Employing the Properties of Tumor Microenvironment to Boost the Drug Delivery and Effectiveness

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論 文 名　：Employing the Properties of Tumor Microenvironment to Boost the Drug Delivery and Effectiveness（ドラッグデリバリーと有効性を高めるために腫瘍微小環境の特性を利用する）

区　　分　：甲

論　文　内　容　の　要　旨

The microenvironment within tumor is structurally and functionally different from normal organs. Based on that, it is possible to utilize these special reactivities of vascular or released active molecules to enhance the therapeutic benefits. Comparing with small molecular chemotherapy drugs, nano-sized macromolecular particles showed more noticeable therapeutic efficacy and less systemic side effect. This phenomenon could attribute to the spontaneous and selective accumulation of macromolecules in the solid tumors by the enhanced permeability and retention (EPR) effect. However, due to the limited tumor blood flow, the drug accumulation through the EPR effect demand to be further improved. Therefore, the author utilizes the special properties of the tumor microenvironment for modifying blood flow to the tumor to enhance the EPR effect by using an endogenous nitric oxide (NO) to improve the chemotherapeutic effectiveness.

In chapter 2, the author employed IRL-1620, an agonist of the endothelin B receptor, and examined for the first time of its effect on the EPR effect for PEGylated liposomes. In a CT-26 murine colon cancer model, the author found that co-injection of IRL-1620 at an optimum dose (3 nmol/kg) nearly doubled the tumor accumulation of liposomes compared with controls, indicating that IRL-1620 enhanced the EPR effect in the present colon cancer model. Co-injection of IRL-1620 could be a promising strategy to improve the therapeutic effects of macromolecular drugs while reducing their side effects.

In chapter 3, the author examined the synergistic effect of NO released from the tumor

associated macrophages (TAM) with chemotherapeutic agent Doxorubicin (Dox) in a mimetic tumor microenvironment. L-Arginine (Arg) which is a substrate of nitric oxide synthase (NOS) expressed in TAM was employed. By using a co-culture system of cancer cells with macrophages, the author found that mildly produced NO from Arg by co-cultured macrophages enhanced the cytotoxic effect of Dox to cancer cells. In addition, it was found the augmentation is affected by the order of the addition of Arg and Dox. Prior addition of Arg to Dox and simultaneous addition showed the same enhancement effect, but prior addition of Dox to Arg abolished the augmentation. This suggests that the co-administration of Arg with Dox may open new treatment modalities to improve chemo-therapies.

In chapter 4, based on the synergistic effect property observed above, the author developed an Arg-Dox co-encapsulating PEGylated liposome. Arg was encapsulated into the liposome during the extrusion procedure and Dox was incorporated through the remoted loading method. The author examined that the encapsulation efficiency (EE%) of Dox was comparable with the conventional Dox-LP. Moreover, the in vitro and in vivo stability of the developed liposome showed the same properties with Dox-LP. This will be a promising strategy to augment the chemotherapies without increasing the toxic effect.

In chapter 5, the author summarized the conclusion of this thesis.