International Research Journal of Biochemistry and Bioinformatics Vol. 12(5) pp. 1-3, October, 2022
Available online http://www.interesjournals.org/IRJBB

Mini Review

Human Lung Adenocarcinoma-Derived A549 Clones: Gene Expression

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Received: 01-Oct-2022, Manuscript No. IRJBB-22-76434; **Editor assigned:** 03-Oct-2022, PreQC No. IRJBB-22-76434 (PQ); **Reviewed:** 17-Oct-2022, QC No. IRJBB-22-76434; **Revised:** 22-Oct-2022, Manuscript No. IRJBB-22-76434 (R); **Published:** 29-Oct-2022, DOI: 10.14303/2250-9941.2022.34

Abstract

The GenSensor Suite consists of four online applications to elucidate connections between genes and proteins. When compared to a background list, GenPath's results show if certain categories of biochemical, regulatory, or other gene sets are over- or underrepresented in an input list. Along with all of the usual gene sets that may be searched, GenPath also provides several unique gene sets. Users can add original backdrop lists. GenPath is used to assess the interaction gene list that GenInteract generates from a single input gene. GenPubMed uses a PubMed query to locate the collection of PubMed IDs in order to derive a gene list from it and query it in GenPath (Kondo H et al., 2015). One gene set can be compared to another in GenPath by GenViewer users. Stem cell therapy appears to have promise for regenerating damaged or irreparable lung tissue. It is difficult to create a simple and reproducible approach for lung progenitor populations since the molecular process driving differentiation of alveolar epithelial cells is not fully understood. We investigated an in vitro system to evaluate the regulation mechanisms of alveolus-specific gene expression using the human alveolar epithelial type II cell line A549. Following the cloning of A549 subpopulations, each clone was separated into five groups based on the cell shape and marker gene expression. Two clones, B7 and H12, received more testing. Both H12 and B7 grew more of the ATII marker surfactant protein C when cultivated in a serum-free environment. Aquaporin 5 (AQP5), an ATI marker, was significantly upregulated in B7 and H12, respectively (Mikkonen L et al., 2010).

Keywords: GenSensor, Lung Progenitor

INTRODUCTION

Transcriptome analysis, high-throughput studies of gene expression and proteomics technologies usually provide lengthy lists of differentially expressed genes or proteins. These lists remain incomprehensible without a second level of analysis that divides them into understandable functional divisions. Several methods have been developed to accomplish this, with Gene Set Analysis being the most well-liked (GSA) (Uehara N et al., 2002). The test list, which is a list of genes having differential expression, is contrasted in GSA with gene sets, which are gene lists that have been categorised and made accessible in searchable databases. Which gene sets the test list's genes substantially over- or under-represent are shown, along with the corresponding statistical significance. This provides a starting point for the analysis of functional genomics (Sussan TE et al., 2005). Initially used to analyse gene sets obtained from Gene Ontology categories, the GSA approach has now been incorporated into a broad variety of applications. KEGG pathways, chromosomal locations, cis-regulatory elements, and other categories of gene sets that are relevant to the experiment at hand are now included in the technique's latest expansion. 68 of these tools have recently been evaluated, and DAVID and GSEA are the two that are most regularly used. It is outside the scope of this study to go into depth about every tool that has lately been developed for comparing test lists against gene sets. The GenSensor Suite will be introduced in this presentation as a versatile, approachable tool with extra functionality not often found in a standard GSA (Canals J et al., 2022). A wet-lab researcher's top priority is to receive a precise response

as quickly as is practical using publicly available, incredibly user-friendly equipment. The ideal tool would also include literature searches and route analysis. The lack of such a tool at the time served as the inspiration for the GenSensor Suite. Idiopathic pulmonary fibrosis and chronic obstructive pulmonary disease are two lung disorders that can be fatal. Lung transplants have historically been used to treat the most severe cases. Histocompatibility issues and a lack of donors are only two of the issues with lung transplantation; there are other issues as well. Stem cell-based regenerative therapy for the lungs is gaining a lot of attention due to its potential as a treatment. Induced pluripotent stem cells (iPSCs) and embryonic stem cells have recently been used to study the regeneration of alveolar epithelial type (AT) cells (ESCs). There are still several developmental steps that need to be completed before ESCs and iPSCs can differentiate into AT cells since it is presently unknown how this embryonic process is regulated. A simple and reproducible model system must be constructed in order to improve our understanding of the molecular mechanisms underlying the differentiation of diverse progenitor populations in the human lung and to advance the field of lung regenerative medicine (Nasako H et al., 2020). The lung alveoli, which are essential for breathing, are made up of type I (ATI) and type II alveolar epithelial cells (ATII). The exchange of oxygen and carbon dioxide takes place in the flat cells known as ATI cells, which form up around 95% of alveoli. These cells also produce surfactant, which is composed of phospholipids, proteins, and surfactant proteins A, B, C, and D (SPA, SPB, SPC, and SPD).

Certain differentiation markers, including aquaporin 5, boidal cells, and surfactant, are present in these cells. The maintenance of alveoli and host defence depend on these surfactants. Clara cells and ATII cells are both capable of producing SPA, SPB, and SPD. SPC can only be produced in ATII cells, making it a distinguishing marker for these cells. Clara and ATII cells' cell-type-specific SPB and SPC expressions are necessary for lung respiratory function (Ishii T et al., 2004). During the development of the lung, Thyroid Transcription Factor 1 (TTF-1) regulates the expression of both genes. Following damage, ATII cells exhibit stem cell-like traits such as self-renewal, proliferation, and differentiation into ATI cells. Setting up a simple, reproducible ATII cell model system and a mechanism to control the differentiation into ATI cells is therefore essential. We employed a cell line derived from human non-small cell lung cancer to assess the suitability of A549 cells for investigating the control of gene expression of differentiation markers (Takano M et al., 2016). The epidermal growth factor receptor (EGFR) gene is increased in the well-studied and known K-RAS mutation-carrying A549 cells (G12S). While A549 cells don't express some genes, such TTF-1, they still resemble ATII cells in some ways. A549 cells have been shown to have variable morphology, engage in a range of proliferative activities, and are resistant to differentiation signals (Difilippantonio S et al., 2003).

DISCUSSION

With GenViewer, gene sets may be explored and choose separately. Then, utilising different gene sets, GenPath may search through the list of genes from any gene set. For instance, some GO keywords within a certain gene set in GO may be examined using KEGG pathways. When GenPath produces a result with an unknown GO term or KEGG pathway, this is extremely helpful. The user may find links to various paths that may also be mentioned in the GenPath repository by further investigating that category in GenViewer. To create an easy-to-use, reproducible in vitro system that may be used to investigate the molecular processes underlying lung alveolar epithelial cell development. We recognised and characterised A549 clones using their morphology and the gene expression patterns of markers. According to the primary expression patterns of alveolar cell markers, two A549 clones, B7 and H12, were further investigated as probable ATII and ATI/II cell representatives. In order to determine if these clones reacted in any manner to the differentiation stimuli, we produced a variety of growing conditions with and without serum, DCIK, and MAPK inhibitors. Both B7 and H12 reacted differently and consistently to those stimuli, displaying characteristics of ATII and ATI/II cells (Yao X et al., 2014).

To learn more about how tightly and reciprocally controlled cell growth and differentiation are, we examined the growth rate with and without serum. We discovered that serum-containing medium made A549 cells extremely proliferative, but that removing the serum decreased growth rate and concurrently increased expression of differentiation marker genes. Furthermore, no SPC nor AQP5 proteins were detected in serum depletion system western blot analyses. Since the cells may be primed but not fully differentiated at this time, it is possible that further signals or environmental stimuli will be required to encourage the creation of proteins.

CONCLUSION

DAVID provides an easy-to-use programme for the analysis of user-selected gene lists. The outcomes are provided in tables of statistically significant gene sets, much as our GSS tool. DAVID analyses user lists to all gene set categories all at once, in contrast to our tool. The user can locate relevant biological features in such lengthy result reports by using the functionally related "Annotation Clusters" formed from the major gene sets that have been generated. Similar "clustering" of related gene sets may be accomplished using the GenViewer function in GSS, but it must be done separately for every gene set. Given that all of the statistical analysis in DAVID is integrated within the Java application, it is one of the GSA programmes that analyses data the rapidly. GSEA offers a whole different method for analysing gene set data, despite the fact that the types of gene sets that may be assessed are relatively constrained. GSEA compares rank-ordered lists using a nonparametric method. This approach

works really well for the analysis of gene data from one or more treatments in which the rank order changes and for the subsequent comparison of the transformed genes to gene sets. GSEA is a great tool for comparing treatment-induced gene changes to genesignature databases compiled from prior research, such those used in the Connectivity Map. This approach cannot be used to analyse gene lists in situations where gene ranking is inappropriate. Therefore, a large number of the functionalities available in our GenInteract, GenPubMed, and GenViewer programmes are not supported by GSEA. Numerous techniques that use the information from GSA analysis and add a data-driven approach have been created by establishing an interaction network inside the condensed gene list of interest. A variety of network visualisation tools have also been made accessible. The sheer number of these tools is mind-boggling, but the crucial point is that the laboratory researcher typically has very little time to comprehend, utilise, and benefit from the wealth of advanced tools accessible.

The GenSensor set of tools may be used by someone who lacks bioinformatics expertise since they are user-friendly, well-integrated, and precise. We isolated A549 clones and determined each one's specific structure and patterns of gene expression. We identified two A549 clones among them, B7 and H12, which exhibit ATII cell- and ATI/ATII cell-like properties and respond to serum depletion stimuli, demonstrating that they have the flexibility in alveolar differentiation markers' gene expression. These A549 clones might be used to build a model system to research the molecular pathways regulating ATII differentiation.

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