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Breaking New Grounds with Emerging Paradigm of Genomic Signatures and Gene Expressions Generated from Single Cell RNA Transcriptomics: Through Molecular Elucidations and Translational Benefits

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ABSTRACT

Transcriptomics is the science of transcript analysis and comprises a list of strings called reads while Transcriptome is the full range of messenger RNA (mRNA) molecules expressed by an organism, or it describes the pool of mRNA transcripts produced in a particular cell or tissue type. As such, this method is called RNA transcriptomics, when focused on the messenger RNA (mRNA) and the inclusion of sequence expositions in the analysis, it is termed RNAsequencing (RNAseq).

The capacity to conduct unbiased single cell transcriptomics analysis on a wide scale and knitted to coordinate referencing at the tissue scale, brings synergy to improvement and holistic use of scRNA transcriptomics technique. Also, it reveals various forms of genomic signatures and gene expressions in examined tissues.

In biomedical research, scientists have found use for RNAseq in the areas of biomarker discovery, characterization of cell heterogeneity and evolution, drug resistance, characterizing cancer immune micro-environment, immunotherapy, among others. This genomic single cell technology has been applied for studies in several diseases, of which includes neurodegenerative and some infectious diseases/clinical conditions, which remain challenges to man.

This technique is breaking grounds and creating new corridors of options for translations in its use to benefit life science research (across animal and crop plants fields) and human health.

Keywords

RNAsequencing, Molecular technology, Genomic signatures, DNA.

Introduction and Compelling need

Single cell sequencing is a molecular technology for analyzing genomic contents for sequence information from individual cell isolates using optimized sequencing technology such as those on next generation sequencing (NGS) platform. Consequently, genomic signatures and various types of gene expressions can be generated. Several types of non-single cell sequencing methods have been used to analyze group of cells (tissues) for genomic

profiles and expressions of DNA and RNA molecules. A good number of them do miss several gene characters of biologically and clinically functional relevance [1,2]. Their genomic profile data obtained was at lower resolution for gene characters that are difficult to identify [3,4]. Thus, there was need to track rare mutations often associated with health anomalies using other methods [5].

RNA sequencing (RNAseq) is a practical concept in Genomics that enables detection and quantitative analysis of mRNA molecules. It is used in genomic transcriptome analysis. This provides expository corridor for unveiling cellular responses and biological heterogeneity. Heterogeneity evaluation is important for assessment for new biomarkers. For instance, cancer biomarkers help differentiate between cancer patients for appropriate treatment and predict response to specific cancer therapies [6,7].

RNAseq over the past decades has been generating wide array of information that are igniting bespoke innovations in Biomedicine, Pharmaceuticals, Agriculture and generally in the life sciences [8-10], and agricultural science such as in cell types and cell type-specific disease processes [11,12].

Furthermore, there has been need to conduct direct assessment of the building unit of tissues from biopsies in biomedical and biological samples. ScRNA-seq helps achieve this [13,14] - when we have need to reveal the gross identity of tissues of mammalian and animal samples, for cell differentiations, track cell lines and regulatory mechanisms, from biological specimens of a heterogeneous nature, spatial transcriptomics comes in handy as a tool [15,16]. A complimentary approach to make-up for limitation of scRNA-seq data is to reference the generated scRNA-seq data to the positions on the tissue coordinates using some established referencing techniques [18].

This review is geared towards linking scRNAseq to translational applications.

Background of single cell RNA-Sequencing (scRNA-seq)

The first description of single cell RNA transcriptome analyses based on NGS platform was published in 2009 by Tang et al., this team analyzed and characterized cells from early developmental stages in a four-cell-stage blastomere, from their mRNA in whole transcriptome analysis (WTA) [18,19]. Then, in 2012, Hashimshony et al. [20] introduced cell expression by linear amplification and sequencing (CEL-seq) to generate scRNA sequence libraries Wu et al. [21]. However, the pioneer role in single cell transcriptome analysis was credited to Brady et al. [22] and Eberwire et al. [23].

Presently, transcriptome technologies have two key contemporary techniques, namely microarrays (quantifying a set of pre-determined sequences) and RNA-seq (using high-throughput sequencing to produce reads of all RNA transcripts in the transcriptome). Pioneer role in single cell transcriptome analysis is credited to Brady et al. [22].

Single cell transcriptomics technologies are used to create reference maps of healthy tissues, organs and systems at single cell resolution in human and non-human organisms [19]. This would help advance our understanding of the biology and diseases. It exposits heterogenous cell populations, reconstructs cellular trajectories related to developmental features, reveals gene signatures and expressions, and other multi-omics information, all in dynamic ways, all in a single cell based transcriptomics analysis and prior to this where masked by pooled transcriptomes [18,19]. These paves was for elucidating differences and evolutionary relationships of various cells, applicable to various fields of life sciences- oncology, infectious diseases, neurology, reproductive biology, immunology, pathology and urinary systems; and in plant and veterinary sciences.

The objectives of this article are to:

- Provide information on the background of transcriptomics analysis.
- Exposit areas of its framework that can be engaged to further biomarker and drug target discoveries, which links scRNAseq to translational science applications.
- Bring to fore, the limitations initially encountered and how they have been surmounted to make this single cell science technique a sheer delight for frontier science, and breathtaking novel discoveries.

Conceptual birth and uses of single cell Transcriptomics analysis

Transcriptomics was first done by hybridization based micro-arrays and later with NGS techniques referred to as RNA sequencing (RNA-seq) from which spatial transcriptomics by RNA-seq sprung forth via its development [18,24]. A typically clinical application of spatial RNA transcriptomics was when spatial RNA-seq analysis was conducted on haematopoietic cells to stratify acute myeloid leukemia patterns into cohorts requiring different treatment regimens [25]. Here, its limitation is that it did not allow detailed assessment of each of the fundamental biological unit cells or individual nuclei that constitute the genome [26,27]. With the ground breaking successes from scRNAseq technology, lots of efforts has gone into spatial transcriptomics methods to make them capable of resolution of its data at the single cell level.

In-situ RNA sequencing-based transcriptomics (on tissues) approach enables unbiased census and quantification of all RNA molecules while preserving localizations [28]. Since mRNA molecules are protein based, encoding these mRNA molecules that collectively make up the transcriptome (when analyzed by RNAseq), unveils the nature of gene expression found in these RNA molecules, proving clues for cellular traits, functions and cellular reponses [13,29].

Initially, scRNA-seq transcriptomics generates simultaneous gene expression data of thousands of cells, though it does not provide data on each cell's position in the tissue of interest during the analyses [13,30]. Following its developments, scRNA transcriptomics now

perform genomic descriptions of RNA molecules in individual cells at high resolution that can be performed up to the whole genomic scale [27]. Some techniques have been developed to generate data of gene expression signatures and expressions for individual cells in an assessed tissue, alongside the positional configuration inside the tissue, to make the overall data comprehensive and more useful [26].

One of such methods is the use of 3-dimensional model (3D) principal component analysis which uses expression data of a few genes that have been previously mapped out using RNA in-situ hybridization via seqRT-PCR, to establish a 3D of the cell lines in the gross shape of a sphere {developed by Stephan Heller's group} [17,31,32]. The method described above is basically for the RT-PCR which can be expensive and rigorous to run. Bioinformatics tools and data, plus robust computational methods for low-level processing, quality control and sophisticate data interpretation in downstream analysis, helped support getting the spatial coordinates to make sc analysis data more useful [33,19].

One of the recently developed alternative techniques engages a transcriptome analysis device called Seq-Scope (SCOPE-Seq) sequencer (developed by Dr Jun Hee Lee, and his team at the University of Michigan Medical School), which modifies some aspects of the RT-PCR procedure [34]. Seq-scope is a cost effective sequencing tool with ease of usage and maintenance of speed and reliability. It is a repurpose illumina sequencing platform that enables single cell and sub-cellular analysis of tissues and organs, showing tissue zonations of single cells in the tissue positions. A typical successful utilization of Seq-scope (SCOPE-Seq) method is that by Cho et al. [35], engaging a spatial bar-coding technology that enables the researcher to see every gene expressed, single cells and other structures within those tissues, at high resolution [36,37]. In this new method, a micro-device is overlaid with the tissue sample and it sequences everything within it with a barcode and its spatial coordinates [35,37].

scRNA transcriptomics spatially resolved in studies was declared the method of the year 2020 by Nature Journal Marx [1], and single cell multimodal Omics as method of the year 2019 Nature Methods [38]. By combining other methods with single-cell RNAseq, researchers can both monitor the behavior of individual cells and see how they fit into the organism's unfolding architecture American Association for Advancement of Science AAAS Science Magazine [39]. The single cell revolution is just starting, says Elizabeth Pennisi AAAS Science Magazine (2021), scRNA-seq transcriptome analysis and bioinformatics algorithms has proven potentials to help generate reference scRNA data at tissue level, do translational screen for biomarkers, and for prediction of treatment outcome and drug targets [6,40]. Spatially resolved single cell transcriptomics was adjudged method of the year 2020 by Nature Journal- Nature Method [41].

As such, single cell transcriptomics has been made to work at spatially resolved level with the help of bioinformatics tools to create in situ atlas mapping and referencing of single cell data to tissue coordinates and through novel sc transcriptomics systems being developed. Findings from molecular diagnostics by scRNA-seq is helping to translate these findings and insights into clinical tools for diagnosis and drug development [42], and assessing drug resistance [28].

Since 2020, scRNA-seq assumed a Gold standard for analyses of single cell genomes and their expressions.

Typical Translational landmark breakthroughs with scRNA-seq

Sc RNA transcriptomics is creating a paradigm for translating bench-side studies and results into bedside applications in its inputs for translation-based research.

Typical translational advances using sc transcriptomics includes:

- scRNA-seq applied to monitor peripheral immune cell landscape changes in Coronavirus-19 patients, and revealed changes in peripheral immune cells, Lymphopaenia, and T-cell exhaustion [43]. This supports tracking of nature of progress from treatment.
- MX2 receptor molecules in naïve B- cells was found as biomarker in patients of Dengue virus (DENV) disease by analyzing PBMCs of patients using scRNA-seq [44].
- Gene fusions are closely related to oncogenesis, now serve as novel cancer biomarkers and drug targets [45].
- Remedies from neuron associated brain problems are on development, following discovery of relationship between brain nerve cells, molecular regulation, and neuron production. This is now engaged for clinical brain cells regeneration therapy [46].
- A new corridor created via scRNA-seq technology to predict infectious disease risk consequences, as the scRNA-seq data-based algorithm is engaged to find specific cell types associated with differential microbial infections [47]. This has disease preventive qualities to support clinical therapy.
- Detection of rare heterogeneities from scRNA-seq is helping to discover diagnostic markers. For instance, single-cell sequencing used to track novel perspectives in hematopoeitc stem cells. It created a multi-omics single cell analytic technology comprising single-cell COOL-seq, scNMT-seq, scTrio-seq and scM& Tseq used in a multi-dimensional screen that produced multi-faceted landscape of each cell in developmental hematopoeisis. Also, this provided high resolution dissection of malignant hematopoiesis [48].
- SARS-CoV-2 ACE-2 receptor and TMPRSS2 are detected in bronchial transient secretory cells using scRNA-seq [49], to present a good platform to monitor course of treatment. There are other studies which have indicated same positive clinically diagnostic relevance.
- Several studies have now shown that gene fusions are closely related to oncogenesis and now serve as novel cancer biomarkers and drug targets. Gene fusion detection complimented diagnosis of acute myeloid leukemia and identified related recurring NRIP1- MIR99AHG gene rearrangements [50]. Fusion genes were detected using

targeted RNAseq in a study by Heyer et al. [51].

- The discovery of receptor genes for drug targets from scRNA-seq has been applicable to development of anti-tumour drugs [52], such as Herceptin [53] and revealing gene expression signatures of Trastuzumab treatment in HER2+ breast cancer [53],
- Following discoveries of relationship between nerve cells, molecular regulation and mechanism of neuron production, an area of investigation now involves steps for clinical brain cells regeneration therapies [32].
- In my own preparations, I have laid down a proposal to probe for the types of diagnostic biomarkers in breast cancer and drug targets in Breast cancer from patients in a specific town in Africa, using scRNA-seq technology in combination with Bioinformatics and Computational Biology tools Ozurumba-Dwight ARPHA [In press]. The is geared towards investigation and screen for cancer type- specific biomarkers and drug target identifications in a study population, based on a few working hypotheses; and using single cell technologies in combination with Bioinformatics and Computational Biology tools. A preamble to this was presented at the WASET conference in Switzerland in 2021 [54].

Challenges

The journey onto impactful insights, elucidations and discoveries through scRNAseq technologies has not come with ease. There have been challenges with steps taken to overcome them. Notable ones are highlighted here.

The first challenge I present in is that earlier generated data from scRNA-seq lacked of information of positional data for the tissue coordinates. New tools have been developed from bioinformatics and computational biology that references these scRNA sequence data to make them scalable to their positions in the tissue architecture [1,9,16,34,35]. Additionally, new scRNAseq technologies are been developed and remodeled to connect single cell transcriptome data to their positional tissue's coordinates [36,37,55]. This has made such data more useful for translations as clinical support tools.

A second challenge is taking steps during whole transcriptome analysis and entire sequencing to ensure whole genome amplification fidelity. One way this has been addressed has been through single cell multiomics multiple and parallel single cell measurements which allows insights into expression dynamics [56], direct nuclear tagmentation and RNA sequencing (DNTR-seq) which enables whole genome and mRNA sequencing done jointly in single cells, as DNTR-seq readily identifies minor sub-clones of specialized cells such as obtainable in leukemia patients. Also, it enables coverage-independent estimation of ploidy which can be used to identify cell singlets [55].

Conclusion

ScRNA-seq has been a useful entry into genomics profiling technologies, for analyzing RNA molecules for genomic signatures and gene expressions. The generated data has been found to be clinically useful in disease diagnosis, translational precision medicine-based therapy, tracking out novel biomarkers and drug targets discovery. It is now widely applied in diverse research fields in the human, animal and plant discoveries and application researches (including specialized fields of immunology, cancer biology, onclology, neurobiology, diagnosis, pharmaceuticals, and crop plants and animal science based -agricultural science. As part of the single cell technologies engaged for research and impacting novel discoveries, single cell RNA sequencing has benefitted the scientific community supporting better understanding of biology of cells, tissues and whole organismal functions. Also, this stems from its proving depths and clearer insights into individual cell-to-cell details in genomic signatures, characters and expressions.

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