

LIFE SCIENCE INNOVATIONS IN REGENERATIVE MEDICINE: A GENOMIC APPROACH

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ABSTRACT

Regenerative medicine has emerged as a transformative field aimed at restoring tissue structure and function through the integration of molecular biology, genomics, and advanced therapeutic strategies. This study investigated the genomic mechanisms underlying tissue regeneration following thermal injury using a transcriptomic and bioinformatics approach. Gene expression profiles from the GSE8056 microarray dataset were analyzed to identify differentially expressed genes (DEGs) between burn wound tissues and normal skin controls. Quality control assessment confirmed distinct transcriptomic patterns between injured and healthy tissues. Differential expression analysis identified 1,183 significant genes, including 587 upregulated and 596 downregulated genes. Functional enrichment analyses revealed significant involvement of cytokine-mediated signaling, extracellular matrix organization, cellular proliferation, immune responses, and tissue remodeling processes. Gene Ontology analysis identified 3,642 enriched biological processes, while KEGG pathway analysis revealed 288 significantly enriched pathways, including cytokine–cytokine receptor interaction, ECM–receptor interaction, PI3K–Akt signaling, focal adhesion, p53 signaling, and cell cycle pathways. Hub gene analysis identified MMP3, S100A12, CXCL8, TDO2, BCL2A1, PROK2, MME, PI15, RPS4Y1, and FPR1 as key regulatory genes associated with regenerative responses. These findings demonstrate that tissue regeneration is orchestrated through coordinated inflammatory, proliferative, and extracellular matrix remodeling pathways. The identified genes and pathways provide valuable insights into the molecular architecture of tissue repair and may serve as potential biomarkers and therapeutic targets for future regenerative medicine applications.

KEYWORDS: Regenerative medicine, Transcriptomics, Tissue regeneration, Genomic biomarkers

1. INTRODUCTION

Regenerative medicine is one of the most game-changing therapeutic areas in contemporary biomedical research that provides novel approaches to repair, replace, or regenerate damaged tissues and organs. The field combines the latest developments in stem cell biology, tissue engineering, biomaterials, gene editing, and precision therapeutics to tackle diseases that are poorly treated with traditional methods. The clinical needs for effective treatments of chronic diseases, traumatic injuries and degenerative disorders have driven the research and development efforts in regenerative medicine to a rapid pace, with many translational studies and clinical trials actively being carried out around the world (Petrosyan et al., 2022; Mathews et al., 2023). The field of regenerative medicine has seen growing applications in modern healthcare, with recent innovations like regenerative engineering, advanced drug delivery systems, natural hydrogels, and stem cell-derived therapeutic products significantly improving the capacity to promote tissue repair and functional recovery (Catoira et al., 2019; Hassanzadeh et al., 2021; Rasekh et al., 2025; Shi et al., 2025).

The primary goal of regenerative medicine is to repair the structure and function of tissue loss due to injury or disease. Tissue repair and regeneration are complex biological processes, which require interactions of inflammatory cells, stem cells, growth factors, and extracellular matrix components. Tissue repair is a process of repairing the tissue after injury, while tissue regeneration is the process of replacing lost or damaged tissue with functionally equivalent tissue to restore normal physiological function (Xia et al, 2018). Growing evidence indicates that regulated inflammatory responses are essential to trigger the regenerative cascades, aid cell communication, angiogenesis and remodeling of the matrix that are necessary for proper tissue restoration (Choi et al., 2023). Moreover, endogenous stem cells and tissue-specific progenitor cells play an important role in regeneration, through their regulation of the proliferation, migration and differentiation of cells in damaged tissues (Xia et al., 2018).

With the increasing use of genomics in regenerative medicine, new opportunities have emerged to study the molecular mechanisms underlying tissue regeneration. By using these genomic technologies, the expression patterns of all genes, regulatory pathways and molecular networks that control the cellular response during tissue repair can be analyzed comprehensively. The ongoing development of genome editing technologies has also further cemented the connection

between genomics and regenerative medicine, allowing for the targeting of genome regions known for their involvement in stem cell function and tissue regeneration (Takata & Eiraku, 2018). With the ongoing development of precision medicine, genomic strategies are playing an increasingly crucial role in discovering new markers, targets, and personalized therapies that will lead to better regeneration outcomes (Patil, 2025).

In recent years, the further advance of high throughput omics technologies has massively increased the potential to investigate the processes of regeneration at the molecular level. The recent development of transcriptomics has provided a powerful means of describing changes in gene expression that occur dynamically with the injury and eventual regeneration of tissue. Transcriptomic analyses can help identify the genes and signaling pathways that are differentially expressed, which can shed light on the biological mechanisms underlying tissue repair (Bhattacharjee, 2021). Furthermore, the new progress of omics technologies and single-cell transcriptomics enable us to explore cellular heterogeneity and lineage-specific regenerative responses at unprecedented resolution, paving the way to a better understanding of regenerative biology (Dai and Shen, 2022; Ruta et al., 2024).

Although significant strides have been made, there are still challenges to overcome that will limit the ability of regenerative medicine to be used in routine clinical settings. While many studies have been published on genes and pathways associated with tissue repair, there are still limited molecular biomarkers available to accurately predict regenerative outcomes. Furthermore, tissue regeneration remains poorly understood due to the intricate genomic regulatory networks involved in regeneration, due to the interactions between multiple signaling pathways and cell populations involved in regenerative responses (Goldman & Poss, 2020). Moreover, although there is a growing volume of large-scale genomic data but its incorporation into the development of new therapies for the regeneration of tissues is limited, limiting the possibilities for identifying new molecular targets and precision interventions. Thus, systematic genomic study of regeneration is necessary to find out molecular signatures, to understand the regulatory mechanisms and facilitate the creation of new and improved approaches in regenerative medicine. These steps could ultimately pave the way for further development of personalized regenerative therapies and better clinical results for patients with tissue damage and degenerative diseases.

Research Objectives

1. To identify differentially expressed genes associated with tissue regeneration.
2. To determine the key biological processes and signaling pathways involved in regenerative responses.
3. To identify hub genes as potential biomarkers and therapeutic targets for regenerative medicine.

2. METHODOLOGY

2.1 Research Design and Data Collection

The research design of this study was bioinformatic approach with the use of publicly available transcriptomic data for the study of the genomic mechanisms associated with tissue regeneration. The gene expression data used was from the Gene Expression Omnibus (GEO) database (GSE8056). The data set includes normal skin tissues and thermally injured wound-margin tissues, which serves as an excellent model for investigating molecular events associated with tissue repair and regeneration (National Center for Biotechnology Information, 2019).

2.2 Data Preprocessing and Differential Expression Analysis

The gene expression data downloaded was preprocessed to ensure data quality and reliability. Prior to statistical analysis, normalization, probe annotation and duplicate removal were conducted. Limma package in R software was used to identify the differentially expressed genes (DEGs) between normal and injured tissue samples. Genes with p-values < 0.05 that showed a log₂ fold change > 1 were deemed to be significantly differentially expressed and were further examined.

2.3 Functional Enrichment Analysis

The identified DEGs were subjected to Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis to gain insight into their biological significance. GO analysis was performed to determine which biological processes, molecular functions and cellular components were enriched during regenerative responses. Using KEGG pathway analysis, it was determined that the signaling pathways that are involved in wound healing, inflammation, remodeling of the extracellular matrix and tissue regeneration. A significance level of p value < 0.05 was obtained when using an adjusted p value.

2.4 Protein–Protein Interaction Network and Hub Gene Identification

The STRING database was used to produce a protein–protein interaction (PPI) network, which was used to investigate functional interactions between the DEGs identified. An interaction network was generated and viewed and analysed with Cytoscape software. The network topological analysis was conducted to determine highly connected genes in the network. Hub genes were identified as genes that were most connected and could be used as potential biomarkers and therapeutic targets in regenerative medicine.

2.5 Statistical Analysis and Ethical Considerations

All Bioinformatics and Statistical Analysis were performed in R software and associated packages. To minimize false discovery rates, multiple testing correction was applied using Benjamini–Hochberg method. To aid in the interpretation of the findings from the genome, data visualization was implemented as volcano plots, heat maps, enrichment plots, and interaction networks are used. This study used publicly available secondary data; therefore, ethical clearance and informed consent were not necessary.

3. RESULTS

3.1 Quality Assessment of Gene Expression Data

To ensure the reliability of data and sampling distribution downstream analyses were performed. The expression distribution was examined in the boxplot visualization, which showed similar distribution in all samples, suggesting good normalization and very low technical variation and hence considered satisfactory (see figure 1). Principal component analysis (PCA) showed separation between burn wound tissues and normal controls indicating different transcriptomic

profiles. The hierarchical clustering also provided group structure based on biological condition, and there were no obvious outliers. The main quality control parameters are summarized in Table 1.

Table 1. Quality control metrics of the GSE8056 dataset.

Metric	Value
Total samples	12
Burn samples	9
Normal controls	3
Total probes	54,675
PC1 variance explained	38.16%
PC2 variance explained	16.65%
Total variance explained (PC1 + PC2)	54.81%
Outliers detected	None

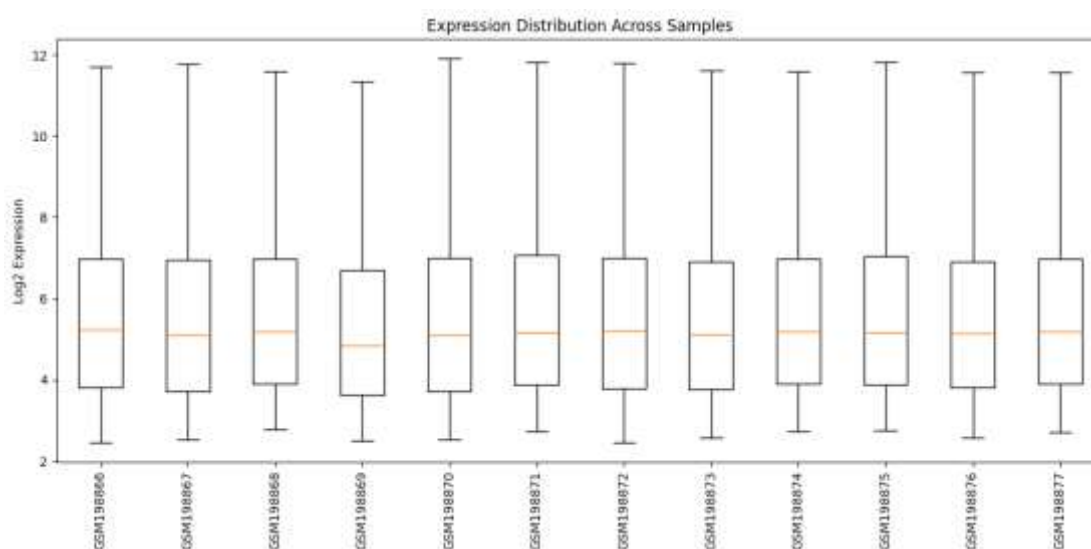


Figure 1. Distribution of normalized gene expression across samples.

The boxplot shows consistent log₂-transformed gene expression distributions across all samples, indicating successful normalization, minimal technical variation, and high-quality data suitable for downstream transcriptomic analyses.

3.2 Identification of Differentially Expressed Genes

A significant number of transcriptional changes were found between tissues with burns and normal skin controls (figure 2), as revealed by differential expression analysis. Fifty-four thousand six hundred and seventy-five probes were evaluated, leading to a total of one thousand four hundred and ninety-six probes that were significantly differentially expressed (SDDE) at an ADJUSTED p-value < 0.05 and an ABS LOG₂ FC > 1. After the probe annotation and removal of duplicates, 1,183 unique DEGs were identified. Of those, 587 genes were significantly upregulated and 596 were significantly downregulated. The overall DEG statistics are shown in Table 2.

Table 2. Summary of differential expression analysis.

Parameter	Count
Total probes analyzed	54,675
Significant probes	1,496
Annotated probes	1,430
Unique DEGs	1,183
Upregulated genes	587
Downregulated genes	596

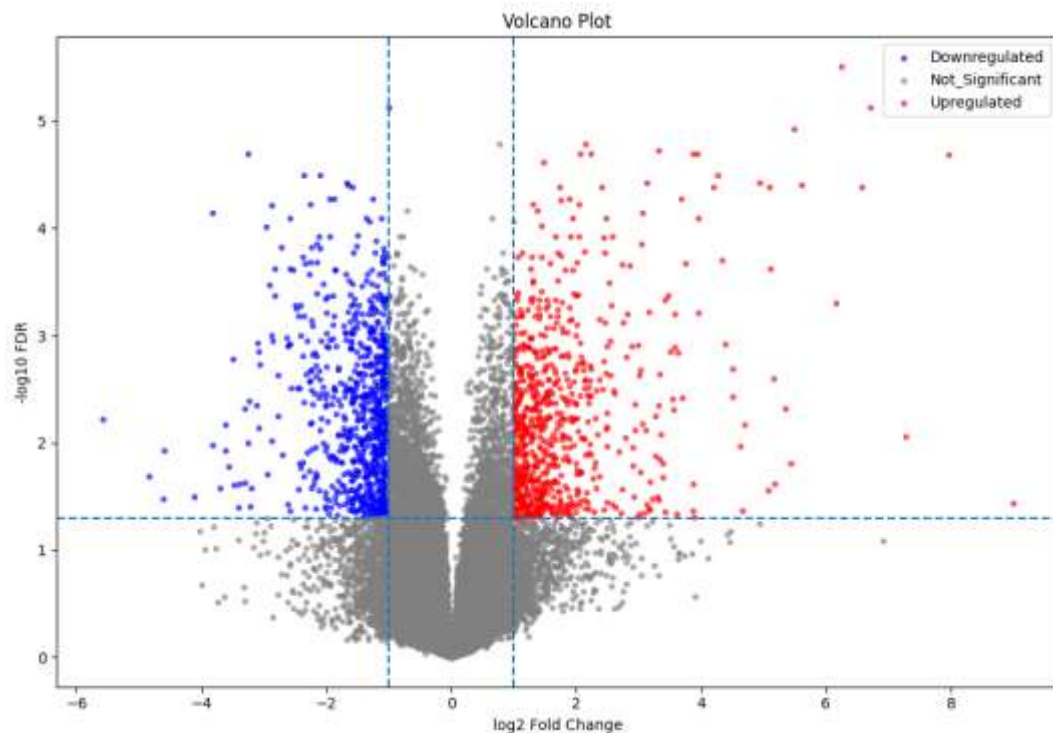


Figure 2. Volcano plot of differentially expressed genes between burn wound and normal skin tissues.

The volcano plot illustrates the distribution of differentially expressed genes based on log2 fold change and statistical significance. A total of 1,183 significant genes were identified, including 587 upregulated (red) and 596 downregulated (blue) genes, highlighting extensive transcriptional alterations associated with tissue injury, inflammation, and regenerative processes.

3.3 Top Differentially Expressed Genes

The top significantly dysregulated genes were ranked by the adjusted p-value and fold-change, and the most significant genes were chosen for further analysis to identify those most associated with regenerative responses. There were significant fluctuations in the expression of several genes related to inflammatory processes, remodeling of the extracellular matrix, immune regulation, and repair of tissues. The top differentially expressed genes are shown in Table 3.

Table 3. Top 10 differentially expressed genes identified in burn wound tissues.

Gene Symbol	log2FC	Adjusted P-value	Regulation
S100A12	6.24	0.000003	Upregulated
CXCL8	6.71	0.000008	Upregulated
BCL2A1	5.49	0.000012	Upregulated
PRR11	2.15	0.000016	Upregulated
CYP27B1	3.32	0.000019	Upregulated
DKK2	-3.26	0.000020	Downregulated
SELL	3.87	0.000020	Upregulated
SAT1	2.06	0.000020	Upregulated
CDC20	2.24	0.000020	Upregulated
SCG5	3.94	0.000020	Upregulated

3.4 Gene Ontology Enrichment Analysis

GO enrichment analysis was performed to explore the biological functions of DEG. 3,642 significant biological processes were identified. The most enriched terms were mainly involved in cytokine signaling, extracellular matrix organization, cellular proliferation and immune responses. The results indicate that inflammation modulation and tissue remodeling play major roles in the regeneration process. Table 4 shows the GO biological processes with the best enrichment.

Table 4. Top 10 enriched GO biological processes.

GO Term	Adjusted P-value
Cytokine-mediated signaling pathway	0.001363
Regulation of cell population proliferation	0.001363
Positive regulation of cell population proliferation	0.001363
Response to cytokine	0.002795

Response to copper ion	0.002828
Extracellular structure organization	0.002828
External encapsulating structure organization	0.002858
Mitotic spindle organization	0.003221
Cellular response to cytokine stimulus	0.003221
Extracellular matrix organization	0.003221

3.5 KEGG Pathway Enrichment Analysis

We used KEGG pathway analysis to identify 288 significantly enriched pathways. Cytokine signaling, extracellular matrix interactions, PI3K–Akt signaling, focal adhesion, and cell cycle regulation were specific pathways that were closely linked to regenerative medicine. All these pathways play a role in the regulation of cell proliferation, migration, differentiation and tissue repair. Table 5 shows the most important pathways.

Table 5. Top 10 enriched KEGG pathways.

KEGG Pathway	Adjusted P-value
Cell cycle	0.002811
Human papillomavirus infection	0.002811
Cytokine-cytokine receptor interaction	0.002811
ECM-receptor interaction	0.002811
Pyrimidine metabolism	0.003085
p53 signaling pathway	0.003085
Proteoglycans in cancer	0.003085
Pathways in cancer	0.003085
PI3K-Akt signaling pathway	0.004181
Focal adhesion	0.004181

3.6 Identification of Potential Hub Genes

The key molecular regulators of the regenerative process were identified by combining a differential expression magnitude and statistical significance to form a composite score for the hub gene analysis. Ten genes had the highest hub scores and could possibly be used as a biomarker or therapeutic target in the field of regenerative medicine. Ten hub genes were identified and listed in Table 6.

Table 6. Top 10 hub genes associated with regenerative responses.

Gene Symbol	log2FC	Adjusted P-value	Hub Score
MMP3	7.96	0.000021	37.33
S100A12	6.24	0.000003	34.40
CXCL8	6.71	0.000008	34.36
TDO2	6.57	0.000041	28.80
BCL2A1	5.49	0.000012	27.04
PROK2	5.61	0.000039	24.72
MME	5.08	0.000041	22.29
PII5	4.95	0.000037	21.91
RPS4Y1	6.16	0.000502	20.31
FPR1	4.27	0.000032	19.17

4. DISCUSSION

In the current work we used the transcriptomic strategy to explore the mechanisms involved in tissue regeneration after thermal injury. A total of 1,183 genes were found to be significantly differentially expressed in GSE8056 microarray data, a total of 587 genes were upregulated and 596 genes were downregulated. The functional enrichment analyses showed a significant enrichment of the genes related to cytokine mediated signaling, extracellular matrix (ECM) organization, cell proliferation and immune related pathways. Moreover, the hub genes were used to identify potential regulators of regenerative responses: MMP3, S100A12, CXCL8, TDO2, BCL2A1, PROK2, MME, PII5, RPS4Y1, and FPR1. Together, these results yield a genomic understanding of the biological mechanisms that regulate tissue repair and regeneration after injury.

With the rapid development of genomics and transcriptomics, the understanding of regenerative medicine has been greatly enhanced, as it helps to characterize the gene regulatory network associated with tissue repair in greater detail (Dai &

Shen, 2022; Ruta et al., 2024). Dynamic molecular programmes control regeneration by regulating inflammation, cell proliferation, differentiation and tissue remodelling (Goldman & Poss, 2020). In line with these, our analysis revealed that many transcriptionally changes were observed after thermal injury, suggesting that multiple complex regenerative pathways are activated. This is likely to be a due to the large number of differentially expressed genes that were seen in the present study, which is representative of the extensive molecular reprogramming necessary to restore tissue integrity after injury.

The enrichment of cytokine-mediated signaling pathways and cytokine response processes were two of the most important results of this study. Cytokines play a crucial role in the communication between immune cells, stromal cells, and regenerating tissues, and control inflammatory responses and tissue reconstruction (Goldman & Poss, 2020). The significant induction of CXCL8 and other genes related to chemokines indicate persistent recruitment and presence of immune cells in the wound site. While inflammation is beneficial in the early stages of healing, chronic cytokine activation could also play a role in delayed healing and fibrosis. Thus, targeting cytokine signaling pathways could be a valuable therapeutic approach in enhancing regeneration.

Another important biological process we found was the organization of the extracellular matrix. Extracellular matrix is a medium that supplies structural support and controls the behavior of cells such as migration, proliferation and differentiation. One of the most important criteria for successful tissue remodeling is ECM remodeling, which is necessary for wound closure and tissue reconstruction (Sonbol, 2018). There was significant dysregulation of several ECM associated genes such as MMP3, MMP9, ADAMTS12 and collagen related genes. Of all these, MMP3 was found to be the most prominent hub gene. Matrix metalloproteinases mediate breakdown of damaged components of the matrix and allow the assembly of the new structures of the extracellular matrix needed for tissue repair. These results are also in line with observations in other studies on ECM remodeling and its role in the process of skin regeneration and wound healing, a process that is said to be essential for successful regeneration (Kamoliz et al., 2022).

Cell population proliferation and cell cycle regulation pathways were also significantly enriched, further emphasizing the role of cellular growth in tissue regeneration. A proper repair necessitates the fast proliferation of keratinocytes, fibroblasts, endothelial cells and progenitor cell population to regenerate damaged tissue. Both GO and KEGG enrichment analyses showed significant enrichment of cell cycle related processes and pathways such as regulation of cell population proliferation and the KEGG pathway for the Cell Cycle. These results are in accordance with previous studies showing that co-ordinated cell proliferation and migration are key mechanisms in the wound healing and regenerative response (Zanca et al., 2022). Further in support of the activation of proliferative programs after injury, genes associated with the cell cycle were identified as enriched genes, such as CDC20, CCNA2, and CCNB1.

Additionally, the KEGG pathway analysis showed that the PI3K–Akt signaling pathway and focal adhesion pathway were remarkably enriched. The PI3K–Akt signaling pathway has been a well-known regulator of cell survival, proliferation, angiogenesis and tissue regeneration. This pathway helps strengthen cells to stress and improves repair abilities in damaged tissues (Jin et al., 2023). Focal adhesion signaling also regulates processes of cell migration and wound healing, by coordinating cell-cell and cell-extracellular matrix interactions. The involvement of coordinated regulation of intracellular signaling networks and extracellular structural remodeling in the enrichment of these pathways indicates that regenerative responses require coordination of these networks.

Hub gene analysis revealed a number of genes that have the potential to be translationally relevant. CXCL8 and S100A12 are well known inflammatory mediators which control both recruitment of leukocytes and immune activation. Your upregulation is of a high strength, suggesting that inflammation is still present in the damaged tissues. Among the selected hubs, MMP3 had the highest hub score, highlighting its crucial role in the extracellular matrix turnover and tissue remodeling. Furthermore, PROK2 and FPR1 have been linked to processes of angiogenesis and immune-cell migration, which are critical to tissue repair. Inflammatory signaling molecules and extracellular matrix regulators have also been shown to be central hub genes involved in regulating tissues' regenerative response after injury to the spinal cord in similar studies (Fang et al., 2021). So, it is likely that these genes could be useful for use as biomarkers and therapeutic targets in regenerative medicine applications.

The results of this research will also highlight the increasing importance of the transcriptomic technologies used in research on regenerative medicine. In addition to the above, high-throughput genomic approaches are used to systematically find molecular targets that may not be able to be identified by traditional experiments (Bhattacharjee, 2021; Dai & Shen, 2022). Single cell transcriptomics has subsequently strengthened the capacity to resolve cellular heterogeneity and dynamics of regeneration with unprecedented resolution, even more recently (Ruta et al., 2024). The combination of transcriptomics and other technological advancements like artificial intelligence (AI) could help speed up the identification of biomarkers and the progress of precision regenerative therapies (Nosrati & Nosrati, 2023).

This study has several strengths, but also some limitations should be noted. The first is that the analysis was done on a dataset of publicly available microarrays, which had a comparatively small sample size. Second, the genes/paths identified were not experimentally validated. Third, changes in transcriptomes do not necessarily mean changes in the activity or protein levels. Further, future research focused on larger cohorts and multi-omics should be combined with experimental validation to validate the role of the genes and pathways identified in the current study.

5. CONCLUSION

A genomic and bioinformatics approach was used to explore the molecular mechanisms involved in tissue regeneration after thermal injury. The GSE8056 transcriptomic data was analyzed and revealed 1,183 genes that were significantly differentially expressed, demonstrating significant molecular reprogramming involved in wound healing and regeneration. Cytokine mediated signaling, extracellular matrix organization, cell proliferation, immune responses, and tissue remodeling were the most over-represented biological processes in functional enrichment analysis. In addition, KEGG pathway analysis revealed the involvement of important pathways associated with the regeneration process such as

cytokine–cytokine receptor interaction, ECM–receptor interaction, PI3K–Akt signaling, focal adhesion, p53 signaling, and cell cycle regulation. Using hub gene analysis, we identified 10 molecular regulators, such as MMP3, S100A12, CXCL8, TDO2, BCL2A1, PROK2, MME, PI15, RPS4Y1 and FPR1, which might play roles in the process of tissue repair and regeneration. These genes could be used as potential biomarkers and therapeutic targets in the development of advancing regenerative interventions. In summary, the results offer broad genome-wide genomic support that a coordinated interplay of inflammatory signaling, remodeling of the extracellular matrix and proliferative pathways is essential for orchestrating regenerative responses. This study is a molecular advance in the field of regenerative medicine and also provides a molecular basis for future precision-based regenerative therapeutic and clinical applications.

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