PREDICTION OF CELL RESPONSES TO SURFACE TOPOGRAPHIES USING MACHINE LEARNING TECHNIQUES

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Abstract

Topographical cues have been repeatedly shown to influence cell fate dramatically (Bettinger et al., 2009). This phenomenon opens new opportunities to design the interaction between biomaterials and biological tissues in a predictable manner. Unfortunately, the exact mechanism of topographical control of cell behavior remains largely unknown. We have therefore developed a technology in our laboratory to determine an optimal surface topography for virtually any application in biomedical field. Previously we have reported that we can control cell shape by our surfaces in a predictable manner (Hulsman et al., 2015). Here we demonstrate that we can successfully predict not only cell shape, but also cell response on protein level based on the properties of our topographies. The results of our study show that we are able to design materials for biomedical applications that require a particular cell behavior. We published our findings in Scientific Reports journ (Reimer et al., 2016).

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1. Introduction

The TopoChip, a micro topography screening platform, enables the assessment of cell response to 2176 unique topographies in a single high-throughput screen. The topographical features were randomly selected from an in silico library of more than 150 million of topographies, which were designed from algorithm that synthesized patterns based on simple geometric elements circles, triangles and rectangles (Unadkat et al., 2011). In our previous studies, we have demonstrated that these surface topographies exert a mitogenic effect on hMSCs (Unadkat et al., 2011), as well as on cell shape (Hulsman et al., 2015). In this paper, we show that these topographies can also be used to modulate the ALP expression in human mesenchymal stromal cells, as well as pluripotency in human induced pluripotent stem (iPS) cells (Reimer et al., 2016). We further show that computational models can be build to predict these protein levels using surface topography parameters.

2. Methods

Cell response to topography was captured by high-content imaging. Using image analysis and data mining methods described previously (Hulsman et al., 2015), multiparametric profiles of cellular response were obtained. Multiple replicates of each topography

were used to estimate the median level of a cellular response of interest either ALP in human mesenchymal stromal cells (hMSCs), or the median number of Oct4 positive cells in population of human induced pluripotent stem cell (hIPSCs). We aimed to predict the cellular response based on surface topography parameters using machine learning methods. To learn and validate these methods (specifically, classifiers), the data were split into training and testing sets in a 3:1 proportion respectively. Each class consisted of 100 samples and 50 features. The data did not contain missing values. In the training step, we performed a 10-fold cross-validation to obtain optimal parameters for each classifier. The caret package in R was used to perform the analysis.

3. Results & Discussion

In the first project, we conducted a screening on the TopoChip with hMSCs in order to find topographies that would be able to increase the ALP level, a protein that is an early marker of osteogenesis. We were able to successfully find such surfaces and confirm results experimentally (publication in preparation). To move further we decided to check how accurately we can make a prediction of ALP level in hMSCs based on topographical features. Focussing only on extreme examples, we selected 100 high- and and low-scoring topographies and used the model validation scheme described in Methods to find the most accurate binary classifier for our data set. We tested several classifiers and identified random forest as most precise, which obtained an accuracy of 96% on the held-out test set. In a second project, we aim to find a topography that will increase proliferation and pluripotency of hIPSCs. We used Oct4 as a marker of pluripotency. The screening was performed on one half of the Topochip (1000+ surfaces), which were then ranked based on the number of Oct4 positive cells. One hundred high- and low-scoring surfaces were chosen to train a classifier. Using logistic regression , we obtained 72% accuracy on a held-out test set. We used this model to predict surfaces that would increase pluripotency in hIPSCs among surfaces that were not included in the initial screening. Topographies were ranked according to their predicted probability score and top 30 surfaces were chosen for experimental validation. We found that 79% of selected surfaces were predicted accurately(Reimer et al., 2016).In summary, the combination of our screening methods and machine learning algorithms open new avenues to design surfaces with desired properties for variable applications. Our next step will be to find a surface with maximum ALP level from our virtual library based on our screening data.

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