

Assessment of stem cell differentiation based on genome-wide expression profiles.

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Abstract

In recent years, protocols have been established to differentiate stem and precursor cells into more mature cell types. However, progress in this field has been hampered by difficulties to assess the differentiation status of stem cell-derived cells in an unbiased manner. Here, we present an analysis pipeline based on published data and methods to quantify the degree of differentiation and to identify transcriptional control factors explaining differences from the intended target cells or tissues. The pipeline requires RNA-Seq or gene array data of the stem cell starting population, derived 'mature' cells and primary target cells or tissue. It consists of a principal component analysis to represent global expression changes and to identify possible problems of the dataset that require special attention, such as: batch effects; clustering techniques to identify gene groups with similar features; over-representation analysis to characterize biological motifs and transcriptional control factors of the identified gene clusters; and metagenes as well as gene regulatory networks for quantitative cell-type assessment and identification of influential

transcription factors. Possibilities and limitations of the analysis pipeline are illustrated using the example of human embryonic stem cell and human induced pluripotent cells to generate 'hepatocyte-like cells'. The pipeline quantifies the degree of incomplete differentiation as well as remaining stemness and identifies unwanted features, such as colon- and fibroblast-associated gene clusters that are absent in real hepatocytes but typically induced by currently available differentiation protocols. Finally, transcription factors responsible for incomplete and unwanted differentiation are identified. The proposed method is widely applicable and allows an unbiased and quantitative assessment of stem cell-derived cells. This article is part of the theme issue 'Designer human tissue: coming to a lab near you'.

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