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NanoScript: A Novel Tool for Gene Regulation Based on Nanoparticles with Benefits and Drawbacks

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Abstract

Transcription factors (TFs) are proteins that act as key regulators of gene expression by binding to specific DNA sequences to activate or repress gene expression by interacting with specific regulatory elements in the genome. TFs typically have multiple functional domains that contribute to their regulatory functions. These basically consist of three domains: the Nuclear Localization Signal (NLS) Domain, the DNA Binding Domain (DBD), and the Activation Domain (AD). Through the coordinated interaction of these domains, TFs modulate the gene expression in response to various internal and external signals within the cell. A defect in the complex mechanism of TFs has been associated with an increasing number of human diseases. Therefore, TF-based gene regulation studies are considered a promising approach for many biological applications. In this context, researchers aimed to mimic the structural and functional properties of TFs using a nanoparticle-based platform known as NanoScript. NanoScript acts like a natural TFs, enabling precise gene regulation and cellular reprogramming, and offering new possibilities for controlled and targeted manipulation of gene expression. The primary goal of NanoScript is to regulate gene expression at the transcriptional level in a non-viral manner. NanoScript can activate specific genes by interacting with endogenous DNA and initiating transcriptional activity, serving as an alternative synthetic structure to proteins for gene manipulation and cellular reprogramming. The platform has potential for a variety of applications in the fields of stem cell biology, cancer therapy, and cellular reprogramming thanks to its tunable components (nanoparticles and surface components) and the ability to effectively regulate gene expression. However, NanoScript also has some limitations, such as the possibility of interacting with off-target genes. This study discusses the current studies and techniques of NanoScript in the field of gene regulation, along with the advantages and challenges of this technique.

Keywords: Gene regulation, nanoparticles, NanoScript, transcription factor, stem cell

Introduction

Stem cells have the ability to renew themselves, trans form into various cell types since they are not yet functionally differentiated, and to repair damaged tissues in the body. They are classified as totipotent, pluripotent, multipotent, and unipotent according to

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their decreasing potential to form different tissue types. While pluripotent stem cells can form any type of cell, the transformation of multipotent and unipotent stem cells is limited to certain cell types (1). Stem cells have a very important function in the repair and regeneration of tissues that have lost their functions and contribute to the development of treatments that will replace organ and tissue transplants, cancer, diabetes, cardiovascular diseases, liver disease, and drug treatments (2). Stem cell differentiation is tightly regulated by various factors, including transcription factors (TFs), which play an important role in controlling gene expression and determining the fate of the cell. Therefore, researchers are developing various strategies to effectively control stem cell differentiation. These strategies target gene regulation mechanisms or alter specific signaling pathways (3). Epigenetic modifications, which promote the differentiation of stem cells by regulating gene expression, can affect gene functions without changing DNA structure (4). In particular, the effect of proteins such as TFs on chromatin plays a central role in the control of gene expression, thereby enabling the transformation of stem cells into desired cell types. These processes may open new horizons in medical treatments, allowing diseases to be treated more effectively (5,6). Therefore, developing tools to regulate the behavior of stem cells is an important research topic in terms of replacing damaged and diseased cells and re-establishing functional connections in tissue repair (5).

TFs are proteins that regulate the transcription of genetic material and key regulators of stem cell differentiation. In 2006, Takahashi and Yamanaka's revolutionary study revealed that it was possible to transform fibroblast cells into embryonic stem cells using only four TFs (Oct4, Sox2, Klf4, and c-Myc), and this discovery accompanied in a new era in stem cell research (7). TFs typically have multiple functional domains that contribute to their regulatory functions. These basically consist of three domains: the Nuclear Localization Signal (NLS) Domain, which helps to pass to the nucleus; the DNA Binding Domain (DBD), which binds to specific DNA sequences; and the Activation Domain (AD), which recruits RNA polymerase II and other proteins to initiate transcription (8). Gene regulation is controlled by these TFs that initiate or stop the expression of specific genes (9). These factors play a key role in gene regulation and control the expression of certain genes in the cell. The ability of TF to bind to specific DNA sequences provides a fundamental mechanism to regulate gene expression (8). It is known that these factors play an important role in determining which cell types of stem cells will transform into by regulating gene expression (10).

To facilitate stem cell differentiation or cellular reprogramming by delivering gene-specific TF proteins into cells, conventional approaches primarily rely on techniques such as liposomes, nanocarriers, electroporation, and similar methods. Alternatively, viral vectors and small molecules have also been employed to induce the expression of gene-specific TFs within cells (8,11–13). These methods show limited effectiveness due to some difficulties such as low delivery efficiency, inability to reach targeted cells or nuclear structures, minimal gene expression, random genome integration, and sensitivity to intracellular perturbations. These disadvantages can attitude significant difficulties in the process of developing and applying stem cell-based therapies (11). However, alternative approaches and innovative solutions are needed to overcome these problems.

In this context, an innovative platform has been developed that mimic the basic function of TFs using a nanomaterial-based small molecule such as Cas9-based transactivators, intracellular production of TFs through recombinant DNA technology, light-activated TFs, and artificial gene circuits (12,14–17). An artificial nanoparticle-based TFs called NanoScript has been developed for effective gene regulation by integrating

functional molecules onto gold nanoparticles (AuNPs) (11).

1. The Characteristics of Nanomaterials: Nanomaterials are defined as materials with dimensions less than 100 nanometers (nm, 10-9 m) and are often structured at nanoscale sizes, such as nanotubes, nanosheet, and NPs (18). The properties of these materials can differ markedly from those of conventional materials and are used in many fields, such as electrical, optical, magnetic, and mechanical. NPs are defined as small particles on the nanometer scale and can be composed of different types of materials, such as metals, ceramics, semiconductors, or organic compounds (19). The properties of NPs vary significantly depending on their size, composition, and shape. These NPs have special properties, such as high surface area, variation of optical, electronic, and magnetic properties, chemical reactivity, and biological interactions. Due to these properties, NPs are used in various fields such as drug delivery, imaging, materials science, catalysis, and biotechnology (20,21).

The distinction between nanoscience and nanotechnology is important. Nanoscience involves the study of structures and molecules at the nanometer scale and is a combination of physics, materials science, and biology. Relatedly, it deals with the manipulation of materials at the atomic and molecular level. On the other hand, nanotechnology involves using structures to control their shape and size at the nanometer scale. It refers to the ability to observe, measure, manipulate, combine, control, and produce matter at the nanometer scale. Therefore, while nanotechnology involves practical applications, nanoscience covers more basic research and manipulation at the molecular level (21,22). Nanoscience and nanotechnology offer effective and permanent solutions to various problems with different approaches in many fields. NPs have several uses in the medical field, including serving as carriers for drugs, enhancing imaging methods and biosensors. They are also employed in environmental applications such as removing pollutants from the water, air, and soil (23,24). Solar cells simultaneously enhance the efficiency of battery technologies and energy storage systems, as well as enhance the performance of electronic devices and provide new qualities for optical device (23,25). However, control of stem cell differentiation by NPs is just one of these areas. Nanomaterials has dimensions that are well-suited for biological systems that function at the molecular and cellular level. For example, a typical human cell is about 10 to 30 mm, while DNA are only about 2 nanometers wide. The small size of nanomaterials allows them to intimately interact with biological molecules and structures, creating new and exciting possibilities for medicinal and biological uses. Nanomaterials such as AuNPs have desirable physicochemical and nanostructural properties and have been successfully created for biological applications (26–28). These unique properties, as well as biological inertness and high stability in physiological conditions, make AuNPs excellent carriers of small molecules and biomolecules (28,29).

2. NanoScript: NanoScript is a synthetic TF formed by combining three basic components of TFs (NLS, DBD, and AD) on AuNPs. NanoScript is designed to regulate gene expression, and the operation of gene regulation is basically based on two principles. The first, gene activation, refers to the increase in the expression levels of the targeted gene. The second one refers to gene suppression, that is, the decrease in the expression levels of targeted genes (9).

Practical applications for gene editing using current methods are limited because proteins added exogenously to cells, especially TFs, have low transduction efficiency, cannot regulate genetic pathways at the transcriptional level, lack cell-specific targeting capabilities, and, above all, are extremely susceptible to degradation by intracellular proteases. Numerous approaches have been developed for intracellular protein delivery, including

electroporation, nanocapsules, lipid micelles, polymer-based carriers, and nanoparticle-based delivery (28,30–33). Rather than designing another protein delivery vehicle, NanoScript, an innovative platform that replicates the core function of TF proteins using a nanomaterial-based small molecule approach, was developed (28). Protein therapy, which involves delivering proteins into cells to replace dysfunctional proteins, has great potential for applications focused on regulating gene expression and cellular behavior, such as cellular reprogramming, cancer therapy, and stem cell therapy (28,34).

The NanoScript platform can be designed to mimic TFs to effectively regulate genes to induce stem cell differentiation. NanoScript replicates the multidomain structure of TF proteins. In addition to serving as a delivery vehicle for synthetic transcription factors (STFs), AuNP itself also serves as a functional component of NanoScript because it mimics the binding domain of natural TF proteins. All three STF components, which also include an NLS peptide, a hairpin polyamide DBD, and a transactivation peptide AD, function synergistically non-virally to regulate the transcriptional activity of the targeted protein (28).

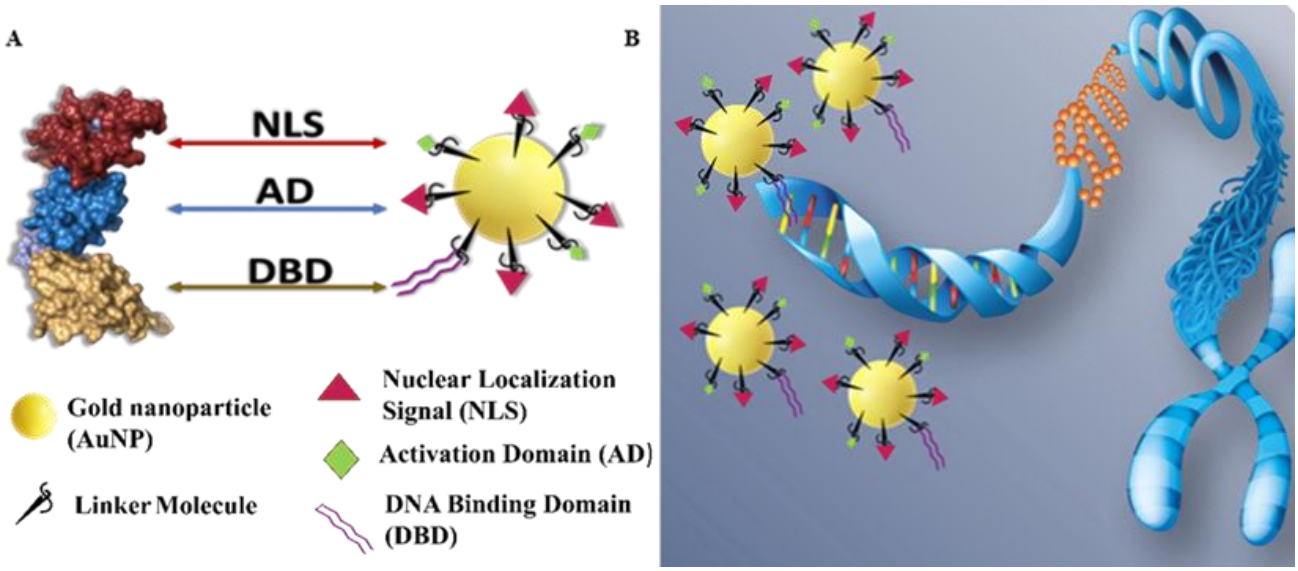

Figure 1. The structure and principle of NanoScript. A. The structure of NanoScript. These basically consist of three domains: the Nuclear Localization Signal (NLS) Domain, the DNA Binding Domain (DBD), and the Activation Domain (AD). B. Interaction of NanoScript with DNA inside the nucleus.

The process by which NanoScript attaches itself to the nucleus is often a consequence of several molecular interactions occurring inside the cell, facilitating its access to the nucleus. Once NanoScript has passed through the cell membrane, it subsequently reaches the nucleus Transport commonly occurs through intracellular vesicles or by binding to cell surface receptors. Cellular internalization processes, such as endocytosis or fusion, are involved in this process (35). To access the nucleus, NanoScript must pass through nuclear pore complexes, which serve as portals in the nuclear membrane. The regulation of this transit plays a crucial role in controlling the efficiency and specificity of its transport to the nucleus (36). Upon entering the nucleus, NanoScript exhibits a high degree of specificity in its ability to attach to nuclear DNA, enabling precise and targeted genetic alterations. The interaction between NanoScripts and targeted genes is often facilitated by certain functional groups or proteins present on the surface of NanoScripts. The nuclear binding capability of NanoScript is often dependent upon the chemical composition and surface

characteristics of the nanomaterial. Thiol groups present on the surface of NPs may engage in interactions. In the study conducted by Patel et al., endogenous expression of green fluorescence protein (GFP) in neural stem cells was successfully suppressed in this way. In this study, NanoScript was used to suppress the neuro-specific gene Sox9 in neural stem cells, allowing them to differentiate into neurons. They also labeled NanoScript with an Alexa Fluor 568 dye and transfected it into rat neural stem cells. In this way, it was tested whether NanoScript was localized within the kernel. NanoScript was detected within the nucleus when fluorescence imaging was performed 24 hours later (37). In another study, NanoScript was designed to regulate muscle cell differentiation by targeting myogenic regulatory factors (MRFs), which play an important role in triggering myogenesis. This NanoScript-MRF is stable in physiological environments, is small enough to localize within the nucleus, induces the differentiation of adipose-derived mesenchymal stem cells (ADMSCs) into mature muscle cells within 7 days, and is naturally excreted from induced muscle cells. Although NanoScript can be applied to almost any cell line, ADMSCs are an excellent multipotent model, and depending on which genes are activated, ADMSCs can differentiate into multiple lines, including muscle, bone, fat, and even neuronal cells (8). It is potent enough to induce muscle differentiation in ADMSCs and is safely cleared from differentiated cells. Moreover, considering that direct TF delivery is hampered by low transfection efficiency, NanoScript-MRF, which mimics the functions of natural TFs, is an alternative method for stem cell-based regenerative medicine. Gene expression levels induced by NanoScript-MRF are higher compared to traditional TF-protein-based delivery methods (8).

Another study used N-(4-Chloro-3-(trifluoromethyl)phenyl)-2-ethoxybenzamide (CTB), a small molecule that functions by altering chromatin architecture to modulate gene expression. Thus, a new CTB derivative with increased solubility was found and incorporated into the NanoScript platform to enhance gene expression and promote stem cell differentiation. It is aimed at modifying NanoScript with CTB and regulating gene expression. For this purpose, the first CTB was bound to NanoScript, and a time-dependent increase in histone acetyltransferase activity was observed. It was subsequently replaced by a Sox9-specific NanoScript CTB to improve chondrogenic gene activity and differentiation, as CTB is known to trigger the pathway involved in the regulation of Sox9, the master regulator of chondrogenic differentiation (38). In brief, the NanoScript platform developed with CTB has been developed as an epigenetic modification molecule that regulates histone proteins and increases gene expression through the histone acetyltransferase-dependent p300 pathway. The study by Pandian, Sugiyama, and their colleagues focused on the design of smart biomaterials inspired by nature, based on the chemical biology of nucleic acids. N-methylpyrrole (P) and N-methylimidazole (I) polyamides (PIPs), sequence-specific DNA- binding molecules, have been developed to display specific DNA sequences and alter gene expression within living cells. The self-assembly property of DNA has been used to enable the programmed assembly of nanostructures of different sizes. Furthermore, advanced DNA structures with well-defined properties have provided vital intracellular mechanical information as they allow real-time visualization of complex single-molecule interactions (39). From a similar perspective, Yang and colleagues examine the relationship between mitochondrial gene transcription and human diseases and introduce MitoScript, a new approach in this field. MitoScript was developed as a NP-based synthetic mitochondrial transcription regulator. It shows that MitoScript can effectively control mtDNA transcription in human cells. Properties of MitoScript include excellent colloidal stability, excellent biocompatibility, efficient cellular uptake, selective mitochondria

targeting, and traceability in living cells. The results of the study reveal that MitoScript affects the cell redox state by down-regulating the transcription of the ND6 gene and increases the formation of reactive oxygen species. This new technology has the potential to understand the mechanisms of mitochondrial disorders and develop new treatments for mitochondrial diseases (40).

3.Advantages and Limitations: The primary advantage of multifunctional NanoScript over traditional approaches is the ability to bind multiple repressor molecules on a single nanoparticle that function through different mechanisms to synergistically repress gene expression. Additionally, NanoScript can be applied to almost any cell type (37). It can easily change structural components, such as NanoScript's AuNPs core, to other types, such as magnetic core-shell nanoparticles or mesoporous silica nanoparticles. In this way, it enables uses such as real-time in vivo monitoring. NanoScript may offer a less invasive and more controlled approach compared to other gene editing technologies such as CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats), ZFN (Zinc Finger Nuclease), and TALEN (Transcription Activator-Like Effector Nuclease).

The most advantageous feature of NanoScript is its tunable components by redesigning the hairpin polyamide DBD sequence to target regulatory genes such as those involved in differentiation. However, it should also be noted that due to the short DBD targeting sequence, there is a possibility of interaction with off-target genes. Therefore, it is necessary to improve the NanoScript platform with further optimization by designing DBDs with longer sequences to target longer DNA sequences (28).

In order for NanoScript to behave and work like natural TFs, it must be highly soluble in aqueous solutions, stable under physiological conditions, and not form aggregates.

Conclusion

In conclusion, the development of NanoScript represents a significant advancement in the field of stem cell research and gene regulation. In regenerative medicine, stem cells are extremely promising since they may be used to treat a wide range of illnesses and restore damaged tissues. Controlling stem cell differentiation effectively has proven to be a substantial difficulty nonetheless. The effectiveness and specificity of conventional techniques for introducing TFs into cells have limits. By using the characteristics of nanomaterials-specifically, AuNPs-NanoScript presents a novel method for simulating TF protein function. NanoScript is able to control gene expression in cells. Stem cell development towards desired cell types can be directed by using this novel platform, which has proven to be able to activate or suppress particular genes. There are still issues, such as reducing off-target effects and ensuring stability and solubility in physiological settings, despite its apparent benefits. However, NanoScript is a promising tool for developing stem cell-based therapeutics and comprehending gene regulatory processes, which will open the door to novel approaches to treating a variety of illnesses and conditions.

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