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Preface

EPR effect based drug design and clinical outlook for enhanced cancer chemotherapy☆

Twenty-five years have already passed since our discovery of the enhanced permeability and retention (EPR) effect [1]. The concept of the EPR effect has prevailed in a wide range of applications including antibody delivery, gene delivery, and other nanomedicine-based delivery systems such as micellar, liposomal and polymer conjugates. After a rather quiet initial two decades, its citations now reached more than 6000 and have been increasing logarithmically, as shown by J. Fang et al. [2] in this issue. It is an ideal time to assess the past and present state in terms of limitations and further development, because the EPR effect is a more general principle for tumor-selective drug delivery compared to "molecular target" drugs. In this connection, the limitations of macromolecular target drugs are discussed by Fang et al. [2] and the impact of the EPR effect in drug delivery is well documented by Torchilin in the Commentary [3].

This issue provides some historical background and covers a number of topics ranging from basic principles to clinical outlook, to advantages and limitations, to key factors involved and nanomedicines under clinical development. Based on the concept of the EPR effect, a more sophisticated drug design is presented by Harashima et al. and Murayama et al., and the circumvention of barriers in drug targeting is also discussed by Fang et al. in this issue [2].

One problem that has caused some concern is the heterogeneity of the EPR effect. When the tumor nodule is very small or at an early stage of cancer development, there is no heterogeneity. However, in larger or later-stage tumors, the EPR effect becomes heterogeneous. In the case of a mouse tumor nodule greater than 500 mg (>1.7 mg in rats), we found less production of nitric oxide, which is one of the major factors for EPR effect (see Fang et al. in this issue [2]). This would incidentally lower the extravasation of macromolecules into the interstitial tissue space. This concept may be applicable to the tumor implanted at a non-orthotropic site, which may exhibit a heterogeneous EPR effect of lower vascular density such as metastatic tumors in the liver, as clinically observed in CT scan images of primary vs. metastatic human liver cancer after intra-arterial injection of SMANCS/Lipiodol. The former was more uniform and exhibited denser vasculature, and thus higher EPR effect, while the latter exhibited a hypovasculature pattern in the central part and thus lower EPR effect (heterogeneity). We (H.M.) recently published basic findings and clinical demonstrations to augment the EPR effect, and circumvention of this heterogeneity is discussed elsewhere [2,4–7].

Whatever minor issues might remain, nanomedicine drug development has been increasing during the past 10 years (for instance, see Ref. [8]). Along this line, the reviews by Sahoo et al., Maruyama et al., and Matsumura et al. give us the present situation of nanomedicine development and future prospects. Recent trends in this area of polymeric drugs are reported by many authors more than ever, yet await for clinical breakthrough (see for instance ref.[9]).

Molecular targeting agents showed promise in the case of imatinib (Gleevec®). However, other cases appear disappointing, including antibody conjugates; some have unremarkable therapeutic effects and also occasionally exhibit serious side effects. The simple reason for this is that we have not yet found cancer-specific molecules that are universally effective for all or specific classes of cancer. Acquisition of information on the molecular biology of cancer is an ongoing process and molecular targeting agents are developed accordingly; however, it is still insufficient for cancer eradication. Consequently, there is an obvious need to clinically introduce the concept of the EPR effect as well as to improve conventional anticancer agents on this basis.

Under these circumstances, clinical application of nanomedicine based on the EPR effect would definitely benefit the patients, as discussed by Matsumura et al. in this issue. Furthermore, development of a method for augmenting the EPR effect, for instance, by using nitroglycerin, a nontoxic nitric oxide generator with proven safety if not overdosed, warrants future investigation and extension to the bedside.

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The EPR effect: Unique features of tumor blood vessels for drug delivery, factors involved, and limitations and augmentation of the effect☆

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ABSTRACT

The enhanced permeability and retention (EPR) effect is a unique phenomenon of solid tumors related to their anatomical and pathophysiological differences from normal tissues. For example, angiogenesis leads to high vascular density in solid tumors, large gaps exist between endothelial cells in tumor blood vessels, and tumor tissues show selective extravasation and retention of macromolecular drugs. This EPR effect served as a basis for development of macromolecular anticancer therapy. We demonstrated methods to enhance this effect artificially in clinical settings. Of great importance was increasing systolic blood pressure via slow angiotensin II infusion. Another strategy involved utilization of NO-releasing agents such as topical nitroglycerin, which releases nitrite. Nitrite is converted to NO more selectively in the tumor tissues, which leads to a significantly increased EPR effect and enhanced antitumor drug effects as well. This review discusses molecular mechanisms of factors related to the EPR effect, the unique anatomy of tumor vessels, limitations and techniques to avoid such limitations, augmenting tumor drug delivery, and experimental and clinical findings.

Contents

Abbreviations: NO, nitric oxide; SMA, styrene maleic acid copolymer; NCS, neocarzinostatin; CT, computed tomography; AUC, area under the concentration–time curve; IgG, immunoglobulin G; HPMA, *N*-(2-hydroxypropyl)methacrylamide; α_2-M, α_2-macroglobulin; XO, xanthine oxidase; RES, reticuloendothelial system; VEGF, vascular endothelial growth factor; SEM, scanning electron microscope; AT-II, angiotensin II; iNOS, inducible nitric oxide synthase; $ONOO^-$, peroxynitrite; VPF, vascular permeability factor; PG, prostaglandin; SBTI, soybean trypsin inhibitor; cPTIO, carboxy-2-phenyl-4,4,5,5-tetramethylimidazoline-1-oxyl-oxide; $O_2^{-\cdot}$, superoxide anion radical; MMP, matrix metalloproteinase; NG, nitroglycerin; COX, cyclooxygenase; ACE, angiotensin-converting enzyme; HCC, hepatocellular carcinoma; ISDN, isosorbide dinitrate; pO_2, partial oxygen pressure.

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