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Communications

CommPath: An R package for inference and analysis of pathway-mediated cell-cell communication chain from single-cell transcriptomics

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ABSTRACT

Single-cell transcriptomics offers opportunities to investigate ligand-receptor (LR) interactions between heterogeneous cell populations within tissues. However, most existing tools for the inference of intercellular communication do not allow prioritization of functional LR associations that provoke certain biological responses in the receiver cells. In addition, current tools do not enable the identification of the impact on the downstream cell types of the receiver cells. We present CommPath, an open-source R package and webserver, to analyze and visualize the LR interactions and pathway-mediated intercellular communication chain with single-cell transcriptomic data. CommPath curates a comprehensive signaling pathway database to interpret the consequences of LR associations and therefore infers functional LR interactions. Furthermore, CommPath determines cell-cell communication chain by considering both the upstream and downstream cells of user-defined cell populations. Applying CommPath to human hepatocellular carcinoma dataset shows its ability to decipher complex LR interaction patterns and the associated intercellular communication chain, as well as their changes in disease versus homeostasis.

1. Introduction

Advances in next-generation sequencing and advent of single cell RNA sequencing (scRNA-seq) enable us to characterize the transcriptomic profiles in individual cells with high resolution and on a genome-wide scale [1]. At present, scRNA-seq has been widely applied in biological and medical researches serving multiple purposes, including identifying new cell types or states, investigating cellular plasticity and stemness, and exploring developmental relationships among different cell populations [2,3]. Despite improvements in technology, it's now becoming a big challenge to delineate the complexities and dynamics of intercellular communication, which play a prominent role in coordinating diverse cellular decisions, including development, differentiation, and inflammation. Several tools have been developed to infer cell-cell communication by examining the expression profiles of ligand-receptor (LR) pairs, such as CellPhoneDB [4], SingleCellSignalR [5], CellChat [6], and scConnect [7]. Although differing from each other in the underlying assumptions and specific algorithm frameworks, these tools are faced with the common difficulty as to accurate identification of functional LR associations that trigger a signaling cascade in the receiver cells. In addition, most existing tools neglected the investigation and interpretation of intracellular signaling pathways in the receiver cells, which orchestrate functional reaction to upstream ligands and mediate signal transduction to further downstream cells.

To resolve these gaps, here we first assume that functional LR interactions are more likely to trigger specific molecular pathways in the receiver cells, and these pathways therefore convey the signal to mediate more downstream responses. This form of communication chain is supposed to comprising the interaction of the receiver cells with both its upstream and downstream cells. In turn, by interrogating the affected pathways in the receiver cells, functionally important LR interactions related to any cells of interest can be identified. In this paper, we introduce CommPath, a new

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R software package and a user-friendly webserver, to analyze and visualize the LR interactions and pathway-mediated cell-cell communication chain from scRNA-seq data. CommPath has three key features: (i) it curates a series of comprehensive signaling pathway databases, including the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways [8], WikiPathways [9], reactome pathways [10], and Gene Ontology (GO) [11] and quantifies their activities within single cells, to interpret the functional consequences of LR associations; (ii) it screens pathway-associated LR interactions by considering the activities of signaling pathways in the receiver cells; (iii) it infers pathway-mediated cell-cell communication chain by considering not only the upstream cell types and LR pairs provoking the specific pathways but also the downstream ones responding to those pathways.

2. Methods and implementation

CommPath package requires an expression matrix of gene × cell produced from scRNA-seq experiments and a label vector indicating cell clusters as input. CommPath first identifies potential LR pairs among cell clusters in a pairwise manner, then screens LR interactions associated with activated pathways in each cluster, and finally determines the communication chain mediated by those activated pathways (Fig. 1). Here, we introduce the workflow of CommPath as follows.

2.1. Statistical identification of potential LR associations from scRNA-seq data

Within CommPath package an LR molecule interaction database was curated based on CellPhoneDB [4] and FANTOM5 [12] (Supplementary Methods). CommPath identifies marker ligands and receptors highly expressed in each cell cluster through differential expression tests based on the input expression matrix and cell labels. Two cell clusters are considered to interact with each other through an LR pair when the ligand is highly expressed in one cell cluster and the corresponding receptor is highly expressed in the other. The interaction intensity score $Intensity_{lr,AB}$ and corresponding statistical $P_{lr,AB}$ value to quantify the evidence of an LR association (l, r) connecting two cell clusters (C_A, C_B), with l expressed from C_A and r expressed from C_B, are defined as follows:

$$Intensity_{lr,AB} = log2FC_{l,A} * log2FC_{r,B}$$

$$P_{lr,AB} = 1 - (1 - P_{l,A}) * (1 - P_{r,B})$$

where $log2FC_{l,A}$ and $P_{l,A}$, and $log2FC_{r,B}$ and $P_{r,B}$, are $log2FC$ and adjusted P values for l and r in the differential expression tests in C_A and C_B, respectively.

The interaction intensity between two cell clusters (C_A, C_B) is determined by both the number and the intensity of significant LR associations between them:

$$Intensity_{AB} = \sum_{l \in A, r \in B} Intensity_{lr,AB}$$

2.2. Screening pathway-associated LR interactions

CommPath identifies signaling pathways containing the upregulated ligands or receptors by searching in KEGG pathways, WikiPathways, reactome pathways, and/or GO terms (Supplementary Methods), and then performs differential activation analysis to determine significantly activated pathways for each cell cluster. CommPath computes several statistics, including the means/medians and their differences, and statistical t/W and P values of pathways for each cell cluster compared with other user-defined clusters. These statistical scores are used to identify activated pathways in the cell clusters of interest and then infer the relevant LR interactions involved in those pathways.

2.3. Identification of pathway-mediated cell-cell communication chain

For a specific cell cluster C_B, CommPath identifies its LR associations with the upstream cluster C_A and downstream cluster C_C, as well as intracellular pathways activated in C_B. To identify pathways mediating the C_A-C_B-C_C communication chain, CommPath examines pathways in C_B to recognize those containing both receptors responding to C_A and ligands sending information to C_C.

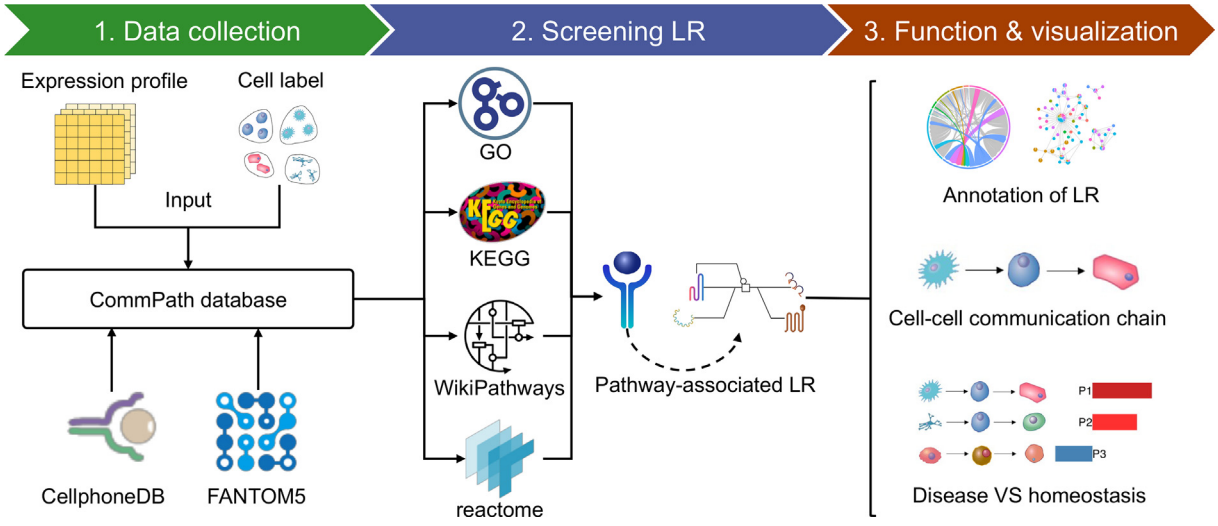


Fig. 1. A flowchart showing the workflow of CommPath. CommPath infers pathway-mediated intercellular communication chain from single-cell transcriptomics. (1) CommPath curated LR molecule interaction database based on CellPhoneDB and FANTOM5 database and takes expression profile and cell annotation labels from scRNA-seq data as input to infer potential LR associations. (2) CommPath screens pathway-associated LR interactions by searching in a variety of signaling pathway databases. (3) CommPath infers LR interactions and relevant biological pathways among cell types, enables comparison between two conditions, and meanwhile provides diverse representations.

2.4. Comparison of cell-cell communication between two conditions

CommPath provides utilities to compare cell-cell communication patterns between two conditions, such as disease and control. To this end, CommPath detects the differentially activated pathways between the same cell cluster in both CommPath objects created from two different conditions. Then it identifies the ligands and receptors involved in these pathways and the communication chain mediated by them. Through CommPath analysis, users can identify the upstream cell clusters triggering and the downstream cell clusters getting influenced by dysregulation of these pathways.

2.5. Application in scRNA-seq data on hepatocellular carcinoma (HCC)

We showcase CommPath's functionalities by applying it to a hepatocellular carcinoma (HCC) scRNA-seq dataset [13]. The processed dataset was downloaded from Mendeley data (https://data.mendeley.com/datasets/6wmzcskt6k/1). This dataset consists of the expression profiles of 73,589 cells across 19,852 genes, including 57,254 and 16,335 cells from the tumor and normal samples, respectively. All cells have been grouped into 29 clusters, including 7 clusters of hepatocytes, 5 of endothelial cells, 4 of NK cells, 3 of myeloid cells, 3 of $CD4^+$ T-helper cells, 2 of $CD8^+$ cytotoxic T cells, and one of each for fibroblasts, bi-potent progenitors, B cells, mast cells, and Tregs. We first split the dataset by tumor or normal tissues. Bi-Potent cells were further removed in data from tumor tissues since they were specific to normal tissues and were rather rare in tumor tissues, and similarly, hepatocytes were removed in data from normal tissues, after which 57,236 and 16,317 cells remained in the tumor and normal data, respectively. These data were then analyzed following the CommPath package pipeline described above.

2.6. Data and code availability

All data used herein are publicly available. The CommPath package is freely available on GitHub at https://github.com/yingyonghui/CommPath and the CommPath webserver is available at https://commpath.omic.tech/.

3. Results

3.1. Application of CommPath in HCC scRNA-seq data

Following the CommPath analysis pipeline described above, we demonstrated the usage of CommPath package by investigating the cell-cell interactions in HCC scRNA-seq data [13]. We first identified the potential LR associations and screened them with activated pathways in the receiver cells. The circos plots showed the counts and intensities of the pathway-associated LR interactions among all cell types in the integrated samples and then in tumor and normal tissues separately (Supplementary Fig. S1), and heatmaps showed the top activated pathways in each cell type (Supplementary Fig. S2).

We next showed CommPath's utilities by focusing on the communication between $CD8^+$ T cells and the other cell types (Fig. 2A and B), as they play prominent roles in anti-tumor immunity [14]. Dot plots were provided to visualize the top LR interactions associated to $CD8^+$ T cells (Supplementary Fig. S3). Investigation of the LR-associated KEGG pathways revealed that the immune-related pathways were significantly activated in $CD8^+$ T cells compared to the other cells in the tumor microenvironment (TME), such as *T cell receptor signaling pathway*, *cytokine-cytokine receptor interaction*, and *PD-L1 expression and PD-1 checkpoint pathway in cancer* (Fig. 2C and Supplementary Fig. S4), in accordance with their essential roles in immune checkpoint pathways [15]. Communication chain analysis focusing on $CD8^+$ T cells revealed that cytokine-cytokine receptor interaction mediated the communication between $CD8^+$ T cells and a variety of cell types (Fig. 2D). Among the associated LR interactions, the CXCL12/CXCR4 pair exhibited the maximum intensity to mediate the communication between $CD8^+$ T cells and its upstream cells, namely the endothelial cells and fibroblasts (Fig. 2E). In line with this observation, CXCL12/CXCR4 interaction has been shown to contribute to the immunosuppressive property of TME [16], and blockade of CXCR4 facilitated the mobilization of $CD8^+$ T cells [17]. CommPath analysis further showed that $CD8^+$ T cells could subsequently transmit the signal to the other immune cells, or back to endothelial cells, by expressing ligands in the same pathway, including CCL5, CD70, *etc.* (Fig. 2D and Supplementary Fig. S5).

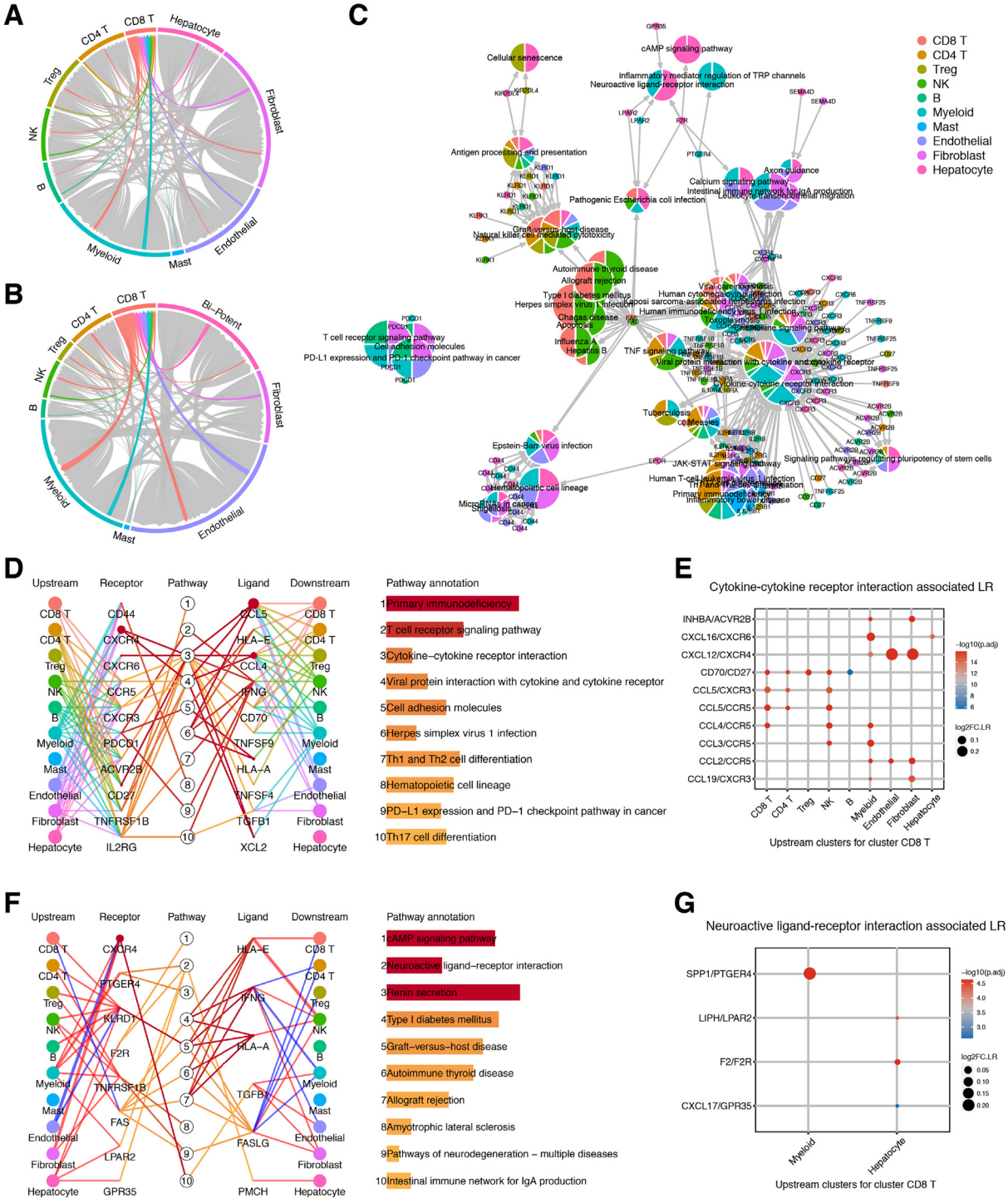
Finally, we utilized CommPath to compare the communication chains involving $CD8^+$ T cells between tumor and normal tissues and identified significantly upregulated communication chains in $CD8^+$ T cells from tumor tissues (Fig. 2F). Of note, the communication chain mediated by *neuroactive ligand-receptor interaction* is one of the top upregulated chain, in accordance with previous finding that this pathway was enriched of the dysregulated genes in tumor tissues [18,19] and involved in the pathogenesis of HCC [20]. Meanwhile, the relevant LR pair SPP1/PTGER4 mediating the myeloid-$CD8^+$ T cell communication was also enhanced in tumor samples (Fig. 2G). These results demonstrated the capability of CommPath in discovering novel cell-cell interactions and the related molecular pathways.

3.2. Web interface of CommPath

CommPath also provides a user-friendly webserver to illustrate the functionalities of the R package (Supplementary Fig. S6). When

Fig. 2. (A and B) Circos plot showing the counts of functional LR interactions among cell clusters (types) identified in tumor (A) and normal (B) tissues with $CD8^+$ T cells highlighted. The directions of lines indicate the LR associations from ligand clusters to receptor clusters, and the widths represent the counts of LR pairs between the associated two clusters. (C) Network graph of the activated pathways in $CD8^+$ T cells and the associated upstream LR interactions. The pie charts represent the activated pathways in $CD8^+$ T cells and the scatter points represent the LR pairs of which the receptors (labels of points) are included in the gene sets of the linked pathways. Colors of scatter points indicate the upstream clusters releasing the corresponding ligands. Sizes of pie charts indicate the *t* values from differential activation tests comparing the pathway scores in $CD8^+$ T cells to those in other cells and the proportions indicate the in-degree from different upstream clusters. (D) Pathway-mediated cell-cell communication chain of $CD8^+$ T cells in tumor tissues. Shown are the top 10 significantly upregulated pathways in $CD8^+$ T cells compared to other cells in tumor tissues and the relevant LR interactions. The widths of lines between *Upstream* (*Downstream*) and *Receptor* (*Ligand*) columns represent the overall interaction intensity between the upstream (downstream) clusters and $CD8^+$ T cells via the specific receptors (ligands); the sizes and colors of dots in the *Receptor* (*Ligand*) column represent the average *log2FC* and $-log10(P)$ values from differential expression tests comparing the receptor (ligand) expression in $CD8^+$ T cells to that in other cells; the lengths and colors of bars in the *Pathway annotation* column represent the mean differences and *t* values comparing pathway scores of $CD8^+$ T cells to other cells in tumor tissues. (E) The upstream top 10 LR pairs provoking the *cytokine-cytokine receptor interaction* KEGG pathway in $CD8^+$ T cells in tumor tissues and the corresponding ligand-expressing clusters. (F) Comparison of pathway-mediated cell-cell communication between $CD8^+$ T cells in tumor and normal tissues. Shown are the top 10 significantly upregulated pathways in $CD8^+$ T cells in tumor tissues compared to $CD8^+$ T cells in normal tissues and the relevant LR interactions. Plots are similar to (D), except that the colors of lines between *Upstream* (*Downstream*) and *Receptor* (*Ligand*) columns indicate the interaction intensity is upregulated (red) or downregulated (blue) in tumor tissues compared to that in normal tissues and the lengths and colors of bars in the *Pathway annotation* column represent the mean differences and $-log10(P)$ values comparing pathway scores of $CD8^+$ T cells in tumor tissues to that in normal tissues. (G) The upstream LR pairs provoking the *neuroactive ligand-receptor interaction* KEGG pathway in $CD8^+$ T cells in tumor tissues and the corresponding ligand-expressing clusters. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

a combined matrix from the expression matrix and the label vector are submitted, the webserver will process the data as described above. The summary table will automatically update, and a review link will be available once a task is completed. The detailed page for this task exhibits different sections of CommPath workflow. To display the overall interaction patterns, CommPath webserver provides circos plot of LR interactions among all cell types and heatmap of significantly activated pathways in each cell type, as well as the downloadable datatable containing the detailed information of LRs and the relevant pathways. For a particular cell type, the webserver provides circos plot and dot plot to display its LR interactions with other cell types, and network and chain graph to illustrate the corresponding pathway-mediated intercellular communication. Additionally, the webserver makes a comparison between this task and all the other historical records per each cell type, demonstrating CommPath's ability to compare communication between different conditions. More detailed information is provided on the documentation page.



4. Discussion

Recent high-throughput scRNA-seq studies have successfully deconvolved the cellular heterogeneity in various tissues and systems and have helped characterize numerous novel or rare cell types and subtypes [21,22]. Prioritization and annotation of functional LR interactions and the relevant cell-cell communication from scRNA-seq experiments are now becoming a big obstacle in delineating the intercellular signal transduction processes. Here we developed CommPath, an open-source R package and webserver, to explore and visualize patterns of LR interactions from scRNA-seq datasets. It screens and interprets functional consequence of LR interactions based on comprehensive pathway databases, and then identifies cell-cell communication chain mediated by activated pathways.

CommPath provides diverse representations and outputs to accommodate users. Besides the circos plots to show the LR interaction patterns among all cell types, CommPath utilizes network graphs and chain plots to illustrate the communication chains between selected cell types (Fig. 2C, D and F). These intuitive presentations provide lots of important and detailed information of signaling pathways and the relevant LR interactions along the communication chains. To ensure the flexibility and interpretability, CommPath functions provide multiple optional arguments to select and show pathways and LR pairs in each diagram. In the network graph to show the upstream or downstream cell types and the mediating pathways, CommPath allows users to sort and select pathways by different statistic measures of enrichment extent (Supplementary Figure 7A). For comparison between two conditions, upregulated pathways are identified in one condition compared to the other and the associated LR interactions are explored by names of pathways directly (Supplementary Figure 7B). For the chain plot showing the communication chains, users would select self-defined upstream and downstream cell types for a particular central cell population and show the mediating pathways and LR interactions (Supplementary Figure 7C). More detailed information about the optional arguments is available in the CommPath package and online tutorial (https://github.com/yingyonghui/CommPath).

A number of tools have been developed to analyze and visualize cell-cell communication from scRNA-seq data. The major features of CommPath and related tools are summarized in Supplementary Table S1. It is noteworthy that many of these methods infer LR interactions only considering the intercellular signaling, including CellPhoneDB [4], CellChat [6], scConnect [7], NATMI [23], and Connectome [24]. It's expected that, as a response to the valid LR binding, the receptor would activate a signaling cascade in the receiver cell and lead to transcriptional activation or inhibition of specific genes, perhaps transmitting the signal to further downstream cells. Among those methods considering both the intercellular and intracellular signaling, including SingleCellSignalR [5], scSeqComm [25], and NicheNet [26], they all integrated prior biological knowledge from signaling pathway databases and/or regulatory network databases. SingleCellSignalR first measured LR intensity based on their average expression levels and related the receptors in each cell type with downstream biological pathways; scSeqComm weighted the association between receptors and downstream TFs and quantified the intracellular signaling by measuring the activity of target genes regulated by these TFs; NicheNet identified target genes of top-ranked ligands and calculated regulatory potential scores of all ligand-target pairs. However, all these tools lack comprehensive examination and visualization of the activated pathways in the receiver cell. In addition, they showed incapability in inferring the communication chain among further downstream cells. By contrast, CommPath evaluates activities of pathways from various resources and provides intuitive presentations of dysregulated pathways and the associated LR interactions, as well as the communication chain mediated by them. We expected that CommPath would contribute to the identification of novel functional LR interactions and the related molecular pathways.

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CRediT authorship contribution statement

Hao Lu: Methodology, Software, Validation, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Jie Ping:** Methodology, Software, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Guangming Zhou:** Investigation, Data curation, Writing – original draft, Writing – review & editing. **Zhen Zhao:** Software, Validation. **Weiming Gao:** Investigation, Data curation. **Yuqing Jiang:** Investigation, Data curation. **Cheng Quan:** Methodology, Software, Writing – original draft, Writing – review & editing, Visualization. **Yiming Lu:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing, Supervision. **Gangqiao Zhou:** Conceptualization, Supervision, Project administration.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.csbj.2022.10.028.

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