Folate receptor-targeted anti-cancer agent delivery

Despite the fact that there have been significant developments in anti-cancer technology, such as radiotherapy, chemotherapy and hormone therapy, cancer still remains as the second leading cause of death following heart disease in the United States (1). Most often, the main cancer treatment is chemotherapy utilizing highly potent drugs, which include mitomycin, paclitaxel and camptothecin. In many cases, these chemotherapeutic agents show a dose-responsive effect, and cell kill is proportional to drug exposure (2). Highly aggressive style of dosing is thus necessary to eradicate neoplasms; however, high-dose chemotherapy is hindered by poor selectivity for cancer cells and severe toxicity to normal cells (3). Clearly, this lack of tumor-specific treatment is one of the many hurdles that needs to be overcome by current chemotherapy.

An ideal solution to current chemotherapy limitations would be to deliver a biologically effective concentration of anti-cancer agents to the tumor tissues with very high specificity. In order to reach this ultimate goal, tremendous amount of efforts were undertaken to develop tumor-selective drugs by conjugating anti-cancer drugs to hormones, antibodies and vitamin derivatives (4). Among them, one low molecular weight vitamin compound, folic acid, shows a great deal of promise as a tumor-homing agent.

Folate is a member of vitamin B family and plays an essential role in cell survival by participating in the biosynthesis of nucleic and amino acids (5). This essential vitamin is also a high affinity ligand that enhances the differential specificity of conjugated anti-cancer drugs by targeting folate receptor (FR)-positive cancer cells (6). The FR, a tumor associated glycosylphosphatidylinositol anchored protein, can actively internalize bound folates and folate conjugated compounds via receptor-mediated endocytosis (7, 8). It has been found that FR is up-regulated in more than 90% of non-mucinous ovarian carcinomas. It is also found at high to moderate levels in kidney, brain, lung, and breast carcinomas while it occurs at very low levels in most normal tissues (9). The FR density also appears to increase as the stage of the cancer increases (10). Exploiting the above-mentioned facts, it is hypothesized that **folate conjugation to anti-cancer drugs will improve drug selectivity and decrease negative side effects.**

Based on the previous research that folate conjugation allows a drug molecule to target and become endocytosed into FR-positive cancer cells, numerous types of anti-cancer drugs were conjugated and evaluated for their biological activity (11). Particularly, folate-mitomycin C conjugates, EC72 and EC118, were found to be highly cytotoxic and outstandingly selective for FR-positive M109 cells (12, 13). In addition, EC72 and EC118 significantly extended lifespan of nu/nu mice with human KB xenografts without evidence of toxicity to major organs or delayed cumulative myelosuppression, the most common negative side effect of mitomycin C (14). Furthermore, combination therapy with paclitaxel produced a synergistic anti-tumor effect without any apparent adverse effects, suggesting a possibility of adjuvant use of folate conjugated drugs. Overall, performance of EC72 and EC118, both *in vitro* and *in vivo*, proves that folate conjugation enhances drug specificity thereby reducing lethal toxicity.

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