Database and ontologies

**RPdb: a database of experimentally verified cellular reprogramming records**

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**Abstract**

Summary: Many cell lines can be reprogrammed to other cell lines by forced expression of a few transcription factors or by specifically designed culture methods, which have attracted a great interest in the field of regenerative medicine and stem cell research. Plenty of cell lines have been used to generate induced pluripotent stem cells (iPSCs) by expressing a group of genes and microRNAs. These iPSCs can differentiate into somatic cells to promote tissue regeneration. Similarly, many somatic cells can be directly reprogrammed to other cells without a stem cell state. All these findings are helpful in searching for new reprogramming methods and understanding the biological mechanism inside. However, to the best of our knowledge, there is still no database dedicated to integrating the reprogramming records. We built RPdb (cellular reprogramming database) to collect cellular reprogramming information and make it easy to access. All entries in RPdb are manually extracted from more than 2000 published articles, which is helpful for researchers in regenerative medicine and cell biology.

**Availability and Implementation:** RPdb is freely available on the web at [http://bioinformatics.ustc.edu.cn/rpdb](http://bioinformatics.ustc.edu.cn/rpdb) with all major browsers supported.

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**Supplementary information:** Supplementary data are available at *Bioinformatics* online.

1 Introduction

Cellular reprogramming is a process in which one cell type transforms into another cell type by expressing a group of genes and microRNAs, adding chemical molecules or changing cell culture environment (Hussein and Nagy, 2012). Cellular reprogramming technology, which mainly includes induced pluripotent stem cell (iPSC) generation, iPSC differentiation and direct reprogramming, is considered one of the most important advances in tissue replacement therapies (Tabar and Studer, 2014; Walmsley et al., 2014). Somatic cells can be reprogrammed to a stem cell-like state, which can differentiate to functional somatic cells. Multiple somatic cells, including blood cells (Giorgetti et al., 2009), fibroblasts (Takahashi et al., 2007) and hair follicle dermal papilla cells (Tsai et al., 2011) have been successfully reprogrammed to iPSCs. There are also many functional somatic cells that have been generated from iPSCs, such as dopaminergic neurons (Theka et al., 2013) and retinal cells (Mellough et al., 2012). Multiple strategies have been used to achieve these goals, including chemical-inducible systems (Nie et al., 2012), virus-free transfection, recombinant proteins and microRNAs (Walmsley et al., 2014). Using similar strategies, various somatic cells have been directly converted into other cell types, which are named direct reprogramming or transdifferentiation.

Although there are several stem-cell-focused databases, such as SyStemCell (Yu et al., 2012) and StemCellDB (Mallon et al., 2013), to the best of our knowledge, there is no database that focuses on comprehensively collecting and analyzing cellular reprogramming...
information, especially the reprogramming factors (genes or chemical molecules). To fill this gap, we collected experimentally verified reprogramming records from published articles and built RPdb (cellular reprogramming database), which is proposed to facilitate the new prescription screening and assist with investigating the mechanism of cellular reprogramming.

2 Methods
We collect reprogramming information from published literature included in the PubMed database and Web of Knowledge by using all the keywords ‘induced pluripotent stem cell’ AND ‘generation’, ‘induced pluripotent stem cell’ AND ‘differentiation’, ‘direct reprogramming’. More than 2000 articles were obtained from PubMed and Web of Knowledge in this way. Based on the keywords, these articles are divided into three categories: iPSC generation, iPSCs differentiation and direct reprogramming. We manually extract reprogramming information from each article and the information is uploaded to RPdb after reviewing (supplementary material).

The flowchart of the construction of RPdb is illustrated in Figure 1. For iPSCs generation, we collect information regarding the cell lines used for reprogramming, reprogramming factors (genes, microRNAs and chemical molecules) and species. Based on the method used to deliver the reprogramming factors, we divide the entries into ‘virus’ and ‘non-virus’. For manually extracted genes and microRNAs, we further map them to NCBI/EMBL Entrez IDs according to the symbols and description. Genes and microRNAs that cannot be found in public databases are removed (Supplement Material). A variety of biological databases, such as mirTarBase (Hsu et al., 2014), STRING (Szklarczyk et al., 2011) and AnimalTFDB (Zhang et al., 2012), are integrated to provide functional and regulatory information about genes and microRNAs (Fig. 1A, B).

To help users find new reprogramming genes, we also provide an online tool for data analysis, which compares multiple tissues and identifies differentially expressed transcription factors and genes (Fig. 1C). We download the expression profiles of 27 human tissues and 6 mouse tissues from ATLAS (Petryszak et al., 2014). The details of data processing and identification of differentially expressed genes can be found in supplementary file. Experimentally validated transcription factors are downloaded from AnimalTFDB and such information is used to identify transcription factors from the differentially expressed genes.

3 Results
The database includes reprogramming records of 250 cell lines, 197 genes and microRNAs, 144 chemical molecules and culture methods and 526 functional annotations. We classify the entries into two categories: ‘Gene and microRNAs’ and ‘Molecules and culture methods’.

Users can explore all entries of the database through the ‘Browse’ page and compare gene expression levels of multiple tissues in the ‘Analysis’ page. All the results can be downloaded for further analysis. A tutorial for the database is available in the ‘Help’ page, including searching genes of interest, using the database to obtain reprogramming protocols and downloading the results for further analysis. Detailed information about genes and microRNAs involved in cellular reprogramming can be found in the ‘Gene’ page, which includes basic gene information, functional information, GO information, protein-protein interactions and regulatory relationships. All functional information is manually extracted from literature describing the role of genes in the reprogramming process. With RPdb, users can find genes, microRNAs and chemical molecules used for reprogramming processes. The ‘Molecules and Culture Methods’ page lists all chemical molecules and culture methods deposited in RPdb.

4 Discussion and conclusions
RPdb is an integrated database comprising plenty of experimentally validated reprogramming information. Our aim is to collect comprehensive information used for cellular reprogramming and make it freely accessible to users. RPdb provides detailed information about experimentally verified genes and microRNAs, including gene descriptions and functional annotations manually extracted from the literature. The development and expansion of RPdb will keep on going and more valuable resources will be integrated into the database in the future. As an efficient bioinformatics tool, RPdb will assist in the discovery of novel reprogramming factors in a broad spectrum of cell reprogramming research.

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