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The hydrodynamics-based procedure for controlling the pharmacokinetics of gene medicines at whole body, organ and cellular levels

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Abstract

Hydrodynamics-based gene delivery, involving a large-volume and high-speed intravenous injection of naked plasmid DNA (pDNA), gives a significantly high level of transgene expression in vivo. This has attracted a lot of attention and has been used very frequently as an efficient, simple and convenient transfection method for laboratory animals. Until recently, however, little information has been published on the pharmacokinetics of the injected DNA molecules and of the detailed mechanisms underlying the efficient gene transfer. We and other groups have very recently demonstrated that the mechanism for the hydrodynamics-based gene transfer would involve, in part, the direct cytosolic delivery of pDNA through the cell membrane due to transiently enhanced permeability. Along with the findings in our series of studies, this article reviews the cumulative reports and other intriguing information on the controlled pharmacokinetics of naked pDNA in the hydrodynamics-based gene delivery. In addition, we describe various applications reported so far, as well as the current attempts and proposals to develop novel gene medicines for future gene therapy using the concept of the hydrodynamics-based procedure. Furthermore, the issues associated with the clinical feasibility of its seemingly invasive nature, which is probably the most common concern about this hydrodynamics-based procedure, are discussed along with its future prospects and challenges.

Keywords: Naked plasmid DNA; Hydrodynamics-based procedure; Intravenous injection; Pharmacokinetics; Nonviral gene delivery; Gene therapy

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Contents

1. Introduction

Development of efficient gene delivery systems is undoubtedly indispensable for successful in vivo gene therapy and their unexpectedly delayed progress might be one of the main causes hindering the application of existing promising gene therapy strategies in clinical situations. The vast majority of approved vectors for current clinical protocols [1] are viral vectors thanks to their high transfection efficiency. However, they have been shown to possess immunogenic properties and the potential ability to produce mutational infection which could limit their dose and frequency of treatment. Indeed, the use of viral vectors could be discouraged by reports of the treatment-related death of a patient who had received an adenovirus vector [2] and of leukemia caused by insertional mutagenesis in patients who had undergone ex vivo transduction with a retrovirus vector [3]. In contrast, plasmid DNA (pDNA)-based nonviral vectors offer the advantages of safety and versatility and, among them, naked pDNA is expected to become one of the simplest nonviral gene medicines. It had been generally considered that naked pDNA could not produce transgene products in vivo due to its inability to enter cells and to its susceptibility to enzymatic degradation by various extracellular or intracellular nucleases [4–7]. This was the situation until Wolff et al. showed for the first time that a direct injection of naked pDNA into mouse skeletal muscle resulted in significant transgene expression with no requirement of a special delivery system [8]. Following this revolutionary report, direct needle injection of naked pDNA was shown to be applicable to various organs and tissues, such as the heart [9], liver [10], brain [11], skin [12], urological organs [13], thyroid [14] and tumors [15,16], resulting in marked transgene expression. Nonetheless, the direct injection achieves transgene expression within a limited area of cells which are close to the injection site. On the other hand, systemic injection via a vascular route would be more favorable for widespread gene delivery in that pDNA would have a greater chance of reaching many more target cells through capillary vessels. However, when applied systemically through the vascular system, naked pDNA by itself is pharmacologically inactive and produces very little transgene expression, if any, since it is rapidly scavenged and degraded by the liver nonparenchymal cells, predominantly by the liver sinusoidal endothelial cells, as demonstrated in our series of studies [17–19]. A lot of studies have attempted to overcome this unfavorable pharmacokinetic property of naked pDNA by employing various carriers such as cationic lipids or polymers [20–25]. While these approaches have resulted in some progress in terms of transgene expression efficacy, current pDNA-carrier systems are still likely to require further improvements in their in vivo pharmacokinetic aspects to overcome a lot of existing delivery barriers before they can be applied successfully to clinical gene therapy.