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REVIEW ARTICLE

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Current Knowledge and Use of Single-Cell RNA Sequencing in Osteoarthritis

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ABSTRACT

Osteoarthritis (OA) is the most common chronic joint disease and it may progressively cause disability and compromise quality of life. Lately, the role of single cell RNA sequencing in the pathogenesis of OA has drawn a lot of attention. Number of literatures were studied, reviewed and analysed to write this review. In this review, use and knowledge on sc-RNA in OA will be outlined. Overall, the use of scRNA-seq has enabled a more comprehensive understanding of the diverse cell populations and molecular signaling pathways involved in osteoarthritis pathogenesis.

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Abbreviations

OA	Osteoarthiritis
scRNA-seq	Single Cell RNA-sequencing
PC	Principal Component
ACL	Anterior Cruciate Ligament
SFs	Synovial Fluids
SPP1	Secreted Phosphoprotein 1
PTN	Pleiotropin

Introduction

Osteoarthritis (OA) is Chronic degenerative joint disease a common condition that can affect the cartilage, synovium, joint ligaments and subchondral bone [1]. In 2005, OA affected around 27 million individuals in the United States [2]. The characteristics of joint lesions include narrowing of joint space, sub chondral sclerosis, osteophytosis, and formation of osteophyte. In later stages of Osteoarthritis (OA), the conventional treatment is joint arthroplasty. However, this approach has limitations, such as its inability to prevent and address early-stage OA effectively, as well as the invasiveness of the procedure. Therefore, investigating the pathogenesis of early OA is crucial. Timely prevention and treatment of Osteoarthritis (OA) is beneficial for improving patient survival. The development of OA involves various biochemical compounds that are considered as the disease's pathogenesis, including lot of inflammatory response proteins (such as tumor necrosis factor, interleukin 1β and interleukin 6, matrix-degrading enzymes, and toll-like receptors secreted by chondrocytes in cartilage [3]. The only cellular component found is the chondrocytes in cartilage. This accounts for approximately 1-5% of the entire cartilage mass [4]. Approximately 9.6% of men and 18% of women over the age of 60 experience symptoms of OA, and 25% are incapable of performing routine tasks due to the condition [5]. The prevalence of OA is anticipated to increase to 130 million individuals by 2050, signifying a substantial social and economic burden [6].

Single-cell RNA sequencing (scRNA-seq) have attracted a lot of attention lately, since they have the potential to identify rare or previously unidentified cell populations, which could provide new understanding into disease progression and treatment. Numerous studies have used scRNA-seq technology in OA and these analysis may contribute to the pathogenesis of OA. The purpose of this article is to review the literature on current knowledge and use of single-cell RNA sequencing in Osteoarthritis and and its effects on the diagnosis and treatment of this disease.

Single Cell RNA Sequencing (scRNA-seq)

Single-celled analysis through global approaches has the capacity to revolutionise our comprehension of entire organisms, as it allows for the tracking of cell lineages and the description of heterogeneity within an organ with unparalleled resolution [7]. Studying cells at the single-cell level provides exclusive chances to analyse how intrinsic cellular procedures and external stimuli, such as the local environment or neighbouring cells, interact in determining cell fate. This also greatly benefits clinics in comprehending how a single 'outlier cell' may impact the result of an infection, drug or antibiotic resistance, and cancer recurrence [8-11]. Single-cell RNA sequencing (scRNA-seq) technology has enabled to provide deeper understanding of the cellular and molecular changes underlying osteoarthritis. Single-Cell RNA-seq provides transcriptional profiling of thousands of individual cells. This level of analysis allows researchers to understand the level and abundance of individual genes and how they differ among thousands of cells in different samples.

Methods

This narrative review of the literature was performed by

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searching in titles and abstracts in the EBSCO, PubMed, Google Scholar database for publications on research, brief report, clinical and observational studies into single cell RNA sequencing analysis in OA that were published between 01-01-2019 and 31-08-2023.

Results

Uses of Single Cell RNA-Seq in OA

Several studies on single-cell RNA in osteoarthritic cartilage have been published in the past few years, synovial fibroblasts and subchondral bone. Most of these studies examine the expression of genes known to be involved in OA pathogenesis and their target genes.

scRNA-Seq in Mouse Knee Joint, Healthy and OA Human Cartilage Chondrocytes

By definition, Single-cell profiling technologies can now assess at high resolution the genome, transcriptome, and epigenome of individual cells, thus allowing us to recognize cell identity, state, and activity, particularly when combining multiple technologies. To analyze populations and identify genome-wide patterns of gene expression Ji et al. conduct research using single-cell RNA sequencing (scRNA-seq) technology to investigate the relationship between osteoarthritis (OA) and expression of gene at the single-cell level [12]. By performing scRNA-seq analysis on samples obtained from patients with different stages of OA, they aimed to identify distinct cell populations and their gene expression patterns, The 50 most important genes correlated, both negatively and positively, were analysed across PC1 and PC2 in 1464 chondrocytes. Using hierarchical clustering, four clusters with PC2 (A, B, C, and D) and three clusters with PC1 (1, 2, and 3) were shown. Notably, Cluster 1 displayed high expression. Genes exhibiting a negative relationship along PC1, including JUN, HES1, ID3 and some others, are primarily involved in RNA metabolic processes and protein binding. In contrast, highly expressed genes in cluster 2 shown a positive relationship with PC1, such as ITGA5ID3, SGMS2, KLHL21, and others which were related with angiogenesis. Cluster A consists mainly of stage 3 and 4 chondrocytes with highly expressed genes, mostly PC2 (TGFBI, TNC, CRTAC1, etc.), which are involved in extracellular matrix organisation. In addition, clusters along PC2 showed correlation with OA stages. Cluster B is characterized by stage 0 and 1 chondrocytes and highly expressed genes that negatively correlate with PC2 (TF, C2orf82, FRZB etc.). These genes are mainly involved in the development of the skeleton, as well as collagen catabolism. Cellular responses to stress indicate the initial changes that take place during osteoarthritis pathogenesis. Their study identified different cell types that represent different cell types in joint tissue, including endothelial cells, synovial fibroblasts, immune cells, and chondrocytes. The researchers looked at the differences between patterns of healthy tissue and tissues affected by OA, as well as patterns at different stages of OA. These findings allowed for the identification of specific genes and pathways that are dysregulated during OA progression. Overall, the research demonstrated the power of scRNA-seq in unraveling the cellular heterogeneity and molecular mechanisms underlying osteoarthritis. In another study Wang et al. used single-cell RNA sequencing (scRNA-seq) to analyze the cellular composition of chondrocytes in healthy human cartilage tissues [13]. The analysis identified seven distinct cell populations. The researchers also performed Immunohistochemistry (IHC) to verify the results of the scRNA-seq analysis. This study compared the individual cell appearances of healthy chondrocytes, Kashin-Beck Disease (KBD), osteoarthritis (OA). Different markers have been identified for specific chondrocyte populations. Analytical results visualized using a variety of techniques such as t-SNE, UMAP, and Monocle pseudotime trajectory analysis. Statistical analysis was performed using SPSS 18.0 package. Researchers compare single-cell structure of Kashin-Beck disease, osteoarthritis, and healthy chondrocytes. They identified different populations of chondrocytes in each condition and found that certain populations were expanded in KBD and OA. However, the study had limitations due to the small sample size and potential statistical bias. The researchers performed additional analyses to verify the results and confirmed similar findings in cartilage from both women and men. Sebastian et al. study involved an ACL injury model in male C57Bl/6J mice used scRNA-seq to analyze periodontal weakness of the accumulation of immune cell in the knee joint after ACL rupture [14]. He used Single-cell RNA sequencing (scRNA-seq) to study the immune landscape in post-traumatic osteoarthritis (OA). This technique allows for the identification and characterization of different Immune cell subtypes found in synovial joints during homeostasis, post-injury, and osteoarthritis progression. Nine chondrocyte subtypes have been reported for the first time in the articular cartilages of healthy rat knee joints by Sebastian et al [14]. These subtypes include Ucmahigh, Cytl1high, Chil1high, Mef2chigh, Krt16high, Tnfaip6high, S100a4high, Neat1high, and divC chondrocyte clusters. Several genes expressed in Cytl1high, Chil1high, Tnfaip6high, and S100a4high clusters had regulatory functions. Conversely, Ucmahigh and Krt16high clusters exhibited high expression of genes associated with protein synthesis and mRNA metabolism.

Previous studies using scRNA-seq have identified heterogeneous immune populations in human OA synovium, including immune regulatory macrophages, inflammatory macrophages, dendritic cells, B cells, T cells, and mast cells [15]. However, these studies have mainly focused on patients with advanced OA, understanding of the immune system changes associated with the development of osteoarthritis or the early stages of joint degeneration remains limited. By analyzing the gene expression profiles of individual cells, scRNA-seq provides insights into the heterogeneity and dynamics of immune cells in osteoarthritis.The results of the Sebastian et al studies have shown that CD45 + CD11b + Ly6C + Ly6G monocytes/macrophages are significantly increased in the knee after injury [14]. This increase peaked at day 3 after injury. The proportions of the different immune systems in the joints also changed over time. The study used single-cell RNA sequencing analysis and flow cytometry to differentiate the immune changes in the mouse knee joint after injury. The results based on single-cell RNA sequencing in the study finds several types of immune system in joints after ACL rupture, also include neutrophils, monocytes, macrophages, B cells, T cells, NK cells, and dendritic cells.

In another study Lv et al. used scRNA-seq analysis to investigate the potential therapeutic targets and molecular characteristics of chondrocyte ferroptosis in osteoarthritis cartilage [16]. Single cell RNA-seq investigation recognizes cluster of ferroptotic chondrocyte and found that TRPV1 as an antiferroptotic target in osteoarthritis. The expression of ferroptotic hallmarks was analyzed in combined intaglio and harmed cartilages from OA patients. Gene profiling

revealed that ferroptosis driver factors were upregulated and ferroptosis suppressor genes were downregulated in OA cartilage damaged areas; this revealed a relationship between chondrocyte ferroptosis and the development of osteoarthritis. Performed scRNA-seq analysis on 17,638 chondrocytes to detect the presence of ferroptotic chondrocyte clusters in human OA cartilage, examine molecular signatures, and suggest their potential therapeutic targets. Sebastian et al talks about the utilization of single-cell RNA sequencing to consider transcriptomic heterogeneity and early molecular changes in mouse articular chondrocytes [17]. ScrRNA-seq allows them to identify the expression of genes in a individual cell from such a complex process as the knee joint. These technologies help understand molecular differences between different cell types and subtypes and discover previously unknown cell types, cell-specific transcriptional information and pathways involved in molecular interactions with the development of osteoarthritis.

Hu et al. collected human subchondral bone samples during total knee arthroplasty operations. The bone samples were then cut into small pieces and digested in type II collagenase [18]. The cells were collected after red blood cell lysis. They used single-cell RNA sequencing (scRNA-seq) analysis to understand the molecular mechanism of subchondral bone cell heterogeneity in the development of osteoarthritis. The study aims to reveal the cellular interactions involved in the subchondral environment of osteoarthritis by analyzing tibial subchondral bone samples from patients undergoing total knee arthroplasty. The scRNA-seq technique was used to map the different cell types and identify novel Endothelial Cell (EC) populations and Osteoblast (OB) subtypes related to vascularization, matrix manufacturing, and matrix mineralization. The study also mentions the limited understanding of biomarkers and the need for further research in isolating and defining EC and OB subtypes in human subchondral bone. Their sudy conclude that based on the single-cell RNA sequencing analysis is that there is molecular heterogeneity in subchondral bone cells in the development of osteoarthritis. Various cell subsets, including endothelial cells and osteoblasts, were identified and their roles in the development of osteoarthritis were discussed. Hu et al. study involved the analysis of scRNA-seq data from GEO datasets [19]. scRNA-seq network was gotten from the GSE104782 dataset uploaded by Ji et al., can find the details in their own research. scRNA-seq was performed on the GSE104782 dataset [12]. After quality control of the recorded data of all 1,600 chondrocytes (the number of genes ranged from 500 to 5,000), 1,343 chondrocytes were selected for further analysis. Uniform manifold was used for the subsequent analysis. Clustering of 1,343 chondrocytes into 8 clusters of known cell lineages using the UMAP method, where the appropriate number of principal components (PCs) was set as 10. The 8 cells were classified based on the canonical gene markers.The different chondrocyte subtypes were identified by clustering analysis and labelled as follows: Chondrogenic Progenitor Cells (CPC), Effector Chondrocytes (EC), Fibrocartilage Chondrocytes (FC), Homeostatic Chondrocytes (HomCs), Hypertrophic Chondrocytes (HTC), Prehypertrophic Chondrocytes (preHTC), Proliferative Chondrocytes (ProC). Regulatory Chondrocytes (RegCs) were identified from the analysis. Gene marker functional annotation showed that endothelial cells were effectively emitted and related with cell enactment and lymphocyte enactment; on the other hand, Fibroblast-Like Cells (FCs) were involved in. Wu et al. observed in their study involved accessing 192 single-cell RNA sequencing files of synovial fibroblasts from 2 osteoarthritis patients [20]. The scRNA-seq data was obtained from the Gene Expression Omnibus (GEO) database. Principal Component Analysis (PCA) and T-Stochastic Neighbor Embedding (TSNE) analysis were performed on the scRNA-seq data. Gene Ontology, Kyoto Encyclopedia of Genes and Genomes, and protein-protein interaction network analysis were used to recognize marker genes and pathways associated with osteoarthiritis occurrence. The analysis on single-cell RNA sequencing of synovial fibroblasts from osteoarthritis sufferers revealed several key findings. The GEO database was used to access scRNA-seq data of SFs from osteoarthritis patients. The data analysis included examining the number of gene in every cell, Total number count of total genes per cell and number of mitochondrial genes as a percentage of all genes per cell. The analysis also involved correlation analysis between different gene features and identification of differentially expressed genes in different cells. Additionally, principal component analysis (PCA) and T-Stochastic Neighbor Embedding (TSNE) analysis were performed to classify the cells into different types. The findings showed that most of the genes were activated in ways related to function and fibroblast development, such as the pathway related to extracellular matrix, cell adhesion molecule binding and immune. Fibronectin 1 (FN1) has been identified as an important gene associated with the development of SFs and play an important role in the occurrence of OA. Overall, the analysis provided valuable insights into the genes and pathways associated with osteoarthritis development in SFs. Zhang et al. study involved obtaining single-cell transcriptome information of chondrocytes from the Gene Expression Omnibus (GEO) database [21]. The data was then analyzed using the R package Seurat to filter out cells with poor quality. The ATDC5 cell line was used as a model for chondrocytes, and L-929 cells were used as fibrocartilage chondrocytes. RNA extraction and reverse-transcription quantitative PCR (RT-qPCR) were performed to determine gene expression levels. Protein-protein interaction (PPI) network analysis was conducted using the STRING database and Cytoscape software, used scRNA-seq to recognize chondrocytes potential markers in OA and to understand the differentiation and function of various chondrocytes type in OA. They reported single-cell profiling of 480 chondrocyte samples and identified Hypertrophic Chondrocytes (HTC), Homeostatic Chondrocytes (HomC), and Fibro Cartilage Chondrocytes (FC) in OA. The study also used Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis to recognize the function of candidate marker genes in chondrocytes. The results of the study showed that samples of 480 chondrocyte from three patients with OA were analyzed using the program Seurat. Distribution model plot showed the number of genes and number of sequences per cell. Most cells contain 1,000-5,000 genes, with the total number being in the range of 950,000-980,000. The study also identified marker genes for different stages of chondrocyte differentiation. single-cell RNA sequencing (scRNA-seq) analysis identified three types of chondrocytes (hypertrophic chondrocyte, homeostatic chondrocyte, and fibrocartilage chondrocyte) in Osteoarthritis (OA). The study also identified candidate marker genes for these chondrocyte types and their specific functions in OA.

Qu et al. authors aim to investigate the relationship between single-cell RNA transcriptome and osteoarthritis [22]. They specifically focus on identifying and characterizing a unique type

of chondrocytes called SPP1+ chondrocytes in the context of osteoarthritis. To achieve this, the authors perform single-cell RNA sequencing on samples obtained from osteoarthritis patients. The transcriptome data obtained from individual cells provides insights into the gene expression patterns and cellular heterogeneity within the osteoarthritic joint tissue. Through their analysis, the authors identify a distinct subpopulation of chondrocytes characterized by the expression of the SPP1 gene. This gene encodes for the protein osteopontin, which has been implicated in various pathological processes, including inflammation and tissue remodeling. The presence of SPP1+ chondrocytes suggests their potential involvement in the pathogenesis of osteoarthritis. The paper provides valuable insights into the cellular heterogeneity and molecular signatures associated with osteoarthritis, highlighting the role of single-cell RNA sequencing in studying complex diseases at a cellular level.

Kang et al. used materials and methods in their study involved single-cell transcriptome sequencing and bioinformatics analysis [23]. The researchers downloaded a single-cell transcriptome sequencing profile and performed transcript quantification and filtering. They also used Tissue Gene-C cell therapy to treat osteoarthritis and transfected nanoengineered mesenchymal stem cells with plasmid encoding TGF-β1 for cartilage repair. This study had several limitations, including the small sample size and the difficulty in obtaining non-OA samples. More experiments and further research are needed to make recommendations and determine the accuracy of communication between cells of the chondrocyte population during osteoarthritic bone degeneration. The mentioned studies focused on the use of bioinformatics analysis of scRNA-seq data to investigate changes in intercellular communication involved in OA pathogenesis. Researchers evaluated chondrocyte heterogeneity and identified specific signaling pathways that influence communication between OA-associated chondrocyte subtypes. These changes in intercellular communication have been shown to be important mechanisms associated with OA progression.

Findings suggest changes in cellular communication between chondrocyte subtypes associated with osteoarthritis. These changes are mediated by specific signals such as VISFATIN, SPP1, TGF-β, PTN, MIF, and MHC-I. The power of the communication unit is represented by the thickness of the communication lines.

Huan et al. research involved processing scRNA-seq data from human hip joint tissue of OA and normal samples [24]. The data was accessed from the Gene Expression Omnibus (GEO) database. The Seurat package was used for screening and analysis of the data, including the identification of highly variable genes, clustering, and trajectory analysis. Explored the biological functions of different genes, created PPI networks and basic models to study gene interactions and identify genes hub. Additionally, mRNA-miRNA regulatory networks were constructed based on credible databases, and some miRNAs were experimentally validated. The research article discusses the relationship between single-cell RNA sequencing (scRNA-seq) data and Osteoarthritis (OA). Their studies shown that changes in osteoblast status and cellular molecular functions in the subchondral bone region may play a role in the pathogenesis of OA. scRNA-seq data were used to identify gene expression of osteoblasts in samples from normal and osteoarthritis patients. Therefore, the relationship between single-cell RNA sequencing and osteoarthritis is that scRNA-seq data can provide valuable information about the molecular changes in osteoblasts associated with the development of OA. The results of the study showed that 577 normal osteoblasts and 3810 osteoarthritis osteoblasts were retained for further analysis after single-cell RNA sequencing data was completed. Sequence data of 5106 records were compiled into a matrix containing a total of 19535 sequenced genes for analysis. They concluded that changes in the status and molecular activity of osteoblasts in the subchondral bone may be associated with the pathogenesis of osteoarthritis. The study also identified specific marker genes and potential miRNAs associated with osteoarthritis in osteoblasts using single-cell transcriptomics.

Tan et al. study involved downloading gene expression data from the GEO database and performing data analysis using R and the Bioconductor software package [25]. The "sva" package was used to remove batch effects and standard files. Gene set variation analysis (GSVA) was used to assess gene set enrichment and identify potential biological function changes. A total of 24 synovial tissue samples were included in GSE98918, including 12 normal joint samples and 12 OA joint samples. The relationship between single-cell RNA sequencing and osteoarthritis is explored in the research article. The authors used single-cell RNA sequencing analysis to evaluate the distribution of specific genes (MMP, VEGFA, SPI1, and IRF8) in synovial tissue from osteoarthritis patients. This analysis helped identify these genes as central genes of the immune system involved in the osteoarthritis cohort. The single-cell RNA sequencing analysis in the synovial tissues of patients with osteoarthritis revealed different cell types involved in the tissues, including progenitor cells, stem cells, osteocytes, osteoblasts, osteoclasts, and mesenchymal stem cells. MMP9 was not particularly shown in the synovial tissues cells. IRF8 was most enriched in osteoclasts, while SPI1 was also enriched in osteoclasts. VEGFA expression was evaluated in the synovial tissues. Single-cell RNA sequencing analysis showed that osteoclasts were the most abundant cells in the synovial tissue of patients with osteoarthritis. Additionally, the analysis revealed specific expression patterns of genes such as MMP9, VEGFA, SPI1, IRF8, and CAMP in different cell types. VEGFA is considered an important immune factor and may play an important role in osteoarthritis.

Zeng et al. used two novel bioinformatic algorithms to sequence data using open scRNA-seq data from hip OA to determine the composition of cells present in subchondral bone [26]. A total of 11 cell types were identified by bulk sequencing and subsequently validated using independent databases. Bulk-seq has been shown to be more efficient and effective than scRNA-seq. Furthermore, it was concluded that subchondral bone-specific scRNAseq is currently non-existent. Newly established deconvolution algorithms were utilized based on signatures of single-cell RNA sequencing (scRNA-seq) from the femoral head of patients with osteoarthritis, which currently represents the most closely comparable dataset with similar subchondral bone histology, including tissue of bone marrow and cancellous bone. It should be noted that the correlation analysis may be affected by the individual heterogeneity of both bulk-seq and scRNA-seq.

Discussion

The applied methodology has identified various key findings relating to osteoarthritis, including disease progression, cell

population, novel biomarkers, distinct cell subtypes, cellular heterogeneity and immunogenicity, intercellular communication, and potential underlying disease mechanisms. The explosion of combinatorial technologies, such as low-cost microfluidics, and the development of sequencing platforms have taken single-cell sequencing technology to the next level. Traditional bulk RNA sequencing provides average gene expression profiles from a mixture of cells, which might mask important cellular heterogeneity. In contrast, scRNA-seq providing a more detailed understanding of cellular diversity within tissues. However, many challenges remain in calculating data, comparing research data with biological progress, and using single experiments in precision medicine.

One challenge in interpreting data is integrating the data into the patient context or clinical questions. In general, many layers of patient complexity will be added when assessing long-term biological patterns. However, in precision medicine, personalized medicine will be developed with the help of computers and machine learning. However, given its application in recent studies, poor studies with small samples may miss accurate signals and lead to incorrect conclusions. In order to achieve adequate quantities of RNA with acceptable quality, cartilage tissue for scRNA-seq necessitates larger samples compared to other tissues. This is due to the fact that bone and cartilage have a lower cell density per unit volume. Therefore, it is challenging to utilize this method in studies involving small animals. The high cost of this procedure results in a small number of samples being analyzed, thereby decreasing the importance of studies or potentially hampering their wider application in orthopaedic research. Collaborations involving multiple centres and between two or more governmental organisation that combines osteoarthritis study and infrastructure capital are necessary to address these challenges. scRNA-seq is extensively used by various groups, but its single-centre data clearly have limitations. However, some papers in the field of orthopaedics refrain from disclosing or sharing sequencing data, thereby hindering further progress.

Machine advanced analytics allows OA researchers to collect and compare results. scRNA-seq technology is so extensible that biologists could begin collecting data regularly in the future. Currently, elucidating processes or find targets using scRNA-seq with bioinformatics tools lack consensus on whether cell relatives should be recorded and used or lead to future research. This will help create a complete cellular map of OA pathogenesis and classify biomarkers found via scRNA-seq. The use of methods to evaluate treatment is increasing and the duration of in vivo and in vitro behavior is decreasing. With the help of single-cell multi-omics technology, better treatment will be developed for each patient.

Conclusion

Herein, we reviewed current knowledge and use of scRNA-seq in Osteoarthritis. scRNA-seq can not only reveal the mechanisms of different phenotypes in the damage pattern associated with OA development, but also find the target, identifying information to develop better healthcare. As scRNA-seq is increasingly used to solve different problems, it will contribute to many programs aimed at understanding the pathophysiology of OA and evaluating the safety and effectiveness of treatment for OA in preclinical studies.

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Authors' contributions

A.G.: Conceptualized, collected literature, drafted the manuscript. G.L.: proof-read the manuscript, gave final permission for submission. X.L., K.D.: read and approved the manuscript.

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