受容体介在型薬物標的指向製剤トランスフェリン－マイトマイシンC結合体のHL60細胞における細胞内動態と細胞毒性

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Intracellular Disposition and Cytotoxicity of Transferrin–Mitomycin C Conjugate in HL60 Cells as a Receptor–Mediated Drug Targeting System

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ABSTRACT A macromolecular conjugate of mitomycin C (MMC) with transferrin (TF) which possessed binding ability for TF receptor was synthesized. The conjugate (TF–MMC) was internalized into the human leukemia cell line HL60 cells and distributed into intracellular fractions, then exocytosed into an incubation medium. Although these phenomena were similar to those of TF, part of the internalized TF–MMC was degraded to a trichloroacetic acid (TCA)–soluble fraction. Therefore, the intracellular disposition of the conjugate was analyzed kinetically. The mean time of internalization of TF–MMC (7.14 min) was longer than that of TF (5.46 min). The mean exocytosis time of TF–MMC (22.1 min) was also longer than that of TF (13.0 min). Although elongation of both the internalization and exocytosis steps was responsible for the increase in recycling time of the conjugate, the binding process to the TF receptor in the internalization stage was found to be markedly retarded. The recycling times of TF–MMC and TF were 29.2 and 18.5 min, respectively. The mean decomposition time of TF–MMC was 76.3 min. Proliferation of HL60 cells was inhibited by TF–MMC in vitro. These results indicate that the TF–MMC was internalized via a TF receptor and a part of the internalized TF–MMC was degraded, so the released MMC might represent antitumor activity. TF–MMC was demonstrated

to be a useful hybrid as a receptor-mediated targeting system.

抄録　トランスフェリン（TF）受容体と結合するマイトマイシンC（MMC）-TF結合体を合成した．結合体はHL60細胞に取り込まれ，細胞内に分布した後，エクソサイトーシスされた．これらの挙動はTFと同様であったが，細胞内に取り込まれた結合体の一部はTCA可溶性の分解物となった．細胞内動態を速度論的に解析したところ，結合体の平均内在化時間や平均エクソサイトーシス時間はTFに比べて長く，結合体は細胞内に滞留しやすいことが示唆された．さらに，結合体はインビトロ系においてHL60細胞の増殖を抑制した．これは，TF受容体を介して内在化を受けた結合体の一部が分解をうけ，MMCを放出したためと考えられた．