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Cell-cell communication analysis for single-cell RNA sequencing and its applications in carcinogenesis and COVID-19

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ABSTRACT

Cell-cell communication is the basis of physiological processes and cell signals. The disease occurs when the cells do not adequately communicate and the messages are blocked. With ligand-receptor interaction databases and single-cell RNA sequencing (scRNA-seq) databases, we can detect intercellular signaling and reconstruct the cell–cell communications among different cell types. This review summarized the computational approaches for analyzing the cell–cell communication based on scRNA-seq data and discussed its applications in carcinogenesis and COVID-19. We believe that this review will accelerate the scRNA-seq data deciphering and facilitate the cell–cell communication studies for complex physiological processes, such as carcinogenesis and SARS-CoV-2 infection.

Contents

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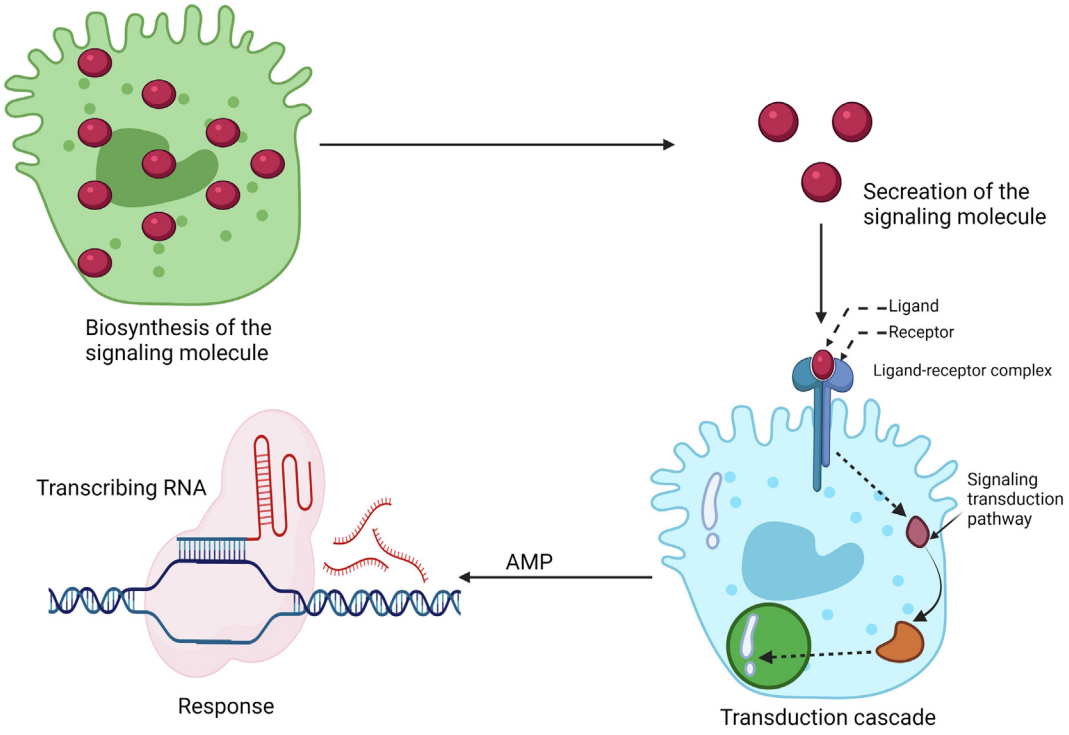

Fig. 1. An illustration of cell-to-cell communication.

1. Introduction

Cell-cell communication generally refers to the possibility of communication between cells in an organism with adjacent cells. The most relevant issue for polygamous organisms is that the present belongs to the span of cell signals [1,2]. Cell-cell communication plays important roles in many fields, such as oncology and virology [3,4]. The biological process of cell–cell communication is summarized (Fig. 1). Cell signals come from the environment, or they come from other cells [5]. The signal can mix with the membrane itself, which can interact with receptor proteins that communicate both the interior and exterior of a cell [6–8]. The correct receptor must be present on the cell's surface to respond to the signal. On the other hand, when signals from protein-protein enter the cell and pass through the cell membrane, the signal can continue its journey to its destination, whether in the nucleus or any other structure or organelle of the cell that contributes equally [9]. Any cell is completely dependent on complex molecules by its signals to respond differently. Next, the signal can straighten a vesicle to fuse through the plasma membrane and express its contents to the exterior part of the cell [10]. Normally, scRNA-seq algorithms or tools such as CellChat [11], COMUNET [12], iTalk [13], CellTalker [14], CellPhoneDB [15], Giotto [16], ICELLNET [17], SingleCellSignalR [18], SoptSC [19], NicheNet [20], CCExplorer [21], SpaOTsc [22], scTensor [23] and PIDC [24] are used to categorize the cell–cell communications through all cell types or tissues types in the microenvironment [3,25,26]. These tools significantly establish a specific cell–cell interaction between different mouse models and specific interactions in human metastatic melanoma [27,28].

There are four types of cell communication based on cell signals: paracrine, autocrine, endocrine, and synaptic [10,29–31]. When they can determine the number of hormones that do their work (e.g., the cause of growth that stimulates cell division) through the activity of hidden cells, they are called autocrine [29,32]. Generally, hormones are collected from cells that bind to protein in nearby cells and affect their activity; they are called paracrine; on the other hand, paracrine also describes the hormone action (e.g., cytokines that contain neurotransmitters in the synapses of the nervous system) [33–35]. The molecules are unexposed into the blood transmitted by the blood and tissues fluids to the cells they act upon (e.g., pancreas contributes insulin and glucagon to keep blood sugar levels) [36,37]. And the process of cell communication with each other is called the cell junction. There are mainly three cell junctions: gap junctions, tight junctions, and desmosomes [2,9,10,37–42].

Most cancer cells communicate with gap junctions, and the proteins types of gap junctions are known as connexins [39,40]. Those connexins had been shown to defend against cancer cells, but this prevention is not the thing of connexins aid. On the contrary, it sometimes aggrandizes tumor progression, ensuring connexins depend on the tumor suppressors [43]. After all, it is observed that the rapidly increasing of cell communication, connexins, to prevent tumors has been a long, ongoing argument that is reinforced by the particulars of various types of cancer, including liver cancer [44,45], colon cancer [46,47], lung cancer [48], breast cancer [49,50], and absence of the cell communication on characterized normal cells or tissues [51]. Therefore, we review the qualitative comparison among these technologies regarding their performance.

2. Computational approaches for cell–cell communication

The scRNA-seq gives us a chance to check the similarity or dissimilarity of the transcriptomes of particular cells [31]. The purpose has been to appraise transcriptional comparisons within a population of cells with initially reported acknowledgment in the past of unthankful levels of heterogeneity, for example, in embryonic and immune cells [52]. So, we can say that the heterogeneity analysis leftover the leading cause for setting on scRNA-seq [30]. Similarly, the measurements of transcriptional differences between individual cells those who have been used to identify scarce cell populations that would otherwise go furtive in analyses of pooled cells [53], for example, hyper-responsive immune cells within a seemingly homogeneous group [54] or malignant tumor cells within a tumor mass [53] are necessary. scRNA-seq is fundamental for the experiment of single cells. In contrast, all are

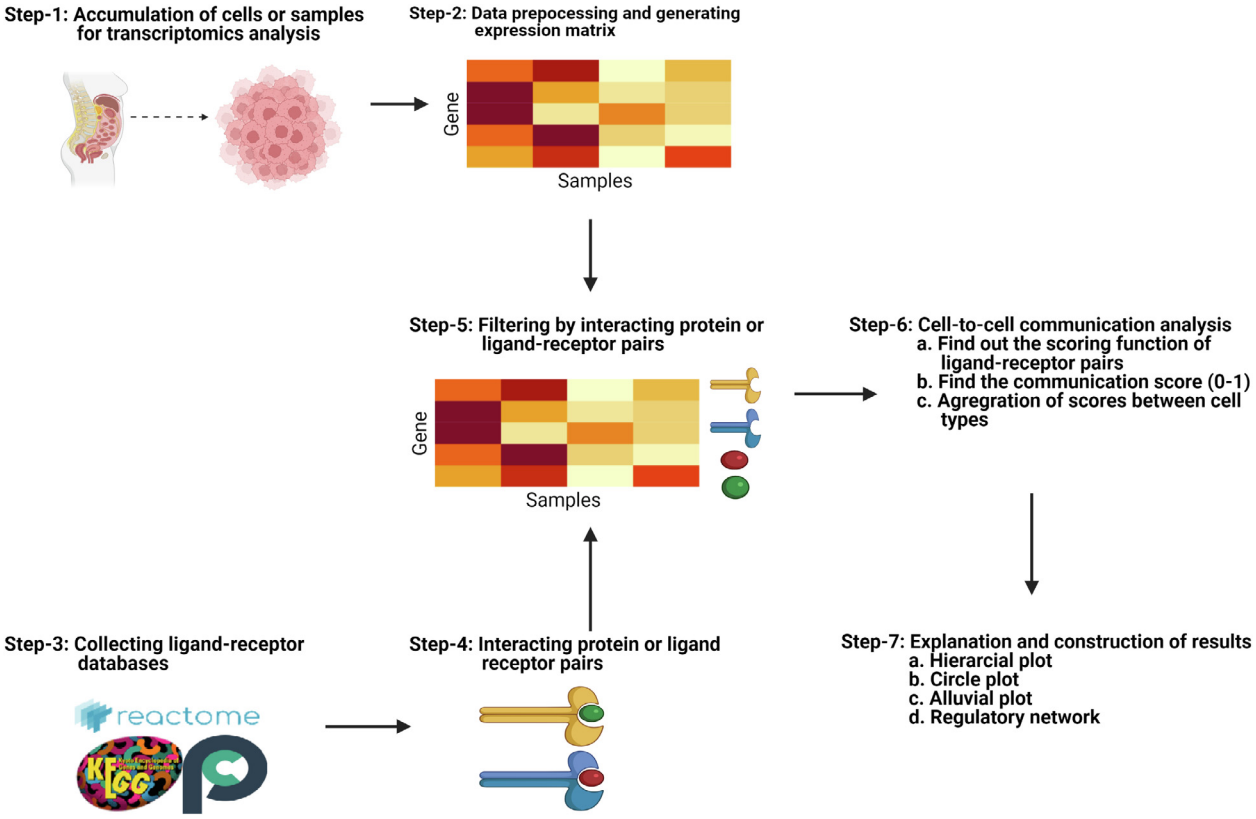

Fig. 2. The workflow of cell–cell communication analysis based on scRNA-seq data.

vitally unique, as are particular T lymphocytes, highly expressed variant T cell reporters [14,55], ne urons within the brain [2,22], or cells within the primary stage of the embryo [25]. Most importantly, studying gene co-expression patterns and cell to cell communication on a single-cell level might accept of detection of co-expression regulated gene modules and gene regulatory networks [39,56].

At an early moment this year, Jin et al. discovered a new software for detecting the cell–cell communication analysis on scRNA-seq datasets by using the TGFb and Wnt singling pathways related to ligand-receptor pairs [57,58]. It has been reported all the tools or software of cell communication from cancer scRNA-seq for different species datasets[59]. That identified particular pathways of the other datasets. Additionally, some agencies identify cell–cell communication from scRNA-seq (Table S1). Through communication technologies, the collected dataset will supply an awareness of the potential ex-plants of the patient as a preclinical model to refine the endogenous cell communication networks. It can be seen that all the technologies are applied to the datasets by using several types of programming language, which are R-language, Python, MATLAB, standalone application, web interface, sc-qPCR. Therefore, we can conclude that most technologies are based on R-language.

Cell communication abilities that have been attempted to build biological processes carry out the computational and illustrate novel bioinformatics [42,60]. Research scientists have been surprised at cells' abilities from informational tankage and speedy systems [61]. Similarly, many features of natural ingredients make synthetic biological processes that are admirable to bioinformatics and biomedical engineering. For example, cell–cell communication organizes bioengineered metastasis, killing bacteria [3]. Various techniques, built by Anderson et al., take advantage of photocell ingredients in E. coli to attack and eradicate cancer cell lines [62]. Synthetic biologists famous for mathematics, statistics, physics, and engineering are specifically concerned about this prosperity conferred the appropriateness of the global positioning system (GPS) [34].

2.1. Workflow of cell–cell communication analysis for scRNA-seq datasets

The workflow of cell–cell communication analysis for scRNA-seq data includes the following steps (Fig. 2):

Step 1: Collecting samples or cells from a transcriptome study

In step 1, the transcriptome estimates the models or cells to calculate the gene expressions [63,64].

Step 2: Data preprocessing and generating the expression matrix

The datasets preprocess genes' expression matrix that accommodates the cell's states or classes [29,65,66].

Step 3: Selection of the interaction ligand-receptor pairs

The user must manually curate the interaction ligand-receptor pairs or protein interaction from different sources (e.g., KEGG, Reactome, and STRING) [11,18].

Step 4: Filtering by interaction protein or ligand-receptor pairs

In this step, the ligand-receptor infrequently pairs corresponding or correlated genes selected by this filtering [67–69].

Step 5: Cell-cell communication analysis

It is finding the $f(L,R)$ ligand-receptor pairs functional scores, communication score that belongs to zero and one (0 to 1), and aggregation of between cell types [11,18].

Step 6: Explanation and construction of the results

Finally, we will explain and construct the hierarchical, circle, alluvial, regulatory network plot based on scoring results [11,20].

2.2. Ligand-receptor pairs database in different species

Often an environmental stimulus is a detective by the cell, the cell response the secreting by the signal chemical, the signal chemical is called ligand [70,71]. The ligand is a detective by the target cells, called receptors. In Table 1, ligand-receptor pairs in specific organs of different species such as humans, mice, zebrafish, and other species to detect the particular cell state, are shown. It can be seen that intercellular signals, cell signal role prediction, prediction of incoming and outgoing signals, signaling pattern, signaling network detection, specific signs, circle plots, bubble plots, and sedimentary plots can be easily made by CellChat. However, the rest of the technology has limitations, making it impossible to perform the above tasks.

On the other hand, 238 (maximum) species were used for PyMINEr [72]. In contrast, two species were used for CellChat and COMUNET, CellTaker, iTALK, CellPhoneDB, ICELLNET, SoptSC, NicheNet and CCExplorer. Only one species was used, SingleCellSignalR and 4 species for SpaOTsc, and 12 species for scTensor. Therefore, we can conclude that CellChat technology is well performed than the comparative technologies.

NF-kB family members are RelA (p65), RelB, c-Rel, NK-kB1(p105), and NK-kB2(p100), those are operated by the output of various cytokines and adhesion molecules which are helping leukemic cells to live with their rapid growth [73]. The specific goal of steam cells must help the long-living of primary malignant B cells in vitro [28,75,75]. NOTCH is another inconsequential signaling pathway of leukemic cells in bone marrow stromal cells. Some researchers suggested that the NOTCH can execute a function in the endothelial differentiation and conserve the total of mesenchymal progenitors in the specific cell [76–80]. The proteolytic transformation of the NOTCH signaling receptor into a transcription substance is based on a mechanical wave established by small polypeptide endocytosis of NOTCH ligands in specific cells [79,80]. WNT, ncWNT, TGFb, PDGF, NGF, FGF, and SEMA3 signaling pathways within the whole weighty forecasted 22 signaling tracks of dermal cells in the embryonic skin. ncWNT signaling interactions network significantly coincide with the canonical WNT pathways [11].

2.3. Scoring of cell–cell interaction by using known ligand-receptor databases

Describing the measured most momentous cell–cell communication among cell states in the tumor microenvironment and used roughly 1800 known communications including the ligand-receptor communications from a cytokine, receptor tyrosine kinases (RTKs), tumor sphacelus factor (TNF) groups, and extracellular-integrin contacts [81]. They detected highly significant cell–cell communications from six syngeneic tumor models [82–85]. Including integrated models for cell–cell communication, Cdc42 was maintained by the Rab11 and acted as a risky penstock of cell–cell interaction likewise through boundary cell movement [86]. Some other reviewers suggested that the cell–cell adhesion molecule and E-cadherin are the branches of the chemical challenge of cell–cell interaction in the boundary cells and cultured mammalian cells [23,88,88].

2.4. Extracellular matrix

ECM is an accumulation of various enormous molecules acquired in a multi-dimensional shape with singular biochemical characteristics of maintaining the development of cells, natural selection, mortality, and separation [69,90,90]. It gives cells across a stage, maintains hydration, pH likewise virtue of swelling factors and cytokines [91,92].

Table 1
Comparisons of intercellular communication analysis tools.

Methods	Results and Interpretations					Data types			Methodology	Analysis		Results and Interpretations		
	Ligand –receptor pairs	No. Species	Intercellular signaling	Multiple subunit	Cofactor	Preprocessing data	Multiple datasets	Low-dimensional Space	Statistical Methods	Cell Proportion	Identify specific signals	Circle plot	Bubble plot	Alluvial plot
CellTalker	2,422	One	1	1	0	1	1	1	Statistical test	0	1	1	0	0
COMUNET	1,396	Two	0	0	0	0	1	0	Statistical test+Law	1	0	0	0	0
iTALK	3,648	One	0	0	0	1	1	0	DE gene Analysisi	0	1	1	0	0
PyMINEr	65,910	238	1	0	0	1	0	0	Selection DEGs	0	1	0	1	1
CellChat	1,939 /2,021	Two	1	1	1	1	1	1	Statistical test+law	1	1	1	1	1
CellPhoneDB	1,396	One	0	1	0	1	0	0	Mean expression	1	1	0	0	0
Giott	1,288	Nine	0	0	0	1	1	0	Mass action law	0	1	0	1	0
ICELLNET	380	One	0	0	0	1	0	0	Statistical test	0	1	1	1	0
SingecellSignalR	3,251	Four	0	0	0	1	1	0	Regulation produces	1	1	0	0	0
SoptSC	1,288	One	0	0	0	1	0	0	Mass action law +related laws	1	1	1	1	0
NicheNet	12,651	One	0	0	1	1	0	1	Mass action law	0	1	1	1	0
CCExplorer	1,433	One	0	0	0	0	1	0	Statistical test +related law	0	1	1	0	0
SpaOTsc	1,001	Four	0	0	0	1	1	0	Mass action law	1	1	1	0	0
scTensor	34,449	Tweelve	0	0	0	1	1	0	Linear decomposition	0	1	1	0	0
PIMC	1,050	Three	1	0	0	1	0	1	Mass action law	1	1	1	0	0

The cell ECM communications rate is a vital character in the tumor microenvironment. Cancer and decay of it are significantly correlated with metastatic propagation of the tumor and cancer studies [93–96]. ECM cell adhesion signaling mainly qualifies communications within cell rectitude and fibronectin [97,98]. Genetically selecting of rectitude-β and downstream signals are Src, Talin, PI3K, MAPK susceptible to apoptosis obstructive with competent cancer cells for TRAIL-spontaneous apoptosis in vitro by growing TRAIL-R grading and losing the termination for mitochondrial apoptosis. Above all of these outputs give a mechanical reason for devoted cancer cells that substance is more unwilling to TRAIL than the circulating cells [99]. The endogenous TRAIL produces the FADD-incapable extravasation of cytokines, highly significant CCL2, producing in the condition of myeloid cells healthy M2-like cells and the collection of such instead treated myeloid cells in the tumor microenvironment as well as cancer [91,100,100]. The elastin microfibril connection-positioned receptor 2, a unit of the ECM of glycoproteins that can link with TRAIL-R1 and a secondary magnitude TRAIL-R2 to produce proteins congregate and co-localization in organic floats, consequently animation of the death cells [101,102].

3. Applications of cell–cell communication with technologies

3.1. Cell-cell communication in microenvironment and carcinogenesis

The cell-to-cell communication arrangement of carcinogenesis is not efficiently implied because it includes the various responses of the loop and the activation of several forms of communication, the obstruction of both paths, a fine-tuning process, and the chaos [103–105]. Cancer is a heterogeneous scheme because it has a lot of cell types or states, including fibroblasts, endothelial cells, cytotoxic cells, neutrophils, T-cells, B-cells, Mast cells, NK cells, macrophages, along with elements of the extracellular matrix, proteases, cytokines coincide and encouragement to the tumor or unfolds of malignant cells in the tumor microenvironment [31,107,107]. Scientists now estimate that about (5–10) % of cancers are activated by mutations, more than 15% by infection, and 80% by “scattered” cancers whose origins have not yet been identified [108–110]. According to cell biologists, “many mutations in esse

ntial genes will be required for metabolism and switching to that metabolic effect [111–113]. Therefore, the clonal theory is generally recommended to describe the rapid proliferation of human cancer cells which cannot count the mutations discovered in this study” [110]. A pathogenic provocatio PyMINEr n alarming or persistent constipation is first communicated with the T contact layer, T superficial proteoglycan layer (glycolic) of a mammalian cell [114,115]. The glycocalyx is surrounded by five several types of adhesive molecules, including immunoglobulins, integrin, cadherin, selectin, and cell adhesive molecules capable of communicating directly with ECM [4,32,47,111,116]. When cells communicate with proteins through inherited signals over the cell membrane [30], the signs communicate with the proteins in the marker cell by communicating the ECM, which accumulates in the plasma membrane of the marker cell [117].

3.2. Application of cell–cell communication in COVID-19

COVID-19 is the most challenging topic worldwide [118]. It pensively turned out that 102 clinical patients were observed three months at the beginning moment in 2020 by one of Hubei Hospital in Wuhan[119,120]. They identified that the 100% of T $CD4^+$ and approximately 70% of $CD8^+$ T cells are most critical types were remarkably under the tolerable types.[121,122]. The highly correlated genes are mature and immature between the cell types of monocyte and neutrophil states. The COVID-19 fixed $CD4^+$ and $CD8^+$ T cells for constructional tools, and ORF1ab receptors contrasted mature and immature reign with setting up particular activity[123]. This study observed that the COVID-19 patients have higher intracellular communication in monocyte cell types from scRNA-seq data[124]. The WHO supports further testing in cell–cell interactions with the outcome and progress of diseases, including different cell–cell communication types across all types of diseases[20]. According to the Chinese National Health Commission Guidelines, 58.8% of patients are privileged among the tolerable types, and 41.2% are divided into critical types[125]. White blood cell count, neutrophil, aspartic aminotransferase, total bilirubin, blood urea nitrogen, c-reactive receptor, prothrombin time, and D-dimer levels are remarkably evaluated critical types than the tolerable types.

4. Conclusions

In this review, we summarized the computational approaches for analyzing cell–cell communication from scRNA-seq datasets, multi-omics datasets, and bulk RNA-seq data, such as CellTalker, SingleCellSignalR, COMUNET, iTALK, PyMINEr, CellChat, CellPhoneDB, Giotto, ICELLNET, SoptSC, NicheNet, CCCExplorer, spaOTsc, scTensor, and PIDC. These methods and tools are qualitatively compared with each other. We are showing the capability and all of the conceptual image analysis of these tools, which are listed with their details. We see that the CellChat technology is a comparatively better performer than all cell–cell communication analysis approaches. We discussed all the methods for applying in cancer and COVID-19. Therefore, we hope that all the researchers will easily understand to use the cell–cell communication analyzing technologies in computational biology and bioinformatics.

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Conflict of interest statement

The authors declare that there are no conflicts of interest.

Author contributions

Md Wahiduzzaman: Writing – original draft, Writing – review & editing. **Yuexing Liu:** Writing – review & editing. **Tao Huang:** Supervision, Conceptualization, Writing – review & editing. **Wu Wei:** Supervision. **Yixue Li:** Supervision.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bsheal.2022.03.001.

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