feature

Ultrasound-targeted microbubble destruction: toward a new strategy for diabetes treatment

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Ultrasound-targeted microbubble destruction (UTMD) is a promising technique with an immense target-specific gene delivery potential deep inside the human body. The potential of this technique has recently been confirmed for diabetic patients. This technology allows the genes to transfer specifically into the inefficient pancreas using ultrasound energy without viral vector utilization. It has been speculated that this idea and the advent of modern gene therapy techniques could result in significant future advances. Undoubtedly, this strategy needs further investigation and many critical questions have to be answered before it can be successfully advanced. Herein, we introduce the salient features of this approach, the hurdles that must be overcome, the hopes associated with it and practical constraints to develop this method for diabetes treatment.

Introduction

The need for localized therapy in specific tissues and organs has led us to a variety of delivery techniques using viral vectors or a wide range of therapeutic nanoparticles [1]. In the case of gene delivery, although the idea of using viral vectors seems to be efficient and interesting, it is always a high risk process compared with using naked DNA [2]. Some novel physical techniques using ultrasound energy have been under investigation as the next generation of gene or drug delivery systems, such as microbubbles [3]. Previous studies showed that by circulating microbubbles in the bloodstream they can act as cardiovascular delivery agents, through the rupture in the specific areas of interest using ultrasound energy [4]. Such microbubbles have been conventionally used to enhance the reflectivity of perfused tissues in clinical ultrasonography but current studies are focusing on their significant potential in therapeutic applications. This technique was further developed as ultrasound-targeted microbubble destruction (UTMD) and different research groups are working on this strategy for different tissues and organs. For example, Phillips *et al.* [5] have recently used this idea for gene delivery to vascular smooth muscle cells using ultrasound-triggered delivery of plasmid DNA from electrostatically coupled cationic microbubbles. They successfully showed that DNA can be locally delivered to vascular smooth muscle cells using microbubble carriers and focused ultrasound.

During the past few years, UTMD has evolved mainly because of its ability to focus deep inside the human body, and to provide a modality for targeted delivery [6]. Many proof-of-principle studies have confirmed the high potential of UTMD as a noninvasive and targeted delivery tool [7,8]. This technique has the potential to transport and release specific substances into target tissues or organs [9], change the microenvironment [10] and promote stem cell homing [11]. Presently, a growing number of researchers are considering UTMD technology as a successful solution for delivery of specific substances in blood vessels [7], skeletal muscle [12], heart [13], lung [14], liver [15], among others. As can be seen from the growing number of publications in this field (Fig. 1), there has been heightened interest in the use of this strategy recently.

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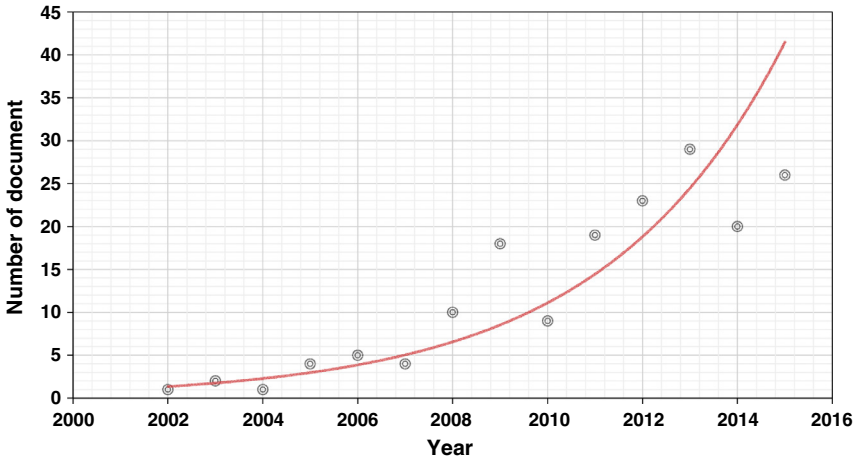

FIGURE 1

Number of scientific papers published per year using ultrasound-targeted microbubble destruction (UTMD) technique, compiled from a literature search in the Scopus database.

UTMD and diabetes

According to the literature review, it is expected that UTMD will also play a significant part in all aspects of diabetes treatment in the near future. Some primary studies have shed light on the potential benefits of this technique for diabetic patients [16]. Diabetes affects ~200 million people, and it is the sixth-most debilitating disease in the world [17]. Diabetes is a serious endocrine disorder that is characterized by chronic hyperglycemia with disturbances in carbohydrate, fat and protein metabolism, causing defects in insulin secretion, insulin action or both. Diabetes has been classified into three main categories: type 1 insulin-dependent diabetes (IDD); type 2 non-insulin-dependent diabetes (NIDD); and type 3 gestational diabetes mellitus [18]. People who suffer from type 1 diabetes do not produce adequate amounts of insulin to sustain life, so they become dependent on exogenous insulin, and daily injections of insulin become necessary for survival. Although people who suffer from type 2 diabetes are not dependent on exogenous insulin for existence, many of them show reduced insulin production over time, which requires exogenous insulin for suitable blood glucose control [19]. Type 3 diabetes occurs mostly in pregnant women without any previous history of diabetes and can either disappear or change to diabetes type 2 after pregnancy [20]. Both types 1 and 2 diabetes involve either partial or complete destruction of beta cells of the pancreatic islets, which can be restored via one of the medical regeneration of islet beta cell methods [21]. Because the rate of beta cell changes in the human pancreas is slow, even after injury, regenerative medicine aims to propose new techniques for either beta cell replication or neogenesis [22,23]. Despite the few pharmacological treatments available for diabetes (e.g. insulin therapy and adequate blood sugar control), new treatment strategies focus on replenishing the deficiency of beta cell mass in the main types of diabetes by either islet transplantation or beta cell regeneration or improvement of beta cell function. Recent studies demonstrate that gene therapy can assist the pancreatic islets in normal rats using UTMD [16]. In this context, the gene delivery to beta cells using UTMD turned out to be successful and promising. This technology allows the genes to transfer specifically into the inefficient pancreas using ultrasound energy without viral vector utilization [24]. Moreover, this novel technology can be used for delivering various bioactive molecules, including therapeutic genes, to tissues available to receive ultrasound energy, such as the heart [to which glucagon-like

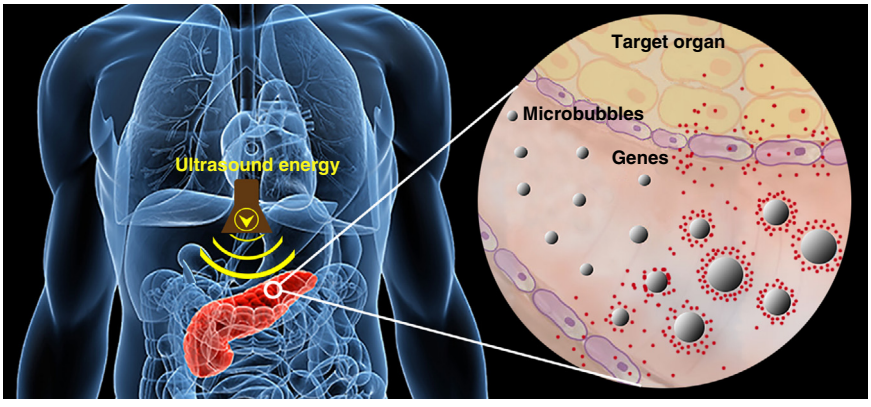

FIGURE 2

Schematic diagram of gene therapy mediated by ultrasound-targeted microbubble destruction (UTMD) for the treatment of diabetes.