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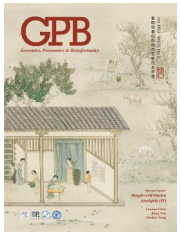

EDITORIAL

Advanced Single-cell Omics Technologies and Informatics Tools for Genomics, Proteomics, and Bioinformatics Analysis

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The newly developed technologies for profiling cellular heterogeneity have spurred a world-wide pursuit of single-cell analysis in the field of omics studies, investigating the genome, epigenome, transcriptome, proteome, metabolome, and their inherent interactions. Knowledge obtained through such analysis facilitates a deeper understanding of how underlying molecular and architectural changes alter cell behaviors, development, and disease processes. Genome-scale amplification of genomic DNAs or cDNAs from mRNAs transcribed in single cells allows for the measurement of genetic alterations and cell types at an unprecedented level. The emerging microchip-based tools for single-cell omics analysis further enable the evaluation of cellular omics with high throughput, improved sensitivity, and reduced cost. On the other hand, single-cell high-dimensional data obtained with high-throughput technologies also pose new challenges in bioinformatics to analyze, process, and make sense of the big data, in order to deliver new biological insights and knowledge.

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This special issue "Single-cell Omics Analysis" aims to highlight the latest advances in single-cell omics technologies and informatics tools for analyzing genomics, epigenomics, transcriptomics, proteomics, metabolomics, and multi-omics at the single-cell resolution.

The special issue collects more than 20 research and review articles, which are published in the preceding issue (I) and this issue (II). In general, these articles can be categorized into application-oriented works and method-oriented works. The application-oriented articles demonstrate the power of utilizing single-cell omics data, *e.g.*, single-cell RNA sequencing (scRNA-seq) data, in addressing specific biological questions, while the method-oriented articles showcase numerous effective and efficient computational methodologies to analyze single-cell omics data.

In issue (I), there are 13 articles with one preview, two review papers, and ten research papers. In the preview article, Huang et al. highlighted progresses in immune pathogenesis in connection to human recurrent miscarriage [1]. In the first review article, Sinha et al. summarized molecular methods and bioinformatic tools for capturing cell-to-cell chromatin variation using single-cell assay for transpo-

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sase-accessible chromatin using sequencing (scATAC-seq) in a scalable fashion [2]. In the second review article, Bai et al. provided an overview of applying cuttinge-dge single-cell omics tools to dissect the heterogeneity of tumor–immune interactions at a systems level [3]. As an application-oriented work, Wang et al. revealed a comprehensive cellular and molecular atlas of decidual and peri-pheral leukocytes in human early pregnancy [4], as highlighted in [1]. Lidgerwood et al. highlighted the transcriptional landscape of human pluripotent stem cell (hPSC)-derived retinal pigment epithelium (RPE) cells as they age in culture, which provides a reference for native and patient samples to be benchmarked against [5]. Balog et al. demonstrated for the first time that mass cytometry, a single-cell protein profiling technology, combined with multidimensional bioinformatic analysis, represents a versatile and powerful tool to deeply analyze the regulation of cell-mediated immunity of *Drosophila* [6]. Wang et al. compared the analyses of 10X Genomics Chromium-based scRNA-seq and Smart-seq2, which promoted better understanding of these two platforms and offered the basis for an informed choice of these widely-used technologies [7]. Huang et al. summarized and compared 10 cell type annotation methods with publicly available scRNA-seq data [8]. In this issue, five method-oriented articles are also included in this special issue. Liang et al. proposed a novel single-cell clustering framework, SSRE, based on similarity learning [9]. Xie et al. proposed redPATH, a comprehensive tool for reconstructing the pseudo development time of cell lineages based on scRNA-seq data [10]. Meanwhile, Wei et al. developed DTFLOW, which can be applied in inference and visualization of single-cell pseudotime trajectory using diffusion propagation [11]. Li et al. proposed the c-CSN method, which can construct the conditional or direct cell-specific network (CSN) for each cell by eliminating the indirect associations between genes [12] based on CSN scheme [13]. Song et al. derived the model, scLM, a gene co-clustering algorithm tailored to scRNA-seq data [14].

In issue (II), there are 12 papers. As an application-oriented work, firstly Wu et al. developed scDPN, which is a single-cell DNA library preparation method without preamplification at the nanoliter scale [15]. Xin et al. provided a systematic theoretical guidance for optimizing the induced PSC (iPSC)-derived red blood cell (RBC) differentiation system, which is a useful model for simulating *in vivo* hematopoietic development and differentiation [16]. Luo et al. provided the first comprehensive catalog and the functional repertoires of long non-coding RNAs (lncRNAs) in human T cells, which provides not only a new point of view but also resource for investigating the mechanisms of T cell regulation in cancer immunity [17]. Also as an application-oriented work, Hu et al. demonstrated that miRNAs are important posttranscriptional regulators for reducing gene expression noise and conferring robustness to biological processes through the integrated analysis of single-cell RNA and miRNA expression profiles [18]. Moreover, Liu et al. elucidated sexual dimorphism in type 2 diabetes (T2D) pathogenicity and provided novel insights towards the development of precision medicine in T2D [19]. Li et al. provided a valuable resource for understanding embryonic osteogenesis and angiogenesis underlying vertebrate thoracolumbar vertebra (TLV) and rib primordium (RP) development at the cell type-specific resolution, which offers a comprehensive view on the transcriptional profile of animal embryonic development [20]. Ge et al. identified different biomarkers during Cashmere goat hair follicle development, which has implications for Cashmere goat breeding in the future [21]. Meanwhile, a webserver, GranatumX was also presented in this special issue, which enables biologists to access the latest single-cell bioinformatics methods in a web-based graphical environment [22]. On the other hand, as a method-oriented work, the computational model proposed by Zhong et al. [23] can explore the gene–gene associations based on scRNA-seq data for critical transition prediction. Li and Li proposed the scLink method, which used statistical network modeling to understand the co-expression relationships among genes and construct sparse gene co-expression networks from single-cell gene expression data [24]. Nguyen et al. described the development of Polar Gini Curve, a method for characteri-zing cluster markers by analyzing scRNA-seq data, which can help users characterize the shape and density distribution of cells in a particular cluster [25]. Conchouso et al. provided engineering details and organized protocols for integrating three droplet-based microfluidic technologies into the metagenomic pipeline to enable functional screening of bioproducts at high throughput [26].

As described above, the articles in this special issue address various technological or biological questions, challenges, as well as future opportunities that will facilitate the development of next-generation single-cell analytical tools and foster broad application of single-cell omics in biology and medicine.

CRediT author statement

Luonan Chen: Writing - original draft, Writing - review & editing. **Rong Fan:** Writing - review and editing. **Fuchou Tang:** Writing - review & editing. All authors have read and approved the final manuscript.

Competing interests

Rong Fan is a co-founder of IsoPlexis, Singleron Biotechnologies, and AtlasXomics, as well as a member of their

scientific advisory boards with financial interests. Other authors declare that they have no competing interests.

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