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The Differential Gene Expression of Squamous Cell Carcinoma Versus Basal Cell Carcinoma Highlights Oxidative Phosphorylation As A Potential Factor in Metastasis: A Single-Cell Gene Expression Analysis Study

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ABSTRACT

Background: Nonmelanoma skin cancer (NMSC) can be classified into basal (BCC) and squamous cell carcinoma (SCC). Combined, they rank 5th among the highest incidences of cancer in the world. Despite their low mortality rate, metastasis remains a significant concern. Basal cell carcinoma grows slowly and rarely metastasizes, unlike squamous cell carcinoma, which usually metastasizes when left untreated. However, it is currently unknown what influences their metastatic potential.

Method: This research uses single-cell RNA expression data from the Gene Expression Omnibus database. The data will be preprocessed, normalized, and integrated before differential expression and enrichment analyses. Additionally, the 5 most upregulated genes in basal cell carcinoma compared to squamous cell carcinoma and vice versa will be discussed.

Results: 165 genes highly expressed in BCC were identified and enriched, with the most significant enrichment for genes promoting apoptosis. We also identified 143 genes highly expressed in SCC, which had the most significant enrichment for genes involved in oxidative phosphorylation. The top 5 upregulated genes in BCC were KRT17, CXCL8, RPS17, CCL20, and IER3, and in SCC were KRT1, LY6D, FABP5, S100A8, and KRT10.

Conclusion: We identified differentially expressed genes, including those related to oxidative phosphorylation and cell multiplication, which may help explain the varying behaviors of these cancers, particularly the higher metastatic potential of SCC. However, further research is needed to examine the effects of oxidative phosphorylation on these cancer cells.

INTRODUCTION

Skin cancer stands as a formidable health challenge globally and can be classified into two types according to the World Health Organization: melanoma and nonmelanoma skin cancer. Nonmelanoma skin cancer (NMSC) constitutes a heavy burden, with more than a million new cases diagnosed each year, ranking 5th among the highest incidence cancers in the world [1]. Despite conferring relatively low mortality compared to other types of cancer, metastasis remains a significant concern for individuals affected by this disease. Metastasis, the process by which cancer cells spread from the primary tumor to distant sites in the body, signifies an advanced stage of the disease and presents complex clinical challenges with a poor prognosis.

NMSC is a group of cancers arising from skin cells other than melanocytes. There are two types of NMSC: basal cell carcinoma and squamous cell carcinoma. In this article, we focus specifically on squamous cell carcinoma that originated in the skin. Both of these cancers develop in sun-exposed skin, although they can develop anywhere in the body. Basal cell carcinoma arises from cells found in the basal layer of the epidermis, which grow relatively slowly and rarely metastasize to other places [2]. This is in contrast to squamous cell carcinoma, which usually metastasizes to other body parts, especially when left untreated. Additionally, these two cancer types also have different predilections, with the head and neck for basal cell carcinoma and mouth, anus, and vagina for squamous cell carcinoma.

The Caucasian race dominates the incidence of skin cancer cases in the world. For example, the United States is the country with the most cases of skin cancer. The incidence of NMSC in people with white skin approaches 75%–80 % for basal cell carcinoma and 25% for squamous cell carcinoma [2,3]. However, the main risk factor in Indonesia is the high amount of sun exposure due to its location in a tropical country. Although no national register of skin cancer is available in Indonesia, a study conducted in the capital city of Jakarta found a similar distribution of basal cell carcinoma (roughly 70%) and squamous cell carcinoma (roughly 25%) [4]. They also found an increasing incidence of NSMC diagnosis from 1996 to 2017, perhaps reflecting increased UV exposure or increased awareness. Therefore, research exploring both these types of cancers is needed to support therapy and reduce the mortality associated with this disease.

One of the factors associated with mortality in NSMC is metastasis. Although these cancers can be treated when found early, the highly different rate of metastasis between these two cancers significantly influences their mortality. The rate of metastasis of basal cell carcinoma is between 0.0028% to 0.55% [5]. These are extremely small, especially compared to the metastatic rate of squamous cell carcinoma, which was known to be around 3-9% [6]. However, what influences their metastatic potential is currently unknown. While previous studies have examined the clinical and molecular differences between BCC and SCC, few have investigated these differences at the single-cell level. The novelty of our study is that applying scRNA-seq to isolate gene expression, specifically in tumor cells, provides a high-resolution view of the cellular processes that differentiate BCC and SCC. We aim to provide new insights into the metabolic pathways that may underlie the aggressive behavior of SCC, a finding that has not been extensively explored in the literature. These findings offer potential avenues for targeted therapeutic interventions that exploit the metabolic vulnerabilities of SCC.

METHODS

This retrospective bioinformatics study is leveraging publicly available single-cell RNA sequencing (scRNA-seq) data from the Gene Expression Omnibus (GEO) database. The study design compares gene expression profiles between basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) at the single-cell level. We specifically analyzed cancer cells from each dataset to identify differentially expressed genes and their potential role in the metastatic behavior of SCC. The data used in this study can be accessed through the following GSE Accession numbers: GSE144236 [7] for the Squamous Cell Carcinoma data and GSE141526 [8] and GSE181907 [9] for the Basal Cell Carcinoma data. All squamous cell carcinomas used in this study originated from the skin; therefore, any mention of squamous cell carcinoma in the article will refer to them. These datasets were chosen based on basal cell and squamous cell carcinoma data availability. This study's single-cell RNA sequencing data were obtained from anonymized datasets in the Gene Expression Omnibus (GEO) database. As the data were anonymized, clinical information such as patient age, sex, tumor stage, and metastasis status was unavailable. This study focuses on the molecular differences in gene expression between BCC and SCC.

The data were then analyzed using R version 4.3.1 [10] through the R package Seurat version 3.2.3 [11]. The data were previously preprocessed, normalized, and integrated before differential expression analysis. We followed the protocol previously published by the creator of the Seurat package [12]. Additionally, dimensional reduction approaches were applied using principal component analysis and the uniform manifold approximation and projection to cluster cells, which were subsequently manually identified and verified. Conserved marker genes were identified for each Seurat cluster, and cell type identities were assigned using Metascape's cell type signature database. We then filter only clusters identified as containing cancer cells for downstream analysis. Therefore, only tumor cells consisting of basal and squamous cell tumors will be compared. The workflow followed in this research can be seen in **Figure 1**.

The resulting genes will be analyzed through gene set enrichment analysis to identify gene functions differentially expressed between the two groups of cancer cells. Gene enrichment analysis will be done using the Metascape web application [13]. We will discuss the five most upregulated genes in basal cell carcinoma compared to squamous cell carcinoma and vice versa. No ethical clearance was sought for this study since it leverages publicly available data with no personal identity trackable to the data donor.

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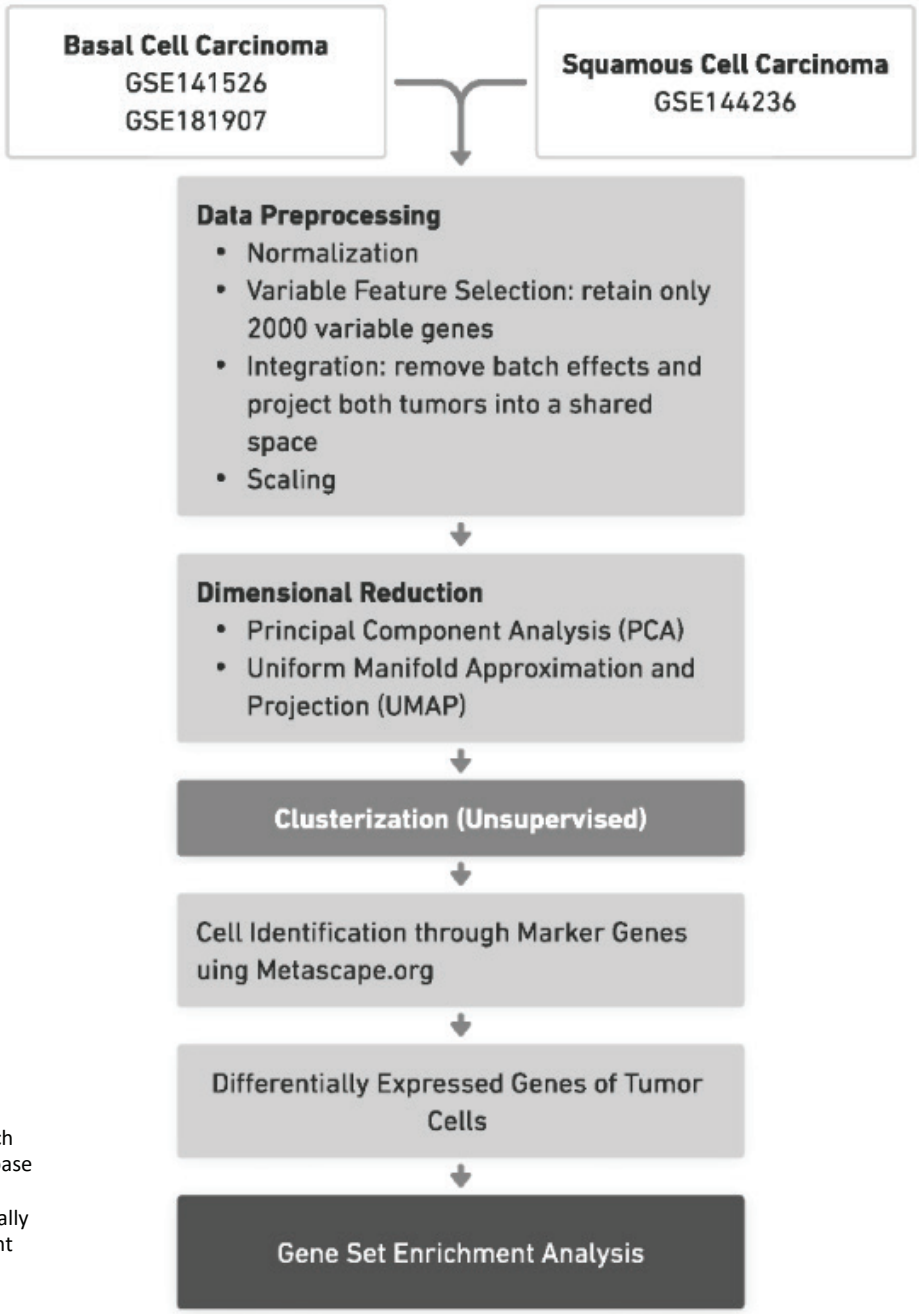

Figure 1. Research workflow. The research initially sourced data from the GEO database before being processed, clustered, and identified using Metascape. The differentially expressed genes were used for enrichment analysis, and the top 5 differentially expressed genes were further examined.

RESULTS

Three datasets were used in this study, and after preprocessing and clustering, we found 29 distinct clusters of cells. These cells were analyzed, and we output their marker genes for further cell-type analysis using Metascape. The cell clusters can be seen in **Figure 2**.

Using the R package Seurat, we output each cluster marker gene. For each cluster, the top 10 conserved markers will be used as input and analyzed using the Metascape cell type signature. The cell type signature that highly represents the gene marker identity will be used as the cell identity. The cell identities can be seen in **Table 1.**

The diversity of the tumor microenvironment is apparent, with several cell types supporting the cancer tissue. However, in this research, we would like to focus solely on the cancer cells. Therefore, we conducted differential expression analysis solely on those cells that were identified as cancer cells. After the analysis, we selected only those genes that were significantly different ($p < 0.01$) and were differentially expressed by at least 1-fold (log2 fold change). In total, 165 genes highly expressed in BCC compared to SCC were identified and were enriched using Metascape. We selected the top 10 gene ontologies based on p-values, which are shown in **Figure 3**

We also conducted a gene enrichment analysis for genes highly expressed in SCC compared to BCC. We used the same criteria as previously stated and identified 143 genes. The enrichment results of these 143 genes are shown in **Figure 4**. The completely differentially expressed gene list can be seen in Tables SII and SIII. The gene enrichment results are in Tables SIV and SV.

We also analyzed the individual genes differentially expressed in BCC compared to SCC and vice versa for further scrutiny. We selected only the top 5 genes for each comparison according to their fold change magnitude. The data can be seen in **Table 2**.

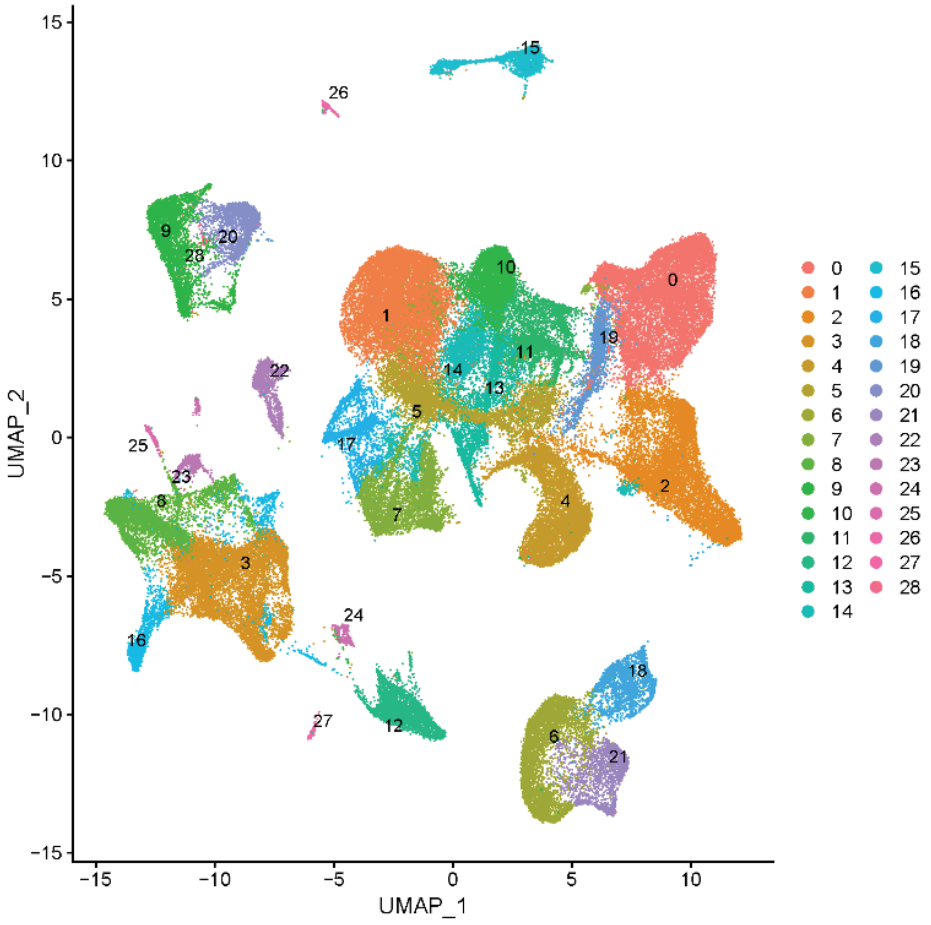

Figure 2. Cell clusters of the combined basal and squamous cell carcinoma population. The figure represents the results of clusterization based on the dimensional reduction approach previously used. We identified 29 distinct cellular populations from 0 to 28. These individual clusters will be analyzed and identified.

Table 1. Cell identities used to identify clusters in the current study

Cluster	Cell Identity	Cluster	Cell Identity	Cluster	Cell Identity
0	Cancer cells	10	Basal cells (epidermis)	20	NK T cells
1	Suprabasal cells (epidermis)	11	Basal cells (epidermis)	21	Stromal cells
2	Vascular smooth muscle cells	12	Melanocytes	22	Epithelial cells
3	Monocytes	13	Squamous epithelial cells	23	Antigen presenting cells
4	Cancer cells	14	Basal cells (epidermis)	24	Plasma cells
5	Suprabasal cells (epidermis)	15	Endothelial cells	25	B lymphocyte
6	Stromal cells	16	Antigen presenting cells	26	Mucous cells
7	Cancer cells	17	Squamous epithelial cells	27	Mast cells
8	Dendritic cells	18	Cancer cells	28	NK T cells
9	CD4 T cells	19	Basal cells (epidermis)		

CD4: Cluster of differentiation 4; NK: Natural killer

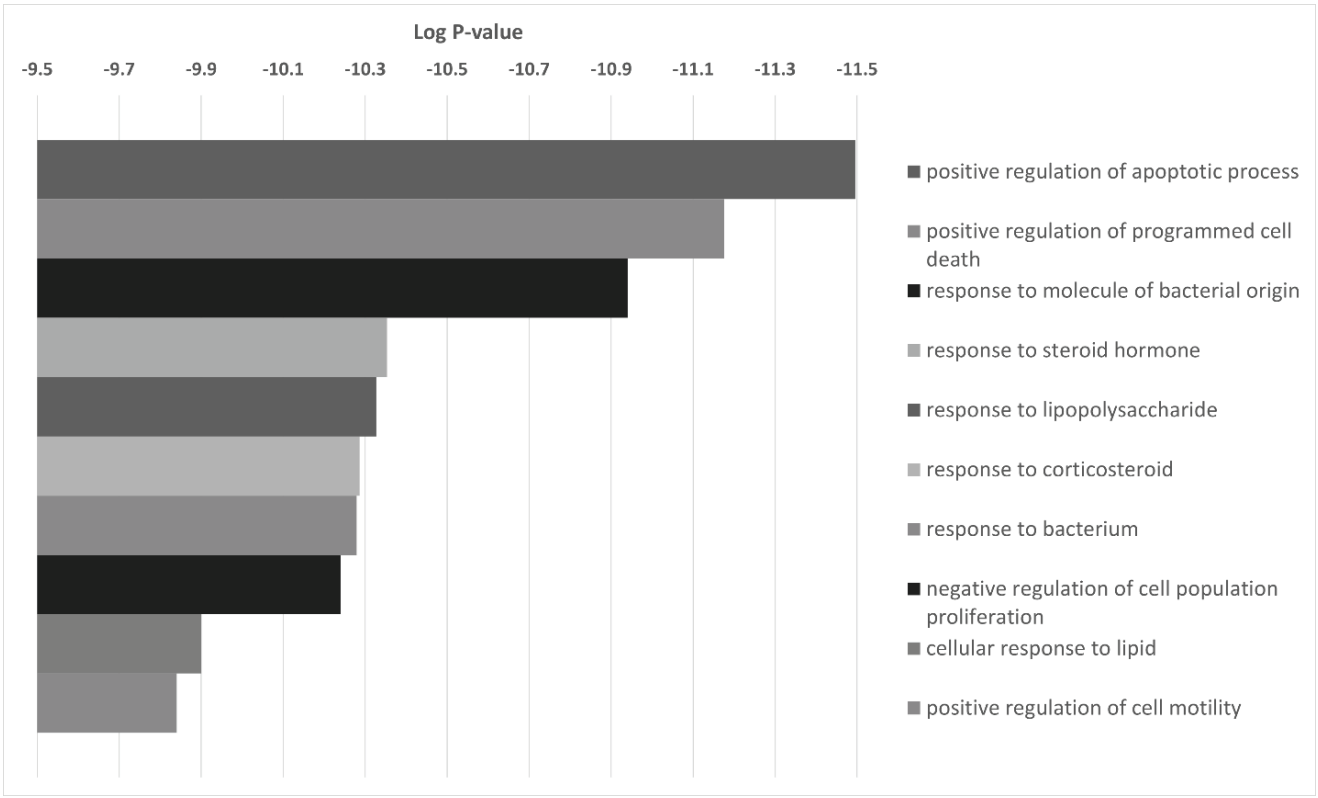

Figure 3. Gene enrichment results for all 165 differentially expressed genes were highly expressed in BCC compared to SCC. The top 10 highly significant gene ontologies are shown. BCC's most upregulated gene function is the positive regulation of the apoptotic process.

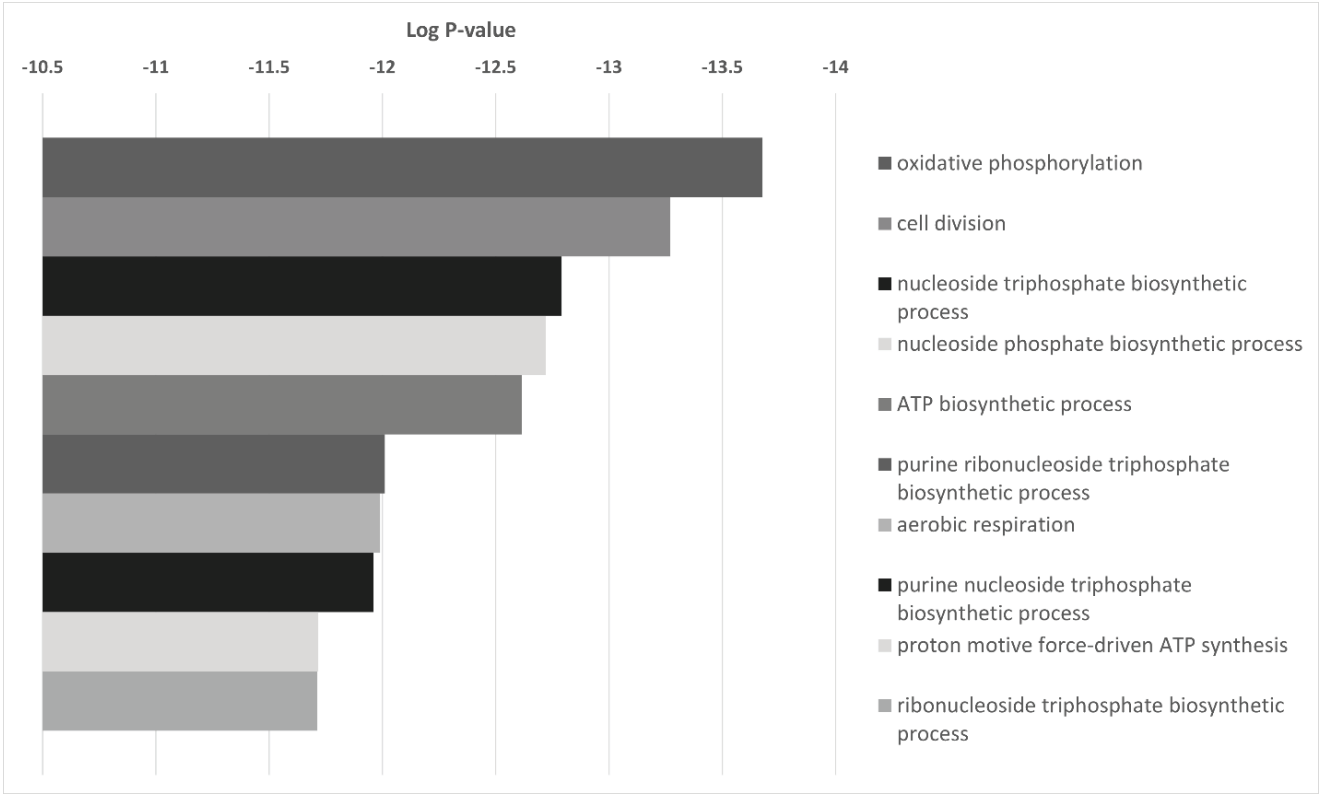

Figure 4. Gene enrichment results for all 143 differentially expressed genes that are highly expressed in SCC compared to BCC. The top 10 highly significant (according to p-value) gene ontologies are shown. Note that SCC's most upregulated genes were oxidative phosphorylation and cell division.

Table 2. Top 5 highly expressed genes in basal and squamous cell carcinoma.

Upregulated in Basal Cell Carcinoma			
Gene	Gene Names	Adjusted p-value	Fold Change (Log2)
KRT 17	Keratin 17	< 0.0001	5.65
CXCL8	C-X-C motif chemokine ligand 8	< 0.0001	5.58
RPS17	Ribosomal protein S17	< 0.0001	4.15
CCL20	C-C motif chemokine ligand 20	< 0.0001	3.8
IER3	Immediate early response 3	< 0.0001	3.47
Upregulated in Squamous Cell Carcinoma			
Gene	Gene Names	Adjusted p-value	Fold Change (Log2)
KRT1	Keratin 1	< 0.0001	4.55
LY6D	Lymphocyte antigen 6 family member D	< 0.0001	4.48
FABP5	Fatty acid binding protein 5, epidermal	< 0.0001	3.98
S100A8	S100 calcium-binding protein A8	< 0.0001	3.3
KRT10	Keratin 10	< 0.0001	3.28

DISCUSSION

Our results have shown the diversity of the surrounding tumor microenvironment of basal and squamous cell carcinoma. Although their analysis is beyond the scope of this article. After cell identification, we focus only on tumor cells of both basal and squamous cell origins and compare them. The resulting gene enrichment analysis showed that basal cell carcinoma cells have higher apoptotic protein expression than squamous cell carcinoma. Out of the top 10, the first two highly significant gene ontologies involved positive regulation of apoptosis and cell death. We argue that this finding perhaps reflected increased immune system control on basal cell carcinoma and explained its slow growth characteristics and its low potential for metastasis [14,15]. Additionally, basal cell carcinoma also expressed genes associated with response to steroid hormones, specifically corticosteroids. Our findings may explain the higher incidence of basal cell carcinoma among oral corticosteroid users [16]. However, the reason behind this increase is currently unknown. Another highly significant gene expression pattern is seen in the response to bacterial molecules and lipopolysaccharides, shown by previous studies to influence cancer cell progression [17].

In contrast to basal cell expression, the gene expression is highly expressed in squamous cell carcinoma, telling a different story. Nine highly significant enriched genes were involved in oxidative phosphorylation and nucleotide biosynthesis. Reflecting the increased metabolic capacity and high nucleotide turnover of squamous cell carcinoma compared to basal cell carcinoma. Although this finding may counteract the previously held view of the Warburg effect [18] in cancer, perhaps the upregulation of these genes may reflect the increased ability of cancer cells to utilize energy and growth. The increased energy is also coupled with increased genes involved in cell division. Several research studies have corroborated our findings by proving that higher oxidative phosphorylation and mitotic numbers are associated with more aggressive growth and metastasis [15,19,20].

To evaluate the differentially expressed genes further, the top five genes upregulated in basal cell carcinoma are further discussed. First is the KRT17 gene, which is a gene that codes type 1 intermediate filaments, which are expressed in nail beds, hair follicles, sebaceous glands, and other structures in the epidermis. KRT17 is overexpressed in many malignant tumors, such as cervical cancer, gastric cancer, and lung cancer, and plays an important role in tumor emergence and progression [21]. This gene is also closely related to the ability of cancer to metastasize, with several studies supporting KRT's 17 roles in epithelial to mesenchymal transition [22]. However, we argue that the high expression of KRT17 reflects the origin of basal cell carcinoma (basal epithelial cells) instead of supporting a more aggressive phenotype than squamous cell carcinoma. Another gene upregulated in Basal Cell Carcinoma is CXCL8. The chemokine CXCL8, or interleukin-8 (IL-8), was originally known as a cytokine expressed by epithelial cells and macrophages for neutrophil recruitment or chemotaxis to inflammation, infection, or injury areas. However, in cancer cells, this gene can be expressed not only by immune cells but also by the tumor cells [23]. Many studies have proven that CXCL8 can promote cell proliferation and inhibit apoptosis in various types of cancer, including breast, prostate, lung, and colon cancers [23,24]. RPS17 is another gene highly expressed in basal cell carcinoma. This gene provides instructions for ribosomes to produce approximately 80 types of proteins. The RPS 17 gene is often found in the basal epithelial cells in the skin, as shown by the Human Protein Atlas (www.proteinatlas.

org) [25]. However, whether this gene played a role in cancer progression is unknown. Therefore, we postulated that the upregulation of this gene reflects the basal epithelial cell origin of basal cell carcinoma. Enterocytes, B cells, neutrophils, and dendritic cells widely express CCL20, another gene significantly upregulated in BCC compared to SCC. This gene functions as a chemotactic agent for lymphocytes and neutrophils. Apart from that, this gene is also involved in the recruitment of IL-17, which is pro-inflammatory and produces T helper cells (Th17) and regulatory T cells in areas experiencing inflammation [26]. This gene was found to promote cancer cell development directly by increasing cancer cell migration and proliferation, and indirectly through poor immune cell control [27,28]. IER3 is an upregulated gene with limited information regarding its role in cancer. This gene is widely expressed in the epithelium of the skin, trachea, gastrointestinal, and genitourinary systems [29]. This gene is a stress-induced gene that causes a reduction in the production of reactive oxygen species (ROS). The increased expression of this gene was associated with conflicting results, with some promoting cancer and others reducing cancer progression [30,31]. Until now, no specific research has discussed the relationship between this gene's expression and basal cell carcinoma.

Through our findings, the top 5 upregulated genes in basal cell carcinoma were shown to be specific markers for basal epithelial cells (KRT17 and RPS17), chemokines (CXCL8 and CCL20), and one novel gene (IER3) with currently no specific findings for basal cell carcinoma. However, we could not conclude whether these genes played a role in the low propensity of metastasis in basal cell carcinoma.

The five genes shown in Table 2 were upregulated in squamous cell carcinoma. The KRT1 and KRT10 genes were upregulated in squamous cell carcinoma and will be discussed to reflect their shared features. The stratum spinosum and the stratum granulosum [25] in the epidermis specifically express the KRT1 and KRT10 genes. These genes are known prognostic indicators, and the loss of these genes was associated with a worse prognosis [32,33]. In our findings, we argued that the upregulation of KRT1 and KRT10 is associated with the squamous epithelial cell origin of the cancer compared to the basal cell carcinoma. The LY6D gene is another gene upregulated in squamous cell carcinoma. This gene is a well-known marker gene for squamous epithelial differentiation. Basal cell tumors expressing this gene possess basal and squamous cell carcinoma-like features [34]. Although their role is still uncertain, a review by Upadhyay concluded that this gene played a role in immune escape and cancer progression [35]. The loss of this gene augmented chemotherapy and influenced the 5-year overall survival in bladder cancer [36]. The upregulation in squamous cell carcinoma probably reflected its squamous epithelial differentiation. FABP5 is an interesting gene upregulated in squamous cell carcinoma. This gene encodes a fatty acid-binding protein found in epidermal cells. FABP5 promotes lipolysis, de novo fatty acid synthesis, and the activation of nuclear factor-kappa B, which may support cancer growth and progression through increased available energy and growth signaling [37]. Several studies have already implicated this gene in highly proliferative and invasive carcinoma [38,39]. These findings reflect squamous cell carcinoma's higher proliferation and metastatic capability than basal cell carcinoma. The ability of squamous cell carcinoma to utilize more energy sources may also explain its higher mitotic capabilities and invasiveness. Another upregulated gene in squamous cell cancer is the S100A8 gene. This gene was shown to promote and inhibit cellular overgrowth, conflictingly. Several studies have found that knockdown of this gene promoted squamous cell differentiation and apoptosis [40], yet its high expression induces cellular growth and motility [41]. Thus, currently, it is unknown what role this gene plays. However, based on our findings, the increased expression supported the notion that this gene promoted squamous cell differentiation, and its overexpression probably induces cell growth and epithelial-to-mesenchymal transition.

Our findings identified several genes that stand out among the upregulated SCC genes: KRT1, FABP5, and S100A8. These genes were known for their established roles in promoting processes such as cell motility and invasion and fueling tumor cell metabolism; together, these genes suggest that the higher metastatic potential of SCC is supported by increased available fuel and the ability to multiply and migrate to distant organs. Traditionally, cancer cells exhibited the Warburg effect, which means that cancer cells rely heavily on glycolysis [42,43]. However, oxidative phosphorylation, as shown by the upregulation of FABP5 and S100A8, is crucial in promoting metastasis and tumor growth by providing the energy required for cellular proliferation and survival under high-stress conditions, such as during metastasis [44–46]. Studies have shown that many metastatic tumors exhibited high oxidative phosphorylation activity to generate ATP efficiently and support rapid cell division. This increased reliance on mitochondrial respiration allows cancer cells to sustain energy demands during migration and invasion. Furthermore, oxidative phosphorylation is associated with the production of reactive oxygen species (ROS), which activate key signaling pathways like hypoxia-inducible factor 1-alpha (HIF-1α) and nuclear factor-kappa B (NF-κB) [47]. These signaling pathways were known to drive epithelial-to-mesenchymal transition (EMT)—a critical step in metastasis. Additionally, oxidative phosphorylation promotes tumor growth by enhancing mitochondrial biogenesis, providing cancer cells with metabolic flexibility

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during metastasis. High oxidative phosphorylation activity has been linked to increased mitochondrial content, which previous studies have associated with enhanced motility and invasion in aggressive tumors [47–50]. Together, these mechanisms suggest that oxidative phosphorylation plays a vital role in both the metabolic adaptation and invasive potential of SCC, making it a potential factor in tumor progression and metastasis. However, further functional studies are needed to validate the roles of these genes in SCC metastasis.

Our study highlights key differences in gene expression between basal cell carcinoma and squamous cell carcinoma, particularly focusing on the upregulation of oxidative phosphorylation-related genes in SCC. These findings suggest that oxidative phosphorylation may contribute to SCC's more aggressive and proliferative behavior than BCC. While BCC is rarely metastatic, the molecular differences between the two cancers offer valuable insights into the pathways that may drive SCC's higher metastatic potential. Further research is needed to validate the role of oxidative phosphorylation and other metastasis-related pathways in squamous cell carcinoma. A key next step would be to experimentally assess the role of oxidative phosphorylation in squamous cell carcinoma metastasis. This can be done by using in vitro cell lines, where FABP5 and S100A8 can be targeted with specific inhibitors. Animal models of squamous cell carcinoma can be used to study the role of oxidative phosphorylation in tumor growth and metastasis in vivo. We can observe how their effects on tumor progression, invasion, and metastasis are achieved through genetic manipulation or specific inhibitors of oxidative phosphorylation.

One of the main limitations of this study is that the single-cell RNA sequencing data used do not contain information on the metastasis status of the tumors. Additionally, the datasets we used were anonymized and therefore lacked clinical details. While we focused on the molecular differences between BCC and SCC, the absence of clinical information limits our ability to correlate gene expression findings with clinical outcomes. Our study relies entirely on in silico bioinformatics analyses, which limits the ability to draw direct causal conclusions about the identified genes and pathways. Further experimental studies are required to establish these pathways' biological relevance and potential as therapeutic targets.

CONCLUSIONS

The main difference between basal and squamous cell tumor cells lies in their multiplicative properties, with basal cells having higher apoptotic activity, as shown in the gene enrichment analysis. This higher apoptotic activity correlates with lower tumor growth and a lower metastatic rate in basal cell carcinoma. This is in contrast to squamous cell carcinoma, which was shown to have higher cell division activity corresponding to its higher growth compared to basal cell carcinoma. Additionally, squamous cell tumor cells have higher oxidative phosphorylation activity, reflecting increased available energy and nucleotide turnover needed to support mitotic activity. However, further scrutiny of the top 5 regulated genes mostly identified cell markers associated with their progenitors, such as KRT1 and KRT10 for the squamous epithelial lineage and KRT17 for the basal cell lineage. The other genes, although differentially regulated, cannot explain the difference between the multiplicative and metastatic properties of basal and squamous cell carcinoma.

DECLARATIONS

Competing Interests
The authors declare no competing interests.

Ethics approval and consent to participate.
Not applicable

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Availability of data and materials
Data are available upon reasonable request to the authors.

Author Contributions
PNS and AS conceived the research idea. PNS, AS, and JJT wrote the first draft of the article. AS analyzed the single-cell expression data. PNS, AS, and JWG revised the article. AS and JWG visualized the data. All authors contributed to the final version of the article.

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