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授与した学位	博士
専攻分野の名称	薬学
学位記授与番号	博甲第 3865 号
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学位授与の要件	博士の学位論文提出者 （学位規則第５条第１４項該当）
学位論文の題目	Development of Novel Polymer-Coated Liposome and Niosome for Efficient Passive Targeting of Doxorubicin to Solid Tumor （ドキソルビシンの固形がんへの効率的なパッシブターゲティングを目指した新規ポリマー修飾リポソーム及びニオソームの開発）
論文審査委員	教授　木村　聰城郎　　教授　黒崎　勇二　　教授　勝　孝

学位論文内容の要旨

Drug delivery systems play a major role in achieving the site-specific delivery of therapeutic agents. Among them, liposomes and niosomes attracted great interest in research field. Previously, surface modified liposome with single polymer like polyethylene glycol (PEG) was investigated to enhance their blood circulating time. However, there has been no report examining the effect of the modification of liposomes with the mixture of different hydrophilic polymers on their in-vivo disposition characteristics. Therefore, we formulated surface-modified liposome with the mixture of PEG and PVA (PEG%/PVA%). It was confirmed that PEG4%/PVA1% liposome further prolonged the blood circulation time of PEG-liposome due to lower hepatic disposition. In addition, the decrease in the affinity to the liver would be attributed to lower amount of serum proteins including opsonins and larger amount of dysopsonins such as albumin adsorbed on the surface of the liposome modified with polymer mixture. The therapeutic activity of PEG4%PVA1% liposomes encapsulating DOX showed significant reduction in the tumor growth rate and extended animal survival time.

Additionally, the feasibility of modifying niosomes with PEG as surface coating was also investigated. In-vivo disposition characteristics and the mechanism by which PEG modified niosomes would interact with receptors on the cell surface following intravenous administration was also addressed. Different naked and PEG-modified niosomes were prepared. It was confirmed that PEGylation of niosomes could result in small and stable vesicles with improved in-vivo disposition characteristics, which could be attributed to the lower hepatic distribution. Additionally, we confirmed that PEGylated niosomes could avoid the hepatic disposition via receptor mediated endocytosis. Furthermore, the therapeutic activity of PEG-niosomes encapsulating DOX showed significant reduction in the tumor growth rate and extended animal survival time.

These findings can form a solid base to develop useful liposomal and niosomal drug carriers with improved in-vivo disposition characteristic.

論文審査結果の要旨

本論文は、PEG修飾リポソームにさらに親水性のポリマーであるPVAで修飾することを試みたところ、特に、PEG4%/PVA1%のとき、肝臓への分布が少なく、血中滞留性が増すことを見出した。また、治療効果を確認するため、そのリポソームにドキソルビシンを封入して担がんマウスに投与したところ、PEG修飾リポソームに比べて腫瘍の増殖速度を遅らせ、延命効果が増すことを示した。

さらに、リポソームに代わって非イオン性界面活性剤によるニオソームに着目し、表面を親水性のポリマーであるPEGで修飾したところ、肝臓による受容体介在性エンドサイトシスを回避して、血中滞留性を増し、腫瘍組織への分布が増すことを見出した。良好な治療効果も、ドキソルビシンを封入して、同様に示した。

これらの知見は、固形がんへの制がん剤のターゲティングに重要な情報を与え、DDS 研究領域の進歩に貢献できるものであり、博士（薬学）の論文として合格と判定する。