EPR-Effect and Nano-medicine Backdoor or Bottleneck?

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Received date: 08 August, 2015; Accepted date: 13 August, 2015; Published date: 25 August, 2015

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Editorial

Cancers are a leading cause of death today as they will be in the future. Chemotherapy is one of the major weapons we have in the ill equipped battle against this important human threat. Despite several drawbacks, nanoparticle based drug delivery systems (DDS) hold promise to ameliorate anticancer chemotherapy. From the beginning of “Nano medicine” by the discovery of liposomes by Bangham et al. in 1965 [1] till the recent boost of papers about various new materials and combined strategies in the last decade, a vast number of chemotherapeutic agents has been loaded or encapsulated into different kinds of nanoparticles. Many approaches have been successfully tested, at least in preclinical studies [2]. Unfortunately, only very few “Nano medicines” are in clinical practice today, despite the fact that they accumulate in human tumors by the same mechanism as DDS do in animal models.

While DDS are unable to penetrate the endothelial barrier in most organs, they extravasate into tumor tissues by the so called “enhanced permeation and retention effect”, often referred to as “EPR-effect”[3]. In contrast to healthy endothelial barriers, neovascularization in growing tumor tissues is usually leaky, showing gaps between 200 nm and 2 μm in size [4]. These gaps allow DDS, usually in a therapeutic range between 50 and 200 nm, to enter the tumor interstitium. Once inside the tumor, they may further penetrate the tumor by diffusion, even though this penetration is limited to a range of a few cell layers around the blood vessels [5]. Since there is no lymphatic clearance of tumor interstitium, the accumulated particles are retained in the tumor. Beside DDS targeting the tumor vasculature, the EPR-effect is the basic entry route of all DDS that are developed for antitumor therapy.

Exploiting the EPR-effect by non-targeted DDS is also referred to as “passive targeting”, and the most successful clinically used DDS-pegylated liposomal doxorubicin – is based upon passive targeting [6]. Unfortunately, the EPR-effect is although the major bottle-neck for new developments. It won’t help to develop new materials, better targeting or highly sophisticated cell killing, only to shipwreck at limitations of EPR first hand. A more detailed understanding of accumulation of DDS into tumor tissue by EPR is urgently needed to improve the use of nanomedicine in future.

References