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Review

Emerging nanomaterials with advanced drug delivery functions; focused on methotrexate delivery

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ABSTRACT

This review focuses on therapeutic applications of various drug delivery nanovehicles encapsulated with the anti-cancer drug, methotrexate (MTX). Currently, a number of studies have been conducted to explore advanced chemotherapeutic systems with nonviral nanovehicles such as liposomes, polymeric micelles, polymersomes, solid lipids, dendrimers, porous metal and metal oxide particles, carbons with various nanostructures, and layered double hydroxides (LDHs). Out of various anticancer drugs, MTX was hybridized with those drug delivery nanovehicles not only to overcome its adverse effects, but also to induce advanced functions into those hybrid systems, such as enhanced solubility, controlled release, passive and active targeting, aimed to eventually enhance bioavailability of MTX. In particular, two dimensional LDHs are introduced rather in detail as one family of inorganic nanovehicles, since the therapeutic efficacies for MTX-LDHs have been systematically studied with *in vivo* orthotopic models, those which are clinically better correlated and therefore, more efficient to predict drug efficacy and toxicity than the standard one like xenograft model. Attempts are also made here to provide therapeutic results on chemically well defined MTX-LDH advanced drug delivery systems, such as their *in vitro* and *in vivo* targeting functions, biocompatibility and nanotoxicities and ability to overcome drug resistance. In addition, recent advances and challenges in advanced hybrid DDSs are discussed from the viewpoint of state-of-the-art nanomedicine.

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1. Introduction

Many attempts are being made to maintain better quality of life and well-being of our society. In particular, medical technology, therapeutics and diagnostics have made remarkable advances, but they should be less costly and burdensome without increasing care services. More recently, efforts have been made to advance nanotechnolgy in terms of novel drug delivery systems with advanced properties that encapsulate conventional chemotherapeutic agents into functional nanovehicles. And therefore, scientists in the medical community have achieved nanomedicine as a breakthrough in the fight against cancer. According to the European Technology Platform Document, nanomedicine can be defined as a medicine using nanotechnology, which is composed of approximately six research fields including drug delivery, biomaterials, *in vitro* diagnostics, drugs and therapies, *in vivo* imaging, and active implants [1,2]. However, drug delivery is thought to be the most significantly studied from the six research fields according to the total number of papers published and patents filed worldwide [3].

To exploit nanosized drug delivery systems (nDDSs), development of new drug delivery nanovehicles with desired properties such as high drug-loading concentration, controllable therapeutic windows, excellent targeting functions, and low toxicity is required. The biggest advantage of DDSs is surely due to therapeutic window control. As shown in Fig. 1, the therapeutic window is defined as the efficacy level of drug concentration by the time between diminished activity and toxic levels. In most drug administrations, it is challenging to maintain the appropriate therapeutic level in terms of plasma concentration, and therefore, repeated administrations are often required, resulting in drug resistance, toxicity scares and eventually inconvenience to patients. However, controlling the therapeutic window through DDS with sustained release functions allows drug efficacy to be maintained at the required plasma concentrations with a single drug administration, which can subsequently lead to minimizing the previously mentioned disadvantages and side effects due to repeated administrations.

Methotrexate (MTX) is considered as one of the first generation anticancer drugs prescribed for human cancers such as osteosarcoma, leukemia, cervical and breast cancer, hematologic malignancies, and even rheumatoid arthritis [4,5]. Though clinical uses of MTX in cancer are well reported [6], its clinical efficacy can be restricted due to its very short plasma half-life, poor pharmacokinetics, susceptibility to development of patient drug resistance, and eventual high dosages required for chemotherapy [6,7].

In order to deliver MTX in an efficient way, many studies in the drug delivery community have been carried out, not only to improve drug efficacy and pharmacokinetics, circulation in the blood, controlled release and therapeutic window, but also to overcome drug resistance. It has further been suggested that the hybridization of MTX with nanocarriers could open new developments in nanomedicine. As shown in Fig. 2, various nonviral nanovehicles, such as inorganic and organic/polymers, are now available.

In this review, various studies highlighting recent advances in MTX hybridized with nanovehicles are presented from the viewpoint of DDSs in nanomedicine, along with the up-to-date issues related to such MTX-nanovehicle hybrids *in vitro* and *in vivo*. In particular, the inorganic nanovehicle, layered double hydroxide (LDH), is discussed in detail. In order to develop such drug delivery vehicles with the desired functions listed above, it is most essential to develop a biocompatible drug delivery carrier with passive and active targeting functions. Among various nanovehicles, the one most intensively studied in various animal models is the injectable nanohybrid DDS, MTX-LDHs. Out of them, the *in vivo* orthotopic model is thought to be clinically better correlated and as a consequence more efficient to predict drug efficacy and toxicity than the standard ones like subcutaneous models. Since tumor cells are implanted directly into the relevant organ, this model reflects real situations (such as tumor microenvironments) seen in cancer patients much more effectively than the conventional one like xenograft tumor model [8].

2. History of methotrexate

Methotrexate (MTX) as an anticancer drug, (2S)-2-[(4-{[(2,4-diamino-7,8-dihydropteridin-6-yl)methyl](methyl)amino}phenyl)form-

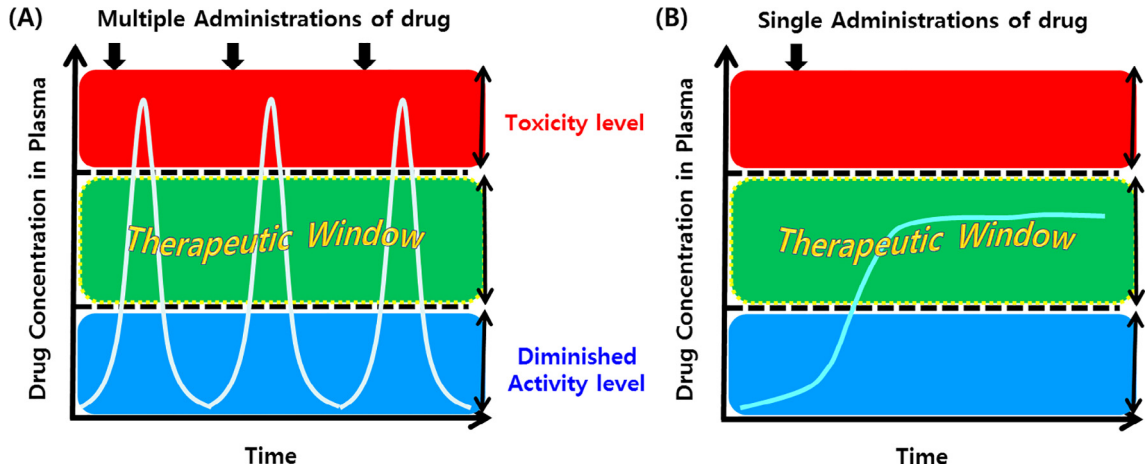

Fig. 1. Schematic diagram of therapeutic window with (A) multiple administrations of a conventional drug, and (B) single administration of drugs through a drug delivery system.