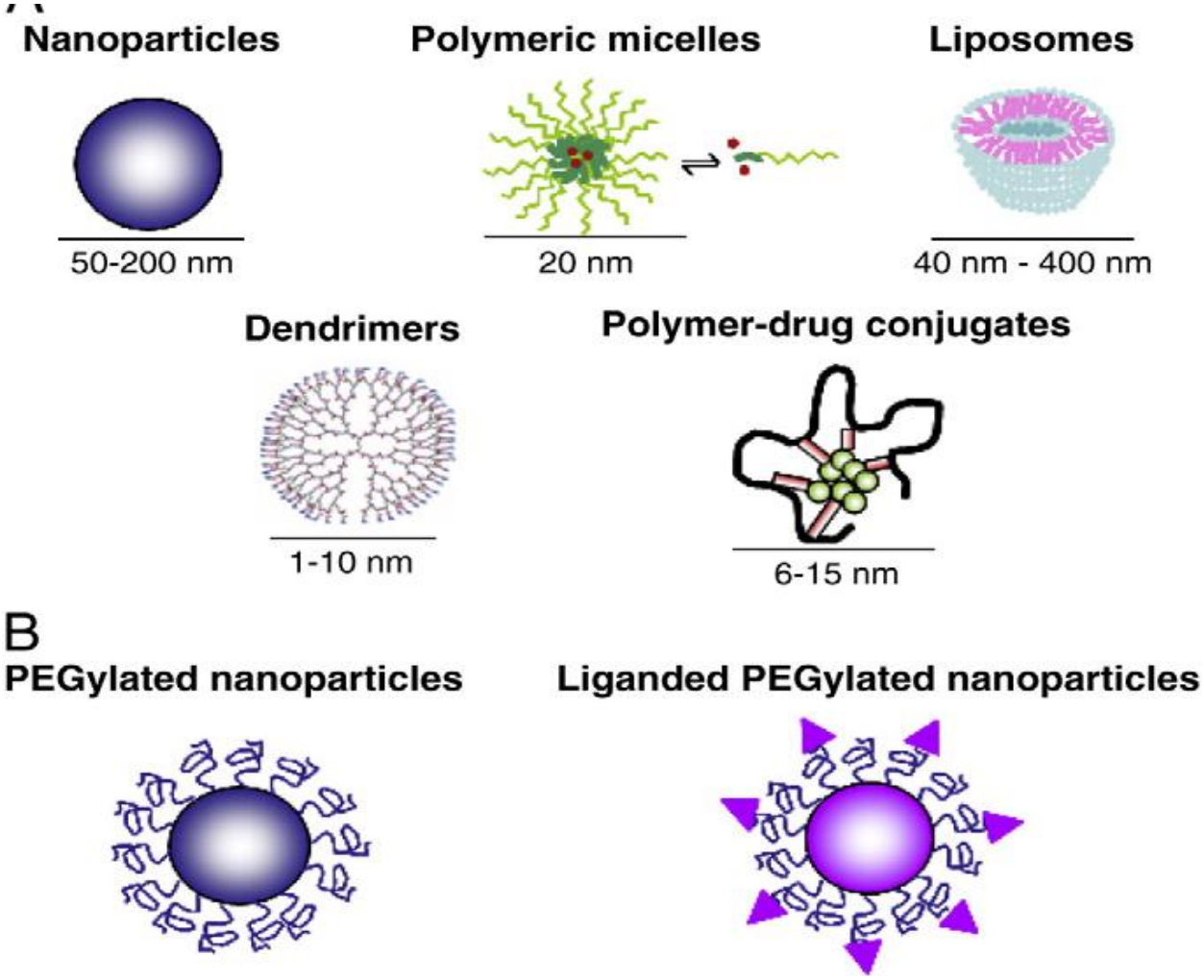

Fig.1. Nanomedicine in drug delivery. A. Types of nanocarriers currently described in Preclinical and clinical studies. B. Schematic representation of PEGylation and ligand grafting.

Tumor microenvironment

In cancer therapy, the tumor microenvironment is one of many areas which are studied to design new therapies. More precisely, the knowledge and the understanding of the tumor microenvironment allow researchers to elaborate different therapeutic strategies, based on numerous differences compared with normal tissue including vascular abnormalities, oxygenation, perfusion, pH and metabolic states. Here, the differences in terms of morphology of tumor vasculature and the pH will be particularly described as they are the more relevant characteristics for the design of nanocarriers as tumor targeted drug delivery systems.

Enhanced Permeability and Retention (EPR) effect

Structural changes in vascular patho physiology could provide opportunities for the use of long-circulating particulate carrier systems. The ability of vascular endothelium to present open fenestrations was described for the sinus endothelium of the liver [10]. When the endothelium is perturbed by inflammatory process, hypoxic areas of infracted myocardium [11]. or in tumors [12].. More particularly, tumor blood vessels are generally characterized by abnormalities such as high proportion of proliferating endothelial cells, pericyte deficiency and aberrant basement membrane formation leading to an enhanced vascular permeability. Particles, such as nano carriers (in the size range of 20–200 nm), can extravasate and accumulate inside the interstitial space. Endothelial pores have sizes varying from 10 to 1000 nm [13].. Moreover, lymphatic vessels are absent or non-functional in tumor which contributes to inefficient drainage from the tumor tissue. Nano carriers entered

into the tumor are not removed efficiently and are thus retained in the tumor. The "Enhanced Permeability and Retention (EPR) effect," discovered by Matsumura and Maeda [14]. The abnormal vascular architecture plays a major role for the EPR effect in tumor for selective macromolecular drug targeting at tissue level that can be summarized as follows and illustrated in fig 6

(1) Extensive angiogenesis and hyper vasculature
(2) Lack of smooth-muscle layer, pericytes
(3) Defective vascular architecture: fenestrations
(4) No constant blood flow and direction
(5) Inefficient lymphatic drainage that leads to enhanced retention in the interstitium of tumors
(6) Slow venous return that leads to accumulation from the interstitium of tumor

Physiological changes in blood flow within the tumors and intran sport properties of tumor vessels are consequences of these vascular abnormalities. In1987, Jain hypothesized that the osmotic pressure in tumors must be high. This high tumor interstitial fluid pressure (IFP) could be a barrier for efficient anti-cancer drug delivery [15]. It is now well known that the IFP of most solid tumors is increased. Many anti-cancer drugs — high molecular weight compounds in particular — are transported from the circulatory system through the interstitial space by convection rather than by diffusion. Increased IFP contributes to a decreased trans capillary transport in tumors, leading to a decreased uptake of drugs into tumor. In addition, IFP tends to be higher at the center of solid tumors, diminishing toward the periphery, creating a mass flow movement of fluid away from the central region of tumor. To ensure that all the tumor get an adequate drug supply, drug molecules or drug-loaded nano carriers should migrate through the tumor interstitial space from a site of entry to remote cells. This process is hindered by high IFP. Due to their greater size, the transport of drug-loading nano carriers is less affected by this enhanced IFP in tumors. Moreover, the microvasculature pressure in tumors is also one to two orders of magnitude higher than in normal tissues. This facilitates extravasation of nano carriers that could otherwise have been precluded by high IFP. Many types of nano carriers successfully overcome these barriers and selectively accumulate in the tumors [16-19] fig 2.

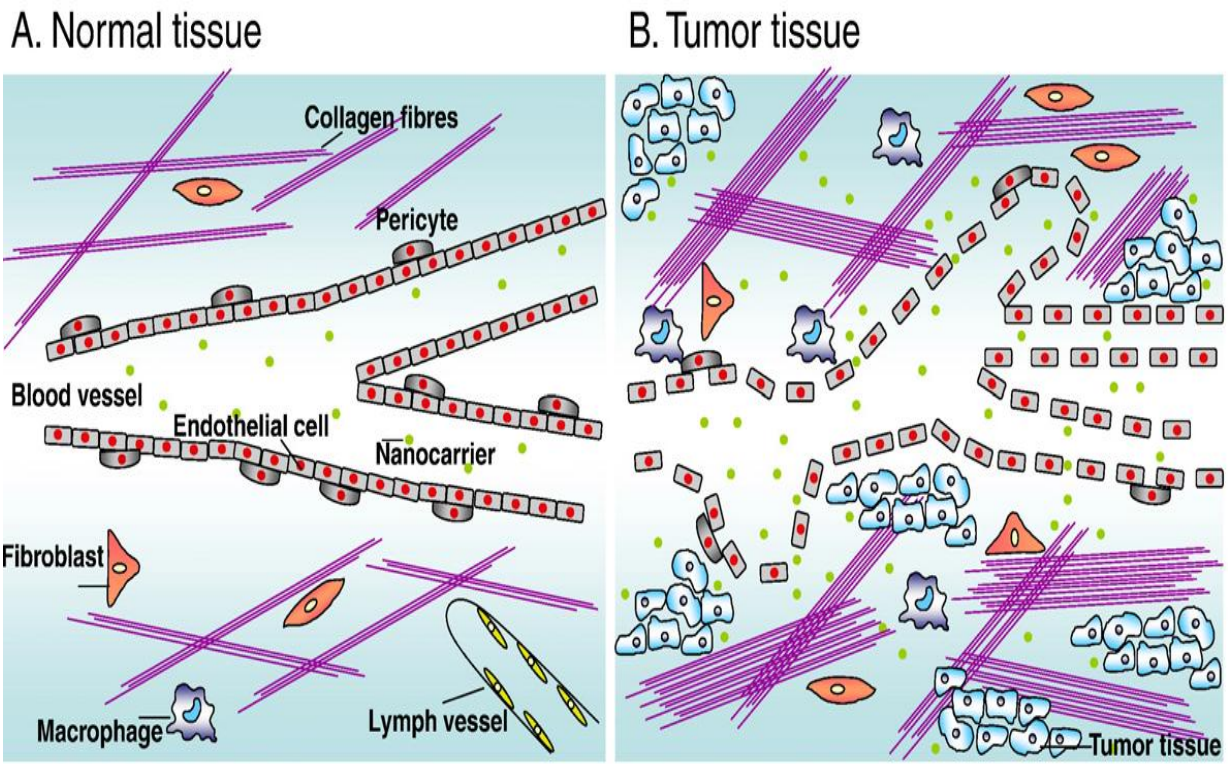

Fig2: Differences between normal and tumor tissues that explain the passive targeting of nano carriers by the Enhanced Permeability and Retention effect. A. Normal tissues contain Linear blood vessels maintained by pericytes. Collagen fibres, fibroblasts and macrophages

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