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Interplay of cell adhesion matrix stiffness and cell type for non-viral gene delivery

Cathy Chu, Hyunjoon Kong *

Department of Chemical and Biomolecular Engineering, University of Illinois at Urbana-Champaign, 114 Roger Adams Laboratory, 600 South Mathews Avenue, Urbana, IL 61801, USA
Institute for Genomic Biology, University of Illinois at Urbana-Champaign, 1206 West Gregory Drive, Urbana, IL 61801, USA

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ABSTRACT

Non-viral gene delivery has the potential to treat a wide array of diseases but has been hindered by limited expression in vivo, possibly due to complex cellular microenvironments at delivery sites. Previous studies have reported that extracellular matrix properties, including stiffness, influence non-viral gene transfection efficiencies. This study reports that the effect of matrix stiffness on non-viral gene delivery differs among cell types due to varying sensitivities to matrix rigidity. Plasmid DNA encoding bone morphogenetic protein (BMP)-2 was delivered to fibroblasts, bone marrow stromal cells, and myoblasts cultured on fibronectin-conjugated poly(ethylene glycol) diacrylate hydrogels with varied elastic moduli, and the cellular uptake and subsequent expression of plasmid DNA were examined. While exogenous BMP-2 expression increased with increasing matrix stiffness for all three cell types, the effects of matrix stiffness were most pronounced for fibroblasts. Mechanistic studies conducted in parallel indicate that matrix stiffness influenced the projected area and nuclear aspect ratio for fibroblasts but had minimal effects on the morphology of bone marrow stromal cells and myoblasts. Overall, we believe that the results of this study will be useful for developing advanced non-viral gene delivery strategies for improved therapeutic efficacy.

1. Introduction

Non-viral gene delivery has the potential to treat a wide array of diseases through the transfer of genetic material while circumventing safety concerns associated with viral vectors [1–3]. To facilitate entry to target cells, therapeutic genes are often packaged with delivery vectors, such as polycations, lipids, dendrimers, and virus-mimicking constructs [4,5]. The resulting polyplexes can be administered directly to the target tissue to induce exogenous expression in host cells or loaded into a provisional matrix for tissue regeneration [6–8]. While non-viral gene delivery holds much promise and has demonstrated impressive results, it still suffers from limited and inconsistent expression in vivo [3,9–11].

Several in vitro studies have recently reported that gene delivery to cells cultured on a synthetic extracellular matrix (ECM) can be regulated with chemical and mechanical properties of the matrix. For example, gene transfection efficiency has been regulated by matrix stiffness [12] and cell adhesion domains [13,14] for cells cultured on synthetic substrates. In these studies, the effects of matrix properties on gene delivery were attributed to changes in cellular proliferation rate affecting gene uptake as well as intracellular activities affecting gene expression.

Recent studies have also reported that the extent to which ECM properties influence cellular activities varies among cell types [15–17]. For example, the proliferation rate of bone precursor cells was shown to increase with increasing matrix stiffness while the proliferation rate of bone marrow stromal cells was less dependent on matrix stiffness [18]. Similarly, the role of matrix properties in gene delivery may be mediated by cell type, but this has not yet been systematically examined to date.

In this study, we hypothesized that the stiffness of a cell adhesion matrix regulates non-viral gene delivery to various extents for different cell types due to changes in gene uptake and intracellular processes affecting gene expression. We examined this hypothesis by evaluating the delivery of plasmid DNA (pDNA) to NIH3T3 fibroblasts, D1 bone marrow stromal cells, and C2C12 myoblasts cultured independently on fibronectin-conjugated poly(ethylene glycol) hydrogels tuned to present various elastic moduli. These three cell types can be found in skeletal muscle tissue, which is a common administration site for genes in preclinical and clinical settings. The elastic moduli of the hydrogels were varied from 10 to 670 kPa, which encompasses the stiffness of skeletal muscle and collagenous bone [19]. pDNA encoding bone morphogenetic protein (BMP)-2, which has been used in tissue regeneration therapies [20,21], was used as a model gene. The uptake of pDNA and resulting BMP-2 expression were quantified to examine the effects

* Corresponding author at: Department of Chemical and Biomolecular Engineering, University of Illinois at Urbana-Champaign, 114 Roger Adams Laboratory, 600 South Mathews Avenue, Urbana, IL 61801, USA. Tel.: +1 217 333 1178; fax: +1 217 333 5052.
E-mail address: hjkong06@illinois.edu (H. Kong).

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