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Augmentation of enhanced permeability and retention (EPR) effect and therapeutic effect of macromolecular drug using nitric oxide generating agents

Jun Fang[1], Waliul Islam[2], Takahisa Imamura[3], Tomas Etrych[4], Vladimir Subr[4], Karel Ulbrich[4], Hiroshi Maeda[5]

[1]Faculty of Pharmaceutical Science, Sojo University, Kumamoto, Japan
[2]Department of Microbiology, Graduate School of Medical Science, Kumamoto University, Kumamoto, Japan
[3]Department of Molecular Pathology, Graduate School of Medical Science, Kumamoto University, Kumamoto, Japan
[4]The Institute of Macromolecular Chemistry, Czech Academy of Sciences, Prague, Czech Republic
[5]Biodynamic Research Foundation, Kumamoto, Japan

Enhanced permeability and Retention (EPR) effect based tumor targeting is becoming a golden standard for designing macromolecular drugs of nanomedicine. However, EPR effect is a blood vessel/blood flow dependent phenomenon, while tumors with good blood flow show better response to nanomedicine, tumors with poor blood supply exhibit less EPR effect and thus less response to nanodrugs. In this study, to further augment EPR effect we focused on a crucial vascular mediator nitric oxide (NO) and evaluated it's potential to enhance therapeutic effect of nanomedicine using 3 NO donors, nitroglycerin (NG), arginine (Arg) and hydroxyurea (HU), all of which are clinically used drugs. All those NO donors induced NO production in tumor selectively, leading to the increase of tumor accumulation of nanomedicine with no apparent influence on normal tissue. Consequently, combination of those NO donors with polymeric anticancer drugs resulted in remarkably superior therapeutic effect compared to polymeric drug alone, in different solid tumor models including carcinogen induced mouse colon cancer model and rat breast cancer model, which are pathologically similar to real human tumors. These results strongly suggested the potential of those NO donors as candidates of EPR enhancers, and we anticipate its clinical application in the future.

fangjun@ph.sojo-u.ac.jp