SciMedCentral

JSM Clinical Oncology and Research

Mini Review

Enhanced Permeability and Retention (EPR) Effect Based Tumor Targeting: The Concept, Application and Prospect

Hongzhuan Yin[1,2], Long Liao[2,3] and Jun Fang[2,4,5]*

[1]*Department of General Surgery, Shengjing Hospital, China Medical University, Shenyang City, Liaoning Province, 110004 China*
[2]*DDS Research Institute, Sojo University, Ikeda 4-22-1, Nishi-Ku, Kumamoto 860-0082*
[3]*Department of Applied Microbial Technology, Faculty of Biotechnology & Life Science, Sojo University*
[4]*Laboratory of Microbiology & Oncology, Faculty of Pharmaceutical Sciences*
[5]*School of Public Health, Anhui Medical University, 81th Meishan Road, Hefei City, Anhui Province, 230032 China*

***Corresponding author**
Jun Fang, DDS Research Institute, Sojo University, Nishi-ku Ikeda 4-22-1, Kumamoto, 860-0082, Japan, Tel: +81-96-326-4137; Fax: +81-96-326-5048; Email: fangjun@ph.sojo-u.ac.jp

Submitted: 15 January 2014

Accepted: 28 January 2014

Published: 30 January 2014

Keywords
- EPR effect
- Solid tumors
- Drug delivery
- Chemotherapy

Abstract

Conventional chemotherapy with small molecule drugs has been used for many types of cancer for decades. However, the therapeutic efficacy remains less successful, mostly because of poor tumor selectivity and severe adverse side effects which hampered the use of high drug doses. The development of tumor-targeted chemotherapy is thus critically important for more successful treatment. The enhanced permeability and retention (EPR) effect is a unique phenomenon of solid tumors based on their anatomical and pathophysiological differences from normal tissues, namely macromolecular drugs could accumulate and retain in solid tumor tissues selectively but they will not distribute much in normal tissue. EPR based chemotherapy is thus becoming an important strategy to improve the delivery of therapeutic agents to tumors for anticancer drug development, and macromolecular agents are potentially usefully for not only cancer therapy, but for cancer diagnosis and imaging. In this commentary, the concept and application of the EPR effect, as well as methods to further augment EPR effect by using factors associated with EPR effect such as nitric oxide, carbon monoxide, are briefly discussed. We believe that understanding EPR effect and EPR based tumor targeting will greatly promote the development of new therapeutic strategies and anticancer drugs for anticancer therapeutics.

DEFINITION OF EPR EFFECT

In 1980's, Maeda and his colleagues found that macromolecules such as polymers and proteins with molecular weight larger than 40-50 kDa showed selective accumulation in tumor tissues, far more than that observed in normal tissues, moreover, they retained in tumor tissues for long periods, i.e., > 24 h [1]. They coined this unique phenomenon enhanced permeability and retention (EPR) effect [1]. Accordingly, an EPR based tumor targeting strategy (macromolecular therapy) was developed by using polymer modification, nanoparticles, micelles, liposome and so on, all of which exhibited more than 10-200 times higher concentrations in tumor than that in normal tissues, such as skin, muscle, heart, and kidney, after systemic administration [1-6]. These findings led to generalization of the concept of the EPR effect, and now it is becoming a "gold standard" for the anticancer drug design.

EPR effect is a phenomenon due to the unique anatomical and pathophysiological characteristics of solid tumor. Namely, in contrast to normal tissues and organs, most solid tumors show a higher vascular density (hypervasculature), i.e., angiogenesis that is one of the most important features of tumors to sustain their rapid growth. Electron microscopy of a vascular cast of tumor blood vessels that was obtained by using polymer resin showed distinct differences between tumor vessels and normal blood vasculature [7-9]. Tumor vascular angiogenesis (vascular bed) could be observed even when tumor nodules were smaller than 0.2 mm [10,11]. Moreover, irregular or inconsistent blood flow is also commonly observed in tumors [12].

Furthermore, most solid tumors have blood vessels with defective architecture, such as large gap between endothelial cells (e.g., ~ 1μm), lack of smooth muscle layers, so that macromolecules will have the opportunity to escape from tumor blood vessels and accumulate selectively in tumor tissues, whereas they could not cross normal blood vessels which will result in less side effects. The enhanced permeability of tumor blood vessels is also partly attributed to the over-produced vascular mediators, such as bradykinin, nitric oxide (NO), vascular endothelial growth factor (VEGF), carbon monoxide (CO) etc. [2,6,7]. These factors further enhance the permeability of tumor vasculature, thus being useful for the augmentation of EPR based tumor targeting which is discussed below.

In addition, defected lymphatic function that is important for the recovery of macromolecules in tissues, is always found in tumor tissues [6-10]. Consequently, once macromolecules accumulate in tumor tissues, they will not cleared from tumor tissues but retain there for long time.

Above-mentioned anatomic and pathophysiological characteristics together lead to the unique phenomenon of EPR effect, the principal mechanism of EPR effect is diagrammatically represented in Figure 1.

APPLICATION OF EPR EFFECT

EPR-based tumor targeting requires macromolecular drugs to have longer half-life time in order to provide a sufficient effective pharmacodynamic level. The usual way to obtain macromolecular drugs is to "mask" conventional small molecular drugs by modifying their surface with certain water-soluble polymers with a well-solvated and flexible main chain, such as polyethylene glycol (PEG), styrene maleic acid (SMA), N-(2-hydroxypropyl)methacrylamide (HPMA), and so on [1,13,14].

Regarding the tumor targeting strategy, two kinds of targeting are always mentioned in literatures, i.e., "passive targeting" and "active targeting". Passive targeting is so far EPR-based tumor targeting. To date, many macromolecular drugs were developed based on EPR effect, some of which are used in clinic and more are in preclinical stages, including liposomes, polymers, micelles, and nanoparticles [3-6, 8-10]. Examples of macromolecular drugs approved for clinical use are DaunoXome® (non-PEGylated liposomal daunorubicin), Abraxane® (albumin-based paclitaxel), DepoCyt® (non-PEGylated liposomal cytarabine), Doxil® (Caelyx in Europe; PEGylated liposomal doxorubicin), Myocet® (non-PEGylated liposomal doxorubicin), Oncaspar® (PEGylated L-asparaginase), and Genexol-PM® (paclitaxel-containing polymeric micelles; approved in Korea). Many other ones are in early- and late-stage preclinical development [15-19], which may be approved for certain cancer patients in few years.

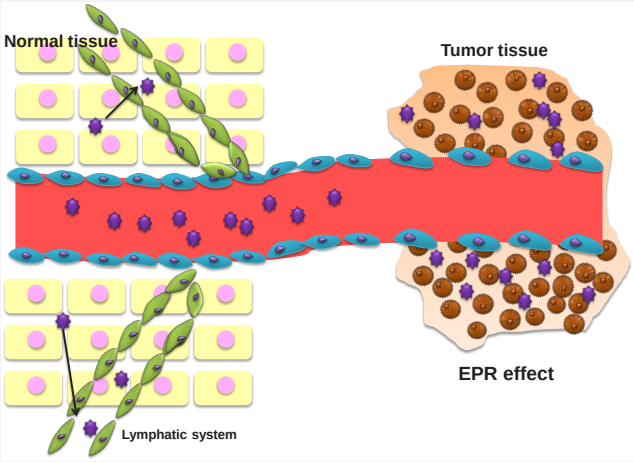

Figure 1 Diagrammatic representation of EPR effect. Normal blood vessels have surrounding smooth muscle-cell layer with tighten the cell-cell junctions which macromolecular agents are difficult to extravasate. In contrast, in tumor tissues, blood vessels are always with loose cell-cell junctions, via which macromolecular agents can escape to tumor tissue. In addition, the defected lymphatic system in tumors leads to the retention of macromolecular agents in tumor tissues.

Another widely used tumor-targeting strategy is aiming at the special molecules or receptors in tumor cells using, for example, transferrin, folate, integrin receptors, epidermal growth factor, antibodies, glycoprotein etc., namely active targeting [20-22]. However, it is critically important and should be noted and emphasized that for targeted tumor delivery, no matter "passive targeting" or "active targeting", EPR effect is the first and necessary step, namely, the drugs need to accumulate first in tumor by EPR effect, and then active targeting using ligands, antibodies could be achieved. Tumor specific Fab with molecular weight less than 40 kDa (no EPR effect) could not accumulate efficiently in tumor, but most were cleared out from circulation [5]. On the other hand, it may be a more effective strategy when active targeting techniques are designed based on EPR effect. In fact, many clinically-approved active targeting drugs are antibody-based nanomedicines which can be taking advantage of EPR effect. For example, Zevalin (CD20-targeted 90yttriumibritumomab tiuxetan), Bexxar (CD20-targeted iodine-131-tositumomab), Ontak (CD25-targeted diphteria toxin-IL2 fusion protein), and Mylotarg (CD33-targeted ozogamycin-gemtuzumab) have been successfully used for non-Hodgkin`s lymphoma, T-cell lymphoma and acute myeloid leukemia [23].

AUGMENTATION OF EPR EFFECT

Because EPR effect is mostly due to the high permeability of tumor vasculature, it is reasonable to use vascular mediators such as NO, CO, bradykinin, VEGF to further enhance EPR effect thus achieving more tumor accumulation of macromolecular drugs. In this section, we discuss this issue by focusing on the effect of NO and CO, using our recent findings.

NO and its Derivatives

NO is a vital molecule in living creatures and is produced from L-arginine by NO synthase (NOS) in the presence of oxygen, which has multiple roles, directly or indirectly as a signaling messenger. It is important to note that tumors tissue also showed extensive iNOS expression, mostly in extensively infiltrated leukocytes and macrophages, indicating that tumors produce significantly more NO compared with normal tissues [24,25] (Figure 2A). The amount of NO produced in tumors has a positive association with tumor weight-up to 1.75 g in AH136B tumor-bearing rats and 250 mg in mice bearing sarcoma 180 (S-180) tumors [26]. iNOS knockout mice evidenced clearly delayed tumor growth [27].

Thus, NO generation is critical for tumor growth, and to maintain the supply of nutrients and oxygen.

Regarding the roles of NO in tumor vessel permeability and EPR effect, by use of an oily formulation of NO (a solution of NO in medium-chain triglycerides), we found a marked extravasation of Evans blue-/albumin complex at the injection site after intradermal injection of this formulation into guinea pigs [26]. The extravasation was significantly inhibited by the NO scavenger carboxy-2-phenyl-4,4,5,5-tetramethylimidazoline-1-oxyl-oxide (cPTIO) [25]. Similarly, using an in vivo experiments with a tumor-bearing mouse model, we found significant increase of extravasation of Evans blue in tumors after intravenous injection (EPR effect), results corresponding to the amount of NO in tumor (Figure 2B,C), and this extravasation (EPR effect) was significantly inhibited by both cPTIO and the NOS inhibitor N^{ω}-monomethyl-L-arginine (L-NMMA) [26].

In addition, like NO, oxidized products of NO including peroxynitrite ($ONOO^-$) and nitrogen dioxide could also potentiate the EPR effect. Among these NO derivatives, $ONOO^-$ is a strong oxidizing and nitrating agent, which forms via the reaction of NO with superoxide anion ($O^-_2{}^{\bullet}$) at a diffusion-limited rate [29], which is also generated extensively in tumor and inflammatory tissues, primarily via NADPH oxidase and cytochrome b_5 reductase in infiltrated macrophages and neutrophils, as well as xanthine oxidase [30, 31]. More important, it has also been known that NOS can catalyze the generation of $O^-_2{}^{\bullet}$, by its reductase domain using oxygen and nitroguanosine (a nitrosated product of guanosine) [32], which may further enhance the production of $ONOO^-$.

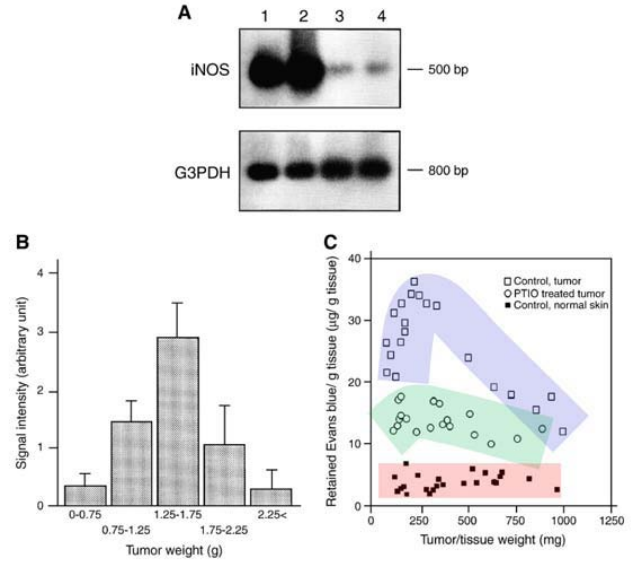

Figure 2 NO production in different tumors. (A) RT-PCR for iNOS mRNA expression in rat AH136B solid tumor: lanes 1 and 2 are AH136B tumors obtained from two different rats, and lanes 3 and 4 are results for two normal livers. (B) Correlation of the concentration of NO in solid tumor (AH136B) with tumor weight. Data are expressed as means ± SE. (C) Association between S-180 tumor weight in mice and the extent of extravasation of Evans blue/albumin in tumor (the EPR effect), and the concentration of NO in tumors of different size. PTIO is an NO scavenger. Tumors weighing up to 1.75 g in rats (B) and 250 mg in mice (C) showed size-dependent NO production and extravasation of Evans blue/albumin. Data are from Refs 24-26, with modifications and with permission.

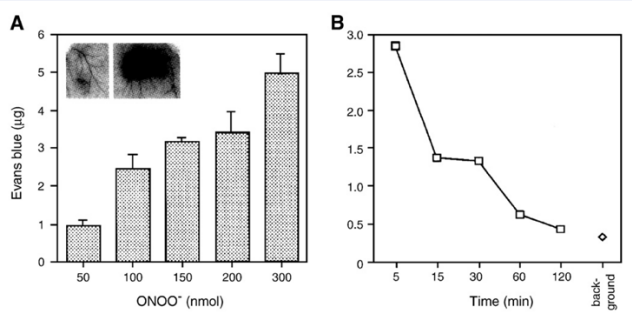

Figure 3 Dose-dependent effect of ONOO- on vascular permeability of dorsal skin in normal mice (A) and duration of the enhancement of vascular permeability (B). (A) ONOO- was injected intradermally at the indicated concentrations. The inset shows authentic ONOO- induced vascular permeability in mouse skin (left: decomposed ONOO-, right: ONOO- 100 nmol). (B) Evans blue (10 mg/kg) was given by i.v. injection at 10, 15, 30, 60, or 120 min after intradermal injection of 100 nmol ONOO- into dorsal skin; dye extravasated for 1 h. Data are from Refs 33, with permission.

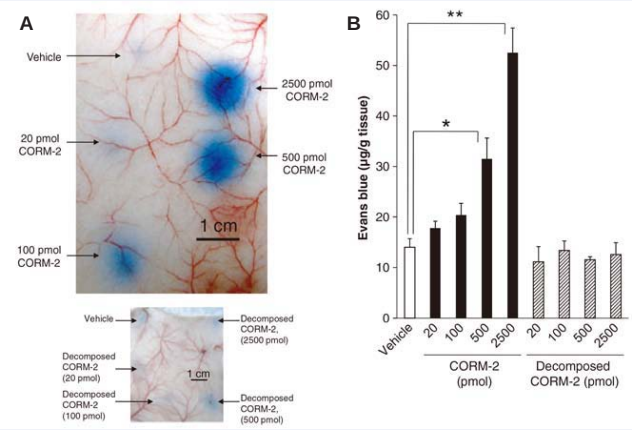

Figure 4 Effect of CO releasing molecule (CORM-2) on the vascular permeability of the dorsal skin of normal mice. Different concentrations of CORM-2 were administered i.d., followed by i.v. injection of Evans blue (10 mg / kg). The dye was allowed to extravasate for 2 h. (A) Representative images showing CORM- 2-induced extravasation of blue dye. (B) Quantification of Evans blue extravasation in the skin. Data are the mean ± SEM (n = 3-4). *P < 0.05, **P < 0.01. Data are from Refs 43, with permission.

In a similar manner, intradermal injection of $ONOO^-$ increased extravasation of Evans blue/albumin in a dose-dependent manner at the site of injection (Figure 3A). This extravasation lasted for a relatively long time (e.g., 2 h) after $ONOO^-$ administration (Figure 3B) [33], even though the half-life of $ONOO^-$ at physiological pH is only a few seconds [34]. These findings suggested a secondary or indirect mechanism in $ONOO^-$ induced enhancement of the EPR effect. One major mechanism may involve matrix metalloproteinases (MMPs) [33], which are classified as zinc-dependent neutral endopeptidases that are expressed at high levels in tumor cells and play important roles in tumor invasion, metastasis, and angiogenesis [35, 36]. Namely, ONOO- may potentially activate MMPs which in turn

cause disintegration and remodeling of the extracellular matrix as a result of collagenolytic action, thus facilitating vascular permeability [33]. Moreover, activated MMPs may probably affect blood vessels as well. Also, $ONOO^-$ can be decomposed to generate NO, which leads to functioning of the EPR effect. In addition, the high reactivity of $ONOO^-$ leads to rapid production of nitrate or nitrosated aromatic residues including proteins and nucleic acids, and thus generation of nitrotyrosine and nitroguanosine [37]. These nitro compounds are likely to release nitrite (NO_2^-) and may serve as a source of NO to augment EPR effect.

CO

CO is an increasingly attractive molecule, being accepted as a cytoprotective and homeostatic molecule with important signalling capabilities in physiological and pathophysiological conditions, with most similar functions as NO [38]. The major source (i.e. > 80%) of CO in biological systems is heme oxygenase (HO)-catalysed heme degradation [39]. CO has been reported as an important endogenous signaling molecule with various biological functions including regulation of vascular tonus, being involved in anti-apoptosis, having anti-inflammatory effects, and inducing angiogenesis [39, 40]. Regarding the effect of CO on vasoregulation, most data support a prodilatory role for CO; however, vasoconstrictor effects of CO have also been reported via inhibition of NO synthesis to antagonize NO-dependent vasodilation [41] or via the induction of a more oxidative stage of the vasculature by CO [42]. In our laboratory, we clearly found that CO increased vascular permeability and blood flow, suggesting a vasodilatory role for CO in the experimental setting and improving the EPR effect (Figure 4) [43]. Inducing the production of CO in tumors, by upregulating HO or by using CO donor, may become a useful tool to enhance EPR effect and tumor delivery of macromolecular drugs, whereas warrants further investigations.

PROSPECT OF EPR EFFECT

Many current tumor drug delivery systems are trying to go further than just providing tumor accumulation. Attempts are under way to combine tumor cell-specific targeting with longevity-sponsored EPR based accumulation. Intracellular delivery of drug-loaded macromolecular conjugates and pharmaceutical nanocarriers accumulated in tumors via the EPR effect can be facilitated by various means.

Accordingly, the opportunities for the tumor drug delivery look just great. But whatever complex schemes are being developed to effectively bring anticancer drugs and genes into tumors, the EPR effect-mediated tumor accumulation remains the first crucial step of any scheme.

REFERENCES

1. Matsumura Y, Maeda H. A new concept for macromolecular therapeutics in cancer chemotherapy: mechanism of tumoritropic accumulation of proteins and the antitumor agent smancs. Cancer research. 1986; 46 (12 Part 1):6387-92.
2. Fang J, Sawa T, Maeda H. Factors and mechanism of "EPR" effect and the enhanced antitumor effects of macromolecular drugs including SMANCS.). Polymer Drugs in the Clinical Stage: Springer; 2004. p. 29-49.
3. Vicent MJ, Ringsdorf H, Duncan R. Polymer therapeutics: clinical applications and challenges for development. Advanced Drug Delivery Reviews. 2009; 61 (13):1117-20.
4. Duncan R. The dawning era of polymer therapeutics. Nature Reviews Drug Discovery. 2003; 2 (5):347-60.
5. Matsumura Y, Kataoka K. Preclinical and clinical studies of anticancer agent incorporating polymer micelles. Cancer science. 2009; 100 (4):572-9.
6. Fang J, Nakamura H, Maeda H. The EPR effect: Unique features of tumor blood vessels for drug delivery, factors involved, and limitations and augmentation of the effect. Adv Drug Deliv Rev. 2011;63(3):136-51. doi: 10.1016/j.addr.2010.04.009.
7. Maeda H, Fang J, Inutsuka T, Kitamoto Y. Vascular permeability enhancement in solid tumor: various factors, mechanisms involved and its implications. International immunopharmacology. 2003; 3 (3):319-28.
8. Iyer AK, Khaled G, Fang J, Maeda H. Exploiting the enhanced permeability and retention effect for tumor targeting. Drug discovery today. 2006; 11 (17):812-8.
9. Greish K. Enhanced permeability and retention of macromolecular drugs in solid tumors: a royal gate for targeted anticancer nanomedicines. Journal of drug targeting. 2007; 15 (7-8):457-64.
10. Maeda H, Bharate GY, Daruwalla J. Polymeric drugs for efficient tumor-targeted drug delivery based on EPR-effect. European Journal of Pharmaceutics and Biopharmaceutics. 2009; 71 (3):409-19.
11. Daruwalla J, Greish K, Malcontenti-Wilson C, Muralidharan V, Iyer A, Maeda H, et al. Styrene maleic acid-pirarubicin disrupts tumor microcirculation and enhances the permeability of colorectal liver metastases. Journal of vascular research. 2008; 46 (3):218-28.
12. Hori K, Suzuki M, Tanda S, Saito S, Shinozaki M, Zhang QH. Fluctuations in Tumor Blood Flow under Normotension and the Effect of Angiotensin II-induced Hypertension. Cancer science. 1991; 82 (11):1309-16.
13. Otsuka H, Nagasaki Y, Kataoka K. PEGylated nanoparticles for biological and pharmaceutical applications. Advanced drug delivery reviews. 2012.
14. Talelli M, Rijcken CJF, Van Nostrum CF, Storm G, Hennink WE. Micelles based on HPMA copolymers. Advanced drug delivery reviews. 2010; 62 (2):231-9.
15. Lammers T, Hennink WE, Storm G. Tumour-targeted nanomedicines: principles and practice. British journal of cancer. 2008; 99 (3):392-7.
16. Allen TM, Cullis PR. Drug delivery systems: entering the mainstream. Science. 2004; 303 (5665):1818-22.
17. Peer D, Karp JM, Hong S, Farokhzad OC, Margalit R, Langer R. Nanocarriers as an emerging platform for cancer therapy. Nature nanotechnology. 2007; 2 (12):751-60.
18. Davis ME. Nanoparticle therapeutics: an emerging treatment modality for cancer. Nature Reviews Drug Discovery. 2008; 7 (9):771-82.
19. Jain RK, Stylianopoulos T. Delivering nanomedicine to solid tumors. Nature Reviews Clinical Oncology. 2010; 7 (11):653-64.
20. Kolhatkar R, Lote A, Khambati H. Active tumor targeting of nanomaterials using folic acid, transferrin and integrin receptors. Curr Drug Discov Technol. 2011;8(3):197-206.
21. Maruyama K. Intracellular targeting delivery of liposomal drugs to solid tumors based on EPR effects. Adv Drug Deliv Rev. 2011;63(3):161-9. doi: 10.1016/j.addr.2010.09.003.
22. Kedar U, Phutane P, Shidhaye S, Kadam V. Advances in polymeric

micelles for drug delivery and tumor targeting. Nanomedicine. 2010;6(6):714-29. doi: 10.1016/j.nano.2010.05.005.

23. Gupta B, Levchenko TS, Torchilin VP. Intracellular delivery of large molecules and small particles by cell-penetrating proteins and peptides. Advanced drug delivery reviews. 2005; 57 (4):637-51.

24. Akaike T, Horie H, Noguchi Y, Fujii S, Beppu T, Ogawa M, et al. Excessive production of nitric oxide in rat solid tumor and its implication in rapid tumor growth. Cancer. 1996; 77 (8):1598-604.

25. Doi K, Akaike T, Fujii S, Tanaka S, Ikebe N, Beppu T, et al. Induction of haem oxygenase-1 by nitric oxide and ischaemia in experimental solid tumours and implications for tumour growth. British journal of cancer. 1999; 80 (12):1945.

26. Maeda H, Noguchi Y, Sato K, Akaike T. Enhanced vascular permeability in solid tumor is mediated by nitric oxide and inhibited by both new nitric oxide scavenger and nitric oxide synthase inhibitor. Cancer science. 1994; 85 (4):331-4.

27. Kisley LR, Barrett BS, Bauer AK, Dwyer-Nield LD, Barthel B, Meyer AM, et al. Genetic ablation of inducible nitric oxide synthase decreases mouse lung tumorigenesis. Cancer research. 2002; 62 (23):6850-6.

28. Wu J, Akaike T, Maeda H. Modulation of enhanced vascular permeability in tumors by a bradykinin antagonist, a cyclooxygenase inhibitor, and a nitric oxide scavenger. Cancer research. 1998; 58 (1):159-65.

29. Hill BG, Dranka BP, Bailey SM, Lancaster JR, Darley-Usmar VM. What part of NO don't you understand? Some answers to the cardinal questions in nitric oxide biology. Journal of Biological Chemistry. 2010; 285 (26):19699-704.

30. Akaike T, Maeda H. Nitric oxide and virus infection. Immunology. 2000; 101 (3):300-8.

31. Akaike T, Suga M, Maeda H. Free radicals in viral pathogenesis: molecular mechanisms involving superoxide and NO. Experimental Biology and Medicine. 1998; 217 (1):64-73.

32. Sawa T, Akaike T, Ichimori K, Akuta T, Kaneko K, Nakayama H, et al. Superoxide generation mediated by 8-nitroguanosine, a highly redox-active nucleic acid derivative. Biochemical and biophysical research communications. 2003; 311 (2):300-6.

33. Wu J, Akaike T, Hayashida K, Okamoto T, Okuyama A, Maeda H. Enhanced vascular permeability in solid tumor involving peroxynitrite and matrix metalloproteinases. Cancer science. 2001; 92 (4):439-51.

34. Okamoto T, Akaike T, Nagano T, Miyajima S, Suga M, Ando M, et al. Activation of human neutrophil procollagenase by nitrogen dioxide and peroxynitrite: a novel mechanism for procollagenase activation involving nitric oxide. Archives of biochemistry and biophysics. 1997; 342 (2):261-74.

35. Przybylowska K, Zielinska J, Zadrozny M, Krawczyk T, Kulig A, Wozniak P, et al. An association between the matrix metalloproteinase 1 promoter gene polymorphism and lymphnode metastasis in breast cancer. Journal of experimental and clinical cancer research. 2004; 23 (1):121-6.

36. Zhou Y, Li G, Wu J, Zhang Z, Wu Z, Fan P, et al. Clinicopathological significance of E-cadherin, VEGF, and MMPs in gastric cancer. Tumor Biology. 2010; 31 (6):549-58.

37. Sawa T, Zaki MH, Okamoto T, Akuta T, Tokutomi Y, Kim-Mitsuyama S, et al. Protein S-guanylation by the biological signal 8-nitroguanosine 3′, 5′-cyclic monophosphate. Nature chemical biology. 2007; 3 (11):727-35.

38. Motterlini R, Otterbein LE. The therapeutic potential of carbon monoxide. Nat Rev Drug Discov. 2010;9(9):728-43. doi: 10.1038/nrd3228.

39. Abraham NG, Kappas A. Pharmacological and clinical aspects of heme oxygenase. Pharmacological Reviews. 2008; 60 (1):79-127.

40. Otterbein LE, Bach FH, Alam J, Soares M, Lu HT, Wysk M, et al. Carbon monoxide has anti-inflammatory effects involving the mitogen-activated protein kinase pathway. Nature medicine. 2000; 6 (4):422-8.

41. Lin H-H, Lai S-C, Chau L-Y. Heme oxygenase-1/carbon monoxide induces vascular endothelial growth factor expression via p38 kinase-dependent activation of Sp1. Journal of Biological Chemistry. 2011; 286 (5):3829-38.

42. Ferrara N, Henzel WJ. Pituitary follicular cells secrete a novel heparin-binding growth factor specific for vascular endothelial cells. Biochemical and biophysical research communications. 1989; 161 (2):851-8.

43. Fang J, Qin H, Nakamura H, Tsukigawa K, Shin T, Maeda H. Carbon monoxide, generated by heme oxygenase-1, mediates the enhanced permeability and retention effect in solid tumors. Cancer science. 2012; 103 (3):535-41.

Cite this article

Yin H, Liao L, Fang J (2014) Enhanced Permeability and Retention (EPR) Effect Based Tumor Targeting: The Concept, Application and Prospect. JSM Clin Oncol Res 2(1): 1010.