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Review Article

The role of multi-omics in biomarker discovery, diagnosis, prognosis, and therapeutic monitoring of tissue repair and regeneration processes

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ABSTRACT

In the last two decades, technological interventions have played a significant role in transforming healthcare with timely diagnosis and novel therapeutic interventions. Advanced technologies such as next-generation sequencing, NMR, mass spectrometry, and non-invasive imaging modalities have made it possible to study biological molecules, cellular processes, and molecular pathways in different diseases. The "omics revolution" is another addition that emerged as a powerful tool in elucidating molecular and cellular processes in diseases. Given the profoundly complex nature of tissue repair, it is important to employ the advanced multi-omics technique to elucidate the cellular, molecular, and inflammatory events in damaged tissues. As proven in various other diseases, these integrative omics can provide a systematic and comprehensive understanding of the biology of tissue repair and regeneration. Proteomics and transcriptomics, in particular, have been widely used for the identification and validation of potential biomarkers such as transforming growth factor-beta (TGF-β), vascular endothelial growth factor (VEGF), interleukin 6 (IL-6), and several matrix metalloproteinases (MMPs) which play a key role in the process of tissue repair and regeneration. Metabolomics, such as NMR and spectroscopies, have also shown potential in tracking energy metabolism and oxidative stress during regeneration. This review article presents a comprehensive overview of the latest multi-omics techniques and technologies that provide valuable insights into the complex processes of tissue repair and highlight the possibilities of early diagnosis, biomarker identification, and novel therapeutic interventions for tissue repair and regeneration. Combining data and key findings from multiple omics layers, such as metabolomics, transcriptomics, and genomics, may provide a comprehensive understanding of the mechanisms and pathways that have been implicated in tissue repair and regeneration. This may lead to the identification and validation of robust biomarkers and the development of therapeutic strategies aimed at improving outcomes in patients with chronic and non-healing wounds.

The Translational Potential of this Article: This article reviews the application of multi-omics technologies in tissue repair and regeneration, highlighting how the integration of genomics, transcriptomics, proteomics, and metabolomics reveals molecular mechanisms of wound healing. By combining these diverse omics approaches, the findings provide critical insights into novel biomarkers, therapeutic targets, and personalized treatment strategies. This integration allows for a more comprehensive understanding of tissue regeneration, enhancing diagnostic accuracy and treatment monitoring. Ultimately, multi-omics technologies can drive advances in personalized medicine, improving clinical outcomes and offering new avenues for treating tissue repair and regeneration.

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1. Introduction

Tissue repair is a compensatory process mediated by homeostasis that is critical in the restoration of structure and function. This repair is a highly complex but critical process in many tissues, including the heart, liver, kidney, and other parts and organs of the body. The process consists of two separate phases: regeneration and replacement [1–5]. While tissue damage is commonly described as open or closed, it is clinically categorized into chronic and acute wounds [6–9]. Chronic wounds have been reported to have increased deregulation of cellular processes [10,11], sustained inflammation [12,13], and irregular matrix remodeling [14], regulated by complex molecular mechanisms that could be explored by applying different multi-omics tools.

Tissue repair can be divided into two general phases, known as regeneration and replacement. Regeneration aims to restore the damaged or wounded tissue, while replacement tends to occur when regeneration cannot be achieved. The healing process involves many complex biological pathways and interactions between various types of cells, cytokines, and other mediators, such as the vascular system [15–17]. Recent multi-omics studies have revealed that the fate of wounds, whether at the regeneration or replacement phase, is linked with the metabolic states and tightly regulated molecular mechanisms and gene expression patterns [18,19]. Integrative proteomics and transcriptomics provide a good avenue to explore the role of genes, proteins, and their possible post-translational modifications.

The process of wound healing has been categorized into three distinct but overlapping phases: the hemostasis and inflammation phase, the proliferation phase, and the remodeling phase [20,21]. The hemostasis phase triggers blood vessel constriction, followed by the activation and aggregation of platelets that lead to the deposition of a provisional fibrin matrix [22,23]. Various inflammatory mediators are also released, including cytokines, platelet-derived growth factor (PDGF), and transforming growth factor-β (TGF-β). The release of these mediators causes the chemotaxis of macrophages and neutrophils, which leads to the beginning of the inflammatory phase [24,25]. Omics technologies, such as single-cell RNA sequencing and transcriptomics, have the potential to identify cell-type-specific gene expression profiles [26]. Studies, particularly those combining transcriptomics and proteomics, have already revealed success in demonstrating the temporal modulation of cytokine networks and immune responses during inflammation [27,28]. Using human skin tissues, a recent single-cell multi-omics study revealed cellular and molecular dynamics in different phases of wound healing, such as proliferation, inflammation, and remodeling [29]. The study identified the *FOSL1 gene as a critical driver of re-epithelialization* [29].

The proliferation phase normally lasts from 3 to 21 days post-injury in the wound healing process. In this phase, the development of granulation tissue, collagen deposition, and angiogenesis takes place [30–33]. A number of studies on proteomics and metabolomics have identified significant changes in the collagen isoforms, glycolytic intermediates, and redox cofactors, demonstrating a metabolic switch that favours cellular proliferation during wound healing [34,35]. The remodeling phase typically begins two to three weeks after the onset of the wound and can last for a year or longer [36–38]. During maturation and remodeling, most blood vessels, fibroblasts, and inflammatory cells disappear from the wound site by emigration processes, apoptosis, or other cell death mechanisms. Subsequently, fibroblasts within the granulation tissue become myofibroblasts, which acquire some contraction properties. Advances in epigenomics have revealed that chromatin remodeling influences fibroblast differentiation and scar formation during this phase [39–41].

Tissue repair is a process that restores the integrity and normal physiological function, consisting of the synchronization of various cell types and other important mediators [42–46]. Current treatment options for wound repair include pro-angiogenic wound dressings, anti-microbial agents, debridement procedures, and surgical interventions; however, no proper evidence-based therapy with definitive clinical outcomes is available for chronic wound repair. Most of these approaches focus on the closure of the wound, but not on the underlying molecular mechanisms that lead to inflammation and impaired angiogenesis. Moreover, the incidence of increasing antibiotic resistance poses a challenge for conventional antimicrobial therapies, underscoring the need for alternative strategies [47–51]. The failure of these interventions in chronic wounds could be effectively addressed using multi-omics approaches.

Integrative or multi-omics refers to the combined analysis of multiple omics disciplines for understanding complex biological systems such as disease progression, molecular pathways, and physiological processes. The ability of multi-omics to uncover the hidden molecular mechanisms behind wound repair, which may be overlooked by traditional methods, makes it a preferred approach [52,53]. For instance, genomics and transcriptomics have been widely used to identify genes and loci that have been implicated in human diseases. Such multi-omics approaches have successfully revealed the complexities of diseases and have provided insights into novel diagnostic, treatment, and preventive strategies [54].

Metabolomics provides how different metabolic pathways and their associated downstream and upstream genes behave in normal and abnormal physiological conditions [55–59]. These advanced research avenues offer diverse opportunities for research to diagnose diseases and explore new therapeutic options [60,61]. In this review article, we have summarized the available literature to address the central question: how can multi-omics play an important role in uncovering molecular mechanisms and therapeutic targets and facilitating the discovery of diagnostic and prognostic biomarkers, in tissue repair and regeneration? This review article aims to provide a comprehensive exploration of the role played by the multi-omics layers, such as proteomics, genomics, epigenomics, transcriptomics, and metabolomics, in the process of tissue repair and regeneration. By integrating data from different omics, it will discuss the molecular interplay between cellular processes, metabolic networks, and signaling pathways involved in tissue repair.

2. Methodological approaches

2.1. Literature retrieval strategy

A comprehensive literature search was carried out across several electronic databases, including Medline, ScienceDirect, PubMed, Web of Science, and Google Scholar, which were thoroughly searched covering publications from 2000 to 2025. Keywords included tissue repair, wound healing, wound repair phases, tissue regeneration, wound repair, multi-omics, integrative omics, proteomics, transcriptomics, genomics, and epigenomics. Logical operators such as “AND” and “OR” were used for different combinations of words. Studies published in high-impact-factor journals were given preference. In addition, studies with clinical relevance to molecular mechanisms, biomarker discovery, therapeutic monitoring, and diagnosis were preferred. A total of 668 articles were retrieved, of which 304 were included in this study, as shown in the flowchart (Fig. 1).

2.2. Eligibility criteria

Inclusion criteria preferred original research articles published in the English language that explored integrative omics and multi-omics applications in tissue repair and regeneration, particularly those providing mechanistic insights, clinical relevance, or biomarker discovery. Other articles, such as meta-analysis and systematic review articles, which aimed at summarizing multi-omics applications in tissue repair and regeneration, were also included (Table 1).

As per the exclusion criteria, articles that lacked primary data, were written in other than English, editorials, commentaries, and correspondence pieces were excluded. Review articles without mechanistic insights were also excluded, as shown in Table 1.

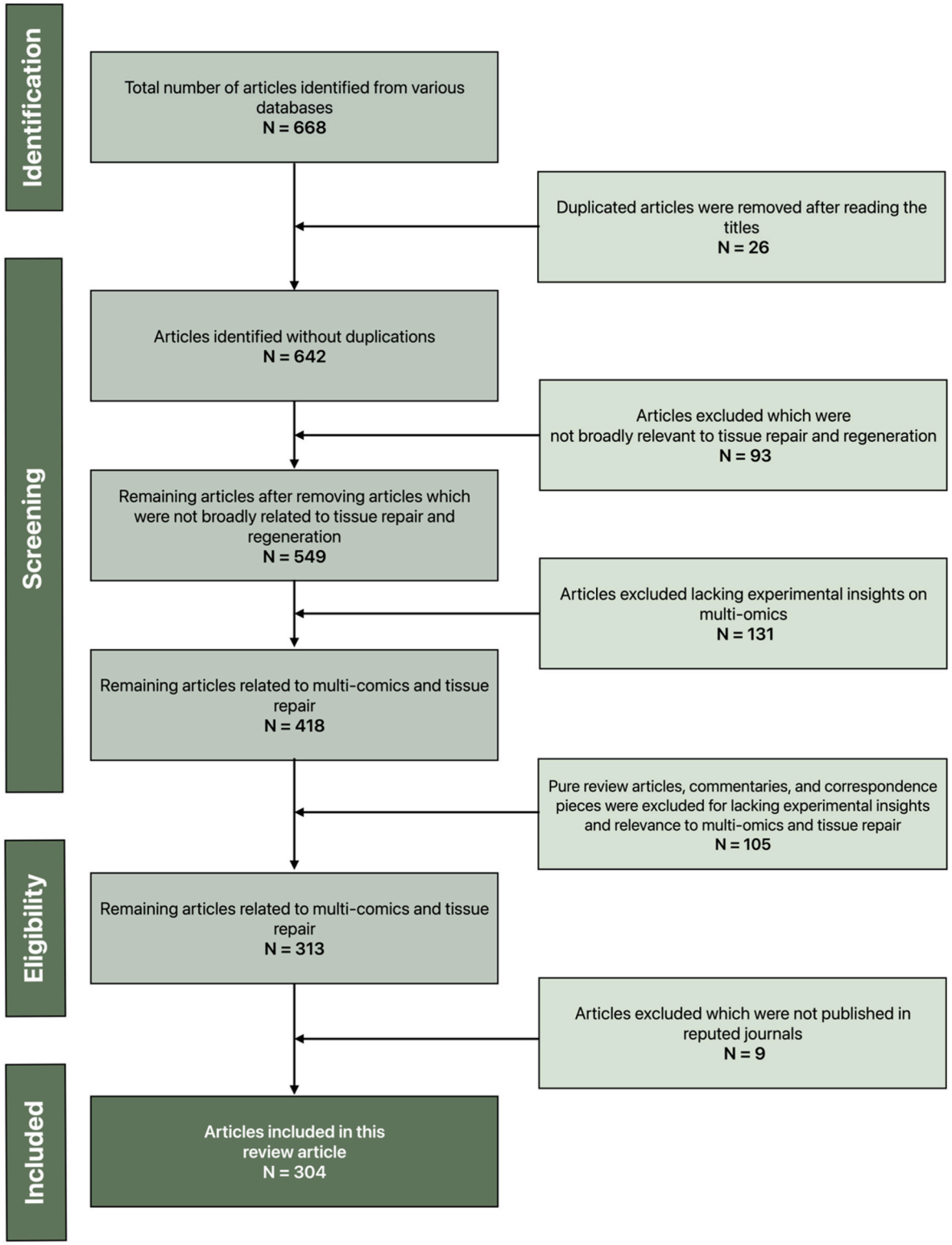

Fig. 1. Flow chart of the selected articles for this review article.

Particular attention was given to studies employing multi-omics strategies in biomarker discovery, diagnosis, prognosis, and treatment monitoring related to tissue repair and regeneration. Strategies specific to individual omics domains, such as proteomics, transcriptomics, and metabolomics, were reviewed for their unique and complementary roles in elucidating biological processes. For instance, in proteomics, both triangular and rectangular strategies were considered. The triangular strategy refers to a phased progression from biomarker discovery to validation, whereas the rectangular strategy emphasizes concurrent validation across multiple independent cohorts. These approaches, though effective, often face challenges such as the necessity for high-quality data, stringent statistical validation, and reproducibility. Moreover, the integration of data across omics layers (e.g., proteomics with transcriptomics or metabolomics) was analyzed for its potential to yield

Table 1
Exclusion and inclusion criteria.

No	Inclusion/Exclusion Criteria	
1	Articles that were written in English	**Inclusion**
2	Articles focused multi-omics, integrative omics and tissue repair and regeneration	**Criteria**
3	Articles discussing applications of nanocarriers in the context of common digestive disorders.	
4	Articles exploring molecular mechanisms of genes and cellular pathways related to multi-omics and tissue repair.	
5	Articles focused on multi-omics, integrative omics and tissue repair and regeneration	
6	Articles exploring molecular mechanisms of genes and cellular pathways related to multi-omics and tissue repair.	
7	Articles addressing multi-omics based tissue repair with potential therapeutics, biomarkers and diagnostic procedures.	
8	Articles discussing applications of nanocarriers in the context of common digestive disorders.	
9	Articles addressing multi-omics based tissue repair with potential therapeutics, biomarkers and diagnostic procedures.	
10	Articles written in languages other than English	**Exclusion**
11	Articles with incomplete or insufficient data	**Criteria**
12	Duplicate articles retrieved from multiple databases	
13	Editorials, correspondence and commentaries	

deeper mechanistic insights into tissue repair.

3. Tissue repair and regeneration

Tissue repair and regeneration is a critical phenomenon in all multicellular organisms; however, their effective mode of treatment is still a challenge in regeneration medicine [62]. According to Brigitte et al. [63], the continuum of tissue repair could be divided into three main processes: The first process refers to healing that leads to complete or partial restoration of function, such as the skin repair process. The second stage involves restoring the function of the injured organ, while the third stage focuses on the regrowth and intricate 3D patterning of complex structures [64–66].

By integrating multi-omics data, such as proteomics, transcriptomics, and metabolomics, researchers can uncover the molecular networks and cellular interactions driving these processes. For example, multi-omics techniques have provided insights into the dynamics of cytokine networks, gene expression, and metabolic shifts during tissue repair, highlighting their importance in wound healing and tissue regeneration [69,71,83].

Multi-omics technologies also play an essential role in unraveling the complexities of tissue repair by offering insights into the molecular processes and interactions at each phase. For instance, proteomics, metabolomics, and transcriptomics technologies enable the identification of key regulatory molecules such as cytokines, growth factors, and matrix components that drive the tissue repair process [67,68]. These tools provide a deeper understanding of the dynamic cellular changes involved in inflammation, proliferation, and remodeling during wound healing. Integrating these multi-omics layers, researchers have identified critical biomarkers that predict the success of tissue regeneration, enabling the development of more precise diagnostic and therapeutic strategies. By integrating data from proteomic and genomic analyses, researchers can pinpoint novel biomarkers and therapeutic targets that may facilitate more efficient tissue repair and regeneration strategies [69–71]. Additionally, epigenomics offers crucial insights into how DNA modifications and chromatin remodeling influence the differentiation and function of stem cells in tissue repair [72]. In particular, the epigenetic modifications regulating gene expression during wound healing have been studied using multi-omics approaches to understand how stem cells differentiate into fibroblasts or keratinocytes, crucial for tissue regeneration [56,72]. These integrative omics increase our understanding of the molecular mechanisms driving tissue repair and regeneration, ultimately leading to more effective therapeutic interventions.

3.1. Tissue repair and regeneration: molecular mechanisms and signaling interplay

One of the profound characteristics of biological systems is the maintenance of homeostasis, in which unusual disruptions such as pathogenic infections, environmental stressors, and tissue damage are addressed [73,74]. Multi-omics technologies, including genomics, transcriptomics, and proteomics, have provided insights into the molecular mechanisms that are involved in homeostasis disruption during tissue damage. By combining these techniques, various signaling pathways have been identified that initiate repair processes, such as inflammatory cytokine release and immune cell migration [27,115,257,268]. Multi-omics technologies have enabled the identification of key molecules involved in the disruption of homeostasis, providing insights into the early signaling events during tissue damage [75,76].

In the inflammatory phase, the complement system prompts immune cell migration to the injury site. Cells that are damaged release damage-associated molecular patterns (DAMPs), stimulating resident macrophages to secrete chemokines that attract immune cells [77–81]. Omics technologies enable the identification of cell-specific gene expression patterns and protein profiles during the inflammatory phase, which are essential for controlling the progression of tissue repair. For example, transcriptomics combined with proteomics has revealed how the inflammatory response can be modulated by cytokine signaling and macrophage activation, leading to efficient wound repair. Transcriptomic analysis has revealed differential expression of inflammatory mediators such as cytokines and chemokines during the early stages of wound healing, providing valuable insights into the regulation of immune cell recruitment and activation [82,83]. These findings highlight the potential of multi-omics technologies to provide a more detailed understanding of the molecular players involved in the wound healing process, thereby advancing the development of targeted therapies for wound healing.

The transition of the inflammatory response is linked to an increase in the recruitment of regulatory T lymphocytes (Tregs) (Fig. 2). Tregs typically reach peak numbers 3–5 days post-injury, playing a vital role in tissue repair by modulating the inflammatory response [84]. Multi-omics techniques, such as single-cell RNA sequencing, have been instrumental in uncovering the cellular dynamics and gene expression profiles of Tregs during tissue repair, offering new therapeutic insights [85,86]. Tregs help attenuate tissue injury by suppressing the activity of neutrophils and pro-inflammatory macrophages while promoting the differentiation of mesenchymal stem cells (MSCs). Moreover, as an excess of active conventional T cells can hinder wound healing, Tregs mitigate $CD4^+$ and $CD8^+$ T cells through the secretion of anti-inflammatory cytokines like IL-10, TGF-β, and IL-35 [87]. This regulatory role of Tregs is further supported by studies showing that their absence enhances pro-inflammatory macrophage activity and IFN-γ expression [88], leading to increased accumulation of $CD8^+$ T cells and fibrotic collagen deposition at the injury site [89]. Thus, Tregs play a crucial role in immune regulation, and the communication between immune cells and MSCs is pivotal in orchestrating wound healing across various tissues.

The degradation and remodeling of the extracellular matrix (ECM) play a crucial role in various cellular processes, including wound healing. These processes are primarily mediated by the family of matrix metalloproteinase (MMP) enzymes. MMPs are believed to be essential for wound healing and tissue repair in conditions such as injury or infection [90]. During the later stages of the wound healing process, several soluble factors, such as IL-10, IL-4, TGF-β, and AMPK activity, work together to enhance anti-inflammatory conditions, resolving inflammation and guiding stem cells towards committed lineages [91]. As inflammation resolves and the proliferation phase progresses,

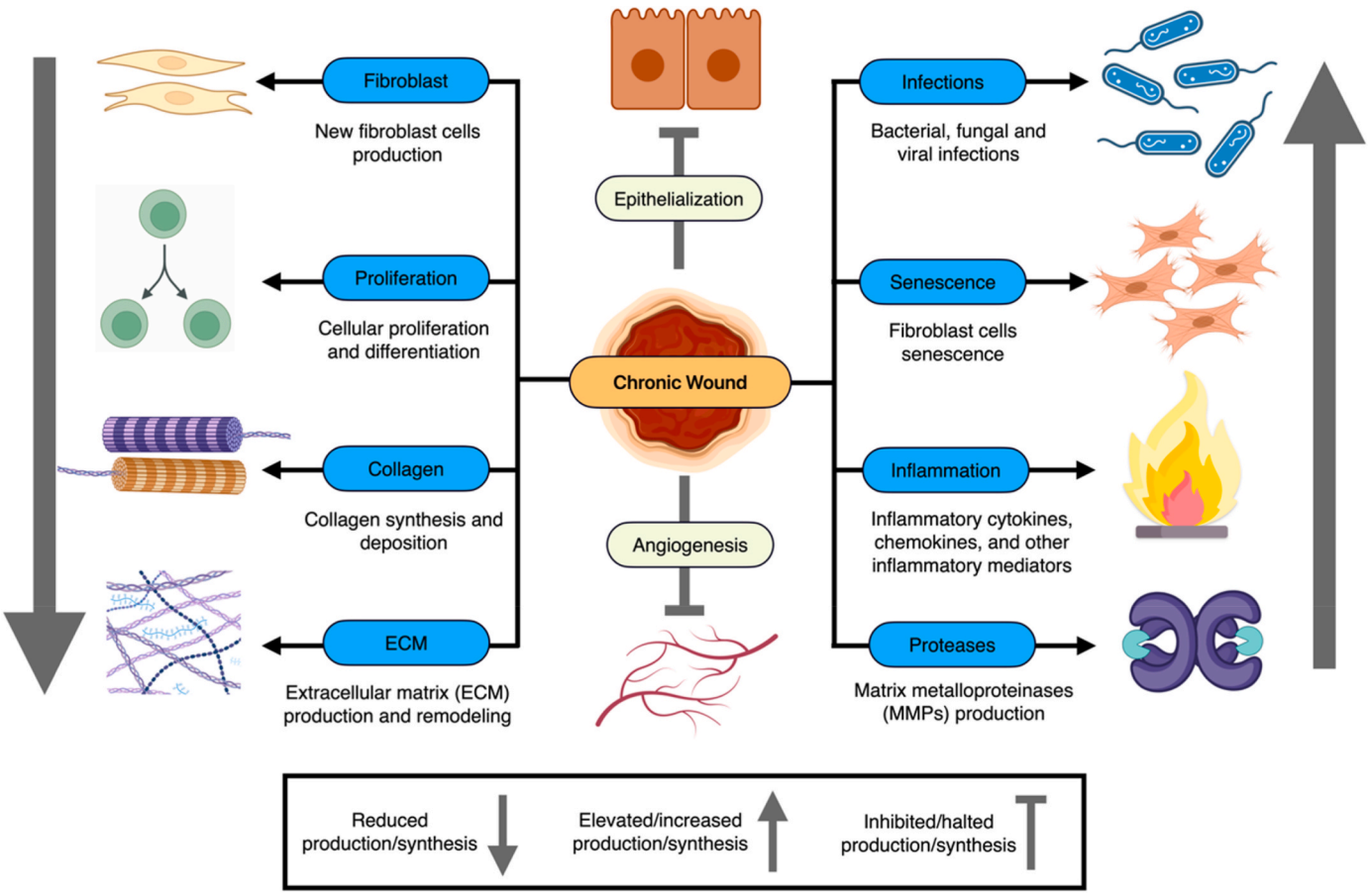

Fig. 2. Shows a visual representation of the mediators that get upregulated or downregulated in the process of tissue repair. For instance, inflammation, senescence, proteases, and infections are increased during tissue repair/healing; however, other mediators are reduced, such as ECM and collagen.

macrophages secrete numerous growth factors, including insulin-like growth factor 1 (IGF-1), platelet-derived growth factor (PDGF), and vascular endothelial growth factor α (VEGF-α). Additionally, macrophages dampen host immune responses by expressing programmed cell death ligands 1 (PDL1) and 2 (PDL2), which initiate Treg signaling and trigger anti-inflammatory responses, ensuring a sustained wound repair process [92,93].

3.2. Phases in tissue repair/wound healing

Both wound healing and tissue repair are simultaneous and continuous processes, interconnected through overlapping phases, functions, and mechanisms. Broadly, healing is described as a response to injury/trauma, while tissue repair is the broader spectrum of restoring that damaged tissue and maintaining homeostasis and integrity [94–96]. Proteomics and metabolomics analyses have identified metabolic changes during the inflammation phase, such as increased glycolysis, which supports immune cell function and energy production required for tissue repair [206,247]. Similarly, transcriptomics has revealed how gene expression changes in response to injury, supporting the transition from inflammation to tissue proliferation and remodeling [28,67]. A detailed description of the events and phases that take place during tissue repair and wound healing is presented below (Fig. 3).

3.2.1. Coagulation and hemostasis phase

The primary aim of this phase is to keep the vital systems and functions unharmed despite the injury (Fig. 3). Secondly, it helps provide a matrix that could be used in the latter stages of wound healing [97,98]. Overall, the hemostasis phase proceeds in three steps: vasoconstriction, followed by primary hemostasis, and then secondary hemostasis [99]. During this phase, transcriptomic and proteomic studies have demonstrated that platelet-derived growth factors and other cytokines are upregulated to initiate the repair process, and these molecular events are essential for triggering the next phase of inflammation [91].

Constriction of blood vessels or vascular spasm is the initial response, followed by the development of a platelet plug and clot formation by the activated platelets. The wound also activates several serine proteases, which help in stopping blood loss [100]. In normal physiological conditions, endothelial cells express thrombomodulin and fibrinolytic heparin molecules, which help prevent clotting. However, during an injury, the endothelial cells stop producing pro-coagulation factors, which lead to coagulation and clot formation at the wound site [101,102]. The endothelial cells also secrete von Willebrand factor that promotes platelet aggregation, which in turn promotes the initial clot that consists of thrombospondin, fibronectin, vitronectin, and fibrin [103].

The hemostasis phase initiates when tissue damage allows blood to escape into the exposed wound site, triggering the extrinsic clotting cascade and the release of mediators such as serotonin that induce localized vasoconstriction [104]. Platelets then aggregate and become activated upon contact with subendothelial collagen, leading to the formation of a hemostatic plug through the secretion of cytokines and growth factors [105]. This also helps facilitate the migration of fibroblasts, keratinocytes, and immune cells [106–108] and the release of inflammatory cytokines [104]. Once hemostasis is achieved, histamine released by the activated complement cascade induces capillary dilation and increased permeability, promoting the migration of inflammatory cells into the wound bed and marking the full transition to the

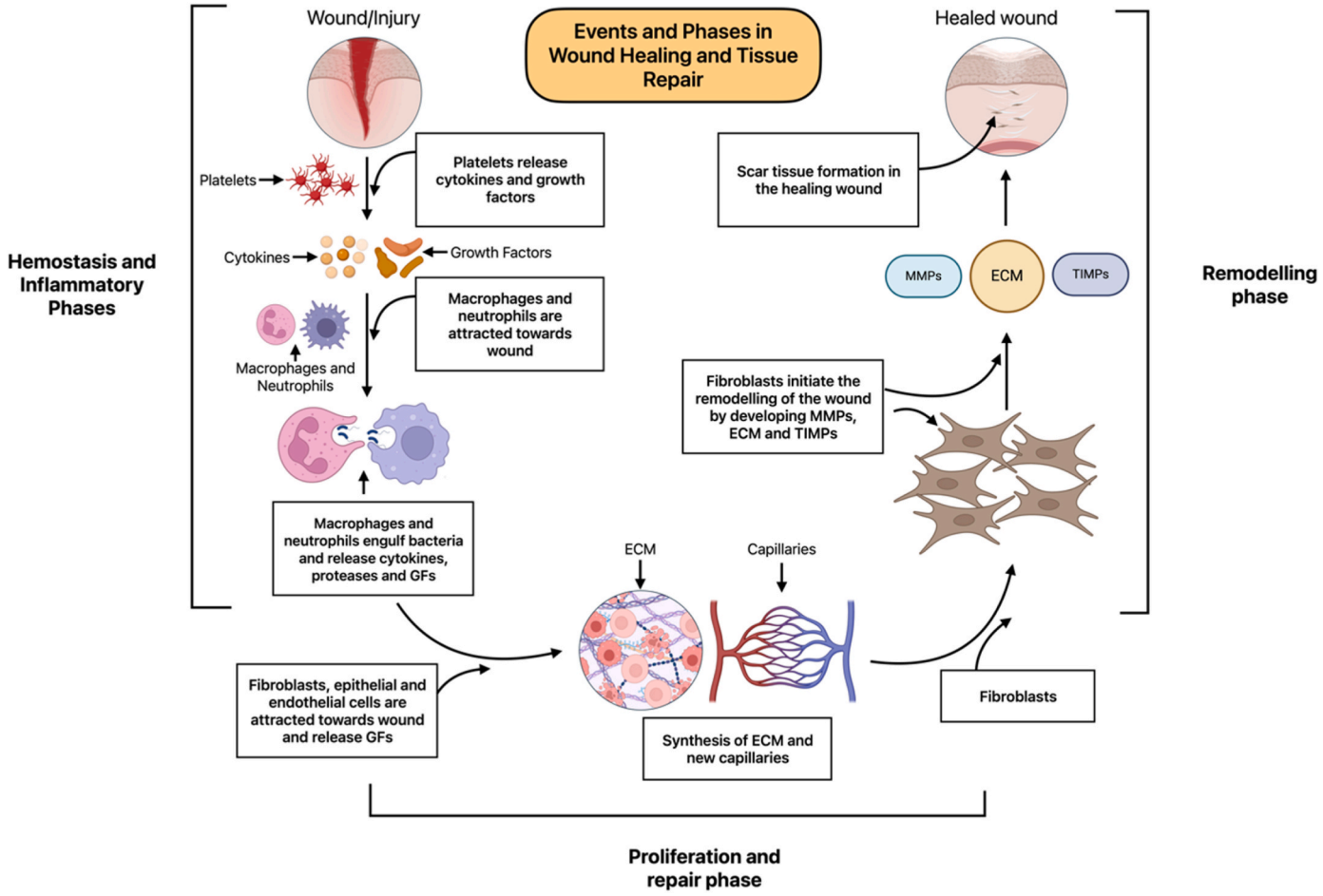

Fig. 3. A graphical depiction of the phases and key events that take place during tissue repair and healing.

inflammatory phase of wound healing [109]. A detailed depiction of important genes expressed in different phases of wound healing is presented in Fig. 4.

3.2.2. *Inflammation phase*

Depending on the intensity of the wound, this phase normally starts within a few minutes after the injury and lasts for 1–2 weeks [110]. The fundamental role of the inflammation phase is to protect the wounds against infections and to prepare the wound for the latter two stages [111–113]. Multi-omics approaches, such as single-cell RNA sequencing, have provided a better understanding of the diversity of immune cell types and their role in modulating inflammation. Macrophage polarization, which plays a critical role in inflammation resolution, has been extensively studied using integrated omics technologies, shedding light on the cytokine signaling and immune response regulation [85,86,91].

In the early inflammatory phase, the expression of adhesion molecules is increased in the endothelial cells, leading to the recruitment of mast cells, lymphocytes, neutrophils, and monocytes. Metabolomics studies have shown that during this phase, inflammatory cells alter their metabolic pathways to support their pro-inflammatory functions. This metabolic shift, observed through the integration of metabolomic and transcriptomic data, is essential for immune cell function and tissue [114,115]. Keratinocytes, degranulating platelets, macrophages, and endothelial cells release pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1, which collectively facilitate the recruitment of leukocytes [116,117]. To eliminate the chances of pathogens at the wound site, the differentiation of monocytes into pro-inflammatory M1 macrophages is facilitated at the early stage of the inflammatory phase, leading to the amplification of more pro-inflammatory cytokines [118,119].

Keratinocytes play a crucial role in initiating the inflammatory phase by expressing various Toll-like receptors (TLRs) such as TLR-3, TLR-4, and TLR-9, which become upregulated in acute wounds [120,121]. These TLRs, situated on the surface of keratinocytes, recognize Damage-Associated Molecular Patterns (DAMPs) released from injured cells, triggering the activation of the receptors and subsequent expression of cytokines (interferon-β (IFN-β), TNF-α, IL-8, IL-18, and IL-36γ) and chemokines (C–C motif ligand (CCL) 20 and CCL27) [120]. Specifically, TLR-4 activates the TLR4/p38 and JNK MAPK signaling pathways, leading to the production of inflammatory cytokines [121]. In the late stage of the inflammatory phase, a range of pro-angiogenic growth factors, including fibroblast growth factor 2 (FGF2), platelet-derived growth factor (PDGF), and vascular endothelial growth factor (VEGF), are released by the anti-inflammatory M2 phenotype of macrophages [122,123].

3.2.3. *Proliferation phase*

A smooth transition from the inflammation phase to the proliferation phase is important as studies suggest that a delay in the transition of the inflammatory phase can lead to adverse effects on the rest of the phases [124,125]. The proliferation phase commences approximately three days after the wound can last for 2–3 weeks. It is comprised of 3 key steps, including re-epithelialization, angiogenesis, and granulation tissue formation [126]. In the re-epithelialization phase of proliferation, keratinocytes and M2 macrophages release TGF-β and EGF, which help the proliferation [127]. After migration to the wound site, keratinocytes adopt their normal phenotype after firmly attaching to the membrane [127]. Omics studies during this phase have identified the upregulation

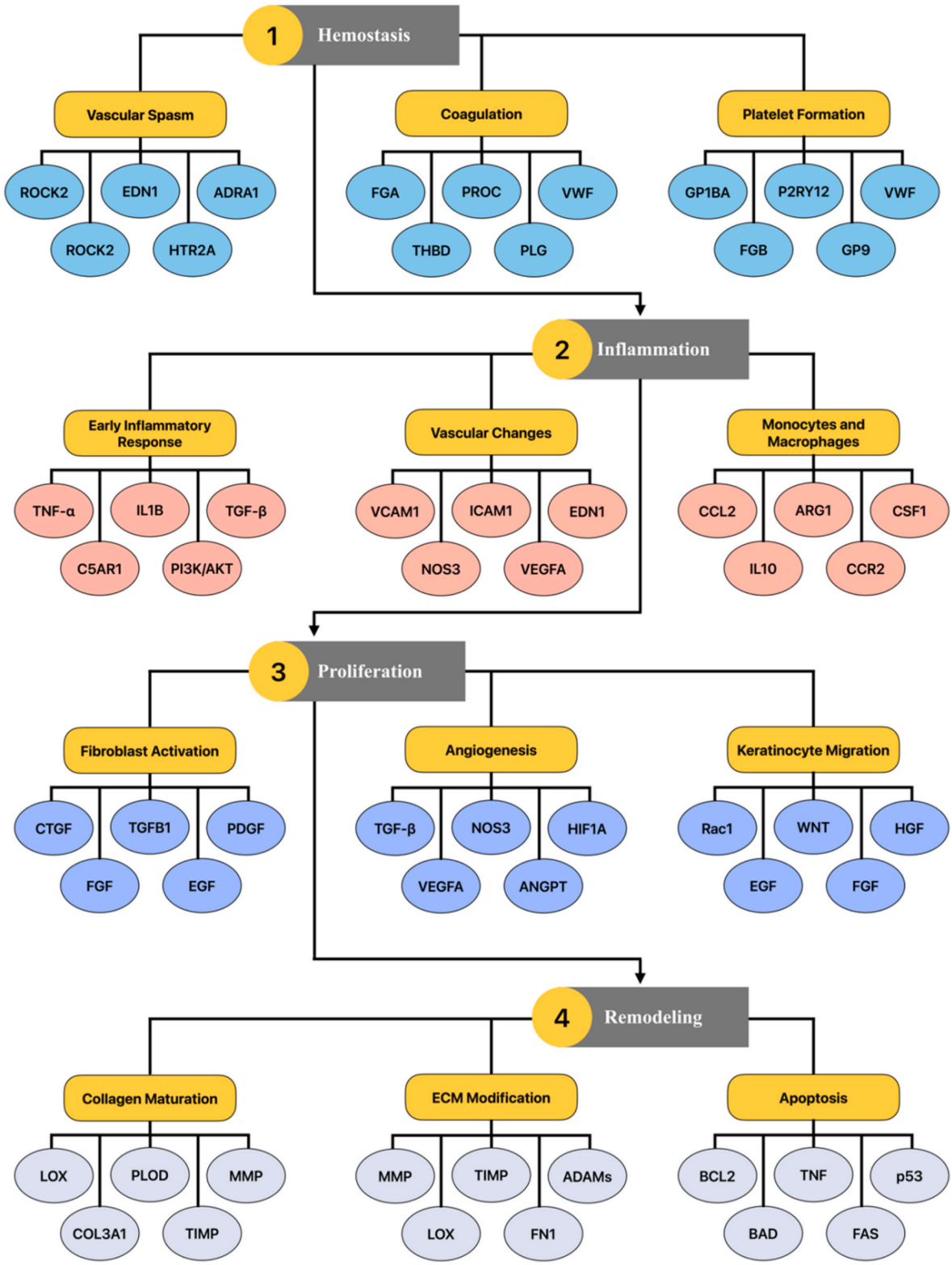

Fig. 4. A graphical representation of several key genes expressed at different phases of wound healing. These genes are reported to have important roles in the regulation and transition of these phases.

of growth factors, such as TGF-β and VEGF, that promote angiogenesis and fibroblast migration, critical for tissue regeneration. Additionally, metabolomic analyses have shown the involvement of specific metabolites in supporting the increased energy demands of proliferating cells during wound healing [127].

Angiogenesis refers to the neovascularization in which new blood vessels grow from the existing ones. As Heun et al. (2017) reported, platelets release a combination of TGF-β, PDGF, and FGF during the angiogenesis phase of wound healing [128]. Hypoxia triggers the release of hypoxia-inducible factor-1 (HIF-1) and vascular endothelial growth factor (VEGF). These transcription factors and growth factors collectively stimulate the expression of various angiogenic genes (Fig. 3),

fostering neovascularization and the restoration of damaged blood vessels at the wound site [129]. As the process of angiogenesis progresses, the wound site develops a dense vascular network, boasting a significantly higher density of capillaries compared to normal tissue, as documented by DiPietro [130].

After the migration and proliferation of fibroblasts, a loose matrix of ECM proteins, collagen, and fibronectin is released by these fibroblasts. When this vascularized fibrous tissue replaces the hemostatic clot, it is called granulation tissue [131,132]. After the formation of granulation tissue, fibroblasts transform into α-smooth muscle actin-expressing myofibroblasts, a process initiated by mechanical tension, the focal adhesion protein Hic-5, and activated TGF-β, as elucidated by Hinz et al. and Varney et al. [133,134]. The myofibroblasts play a pivotal role in wound contraction, which typically begins around 7 days post-injury. Ultimately, this process results in the filling of the wound gap with granulation tissue overlaid by surface epithelium, marking the preparation for the final phase, remodeling [135].

3.2.4. Remodeling phase

Remodeling is the last phase of wound healing that can last for a few months to over a year, depending on the wound. The changes, such as ECM turnover, vascularization, contraction, and decline in cellular proliferation, lead to remodeling, which paves the way for structural and functional restoration of the tissue [136–138]. At this stage, the integration of proteomics, metabolomics, and transcriptomics has provided an excellent understanding of the extracellular matrix (ECM) remodeling processes and how collagen maturation occurs. Studies have shown that MMPs and other ECM proteins are key players in the remodeling of scar tissue, and their expression is tightly regulated during this phase [137,90].

During remodeling, TGF-β1 produces collagen type I and III in fibroblasts, and thus a stronger collagenous matrix replaces the fibronectin-rich matrix [139]. The crosslinking, which stabilizes and facilitates the structural modifications, is induced by lysyl oxidases and transglutaminases [140–143]. A variety of extracellular endopeptidases in the matrix metalloproteinases (MMPs) help replace type III collagen with type I collagen [144–150].

The quantity of newly formed blood vessels decreases, along with a reduction in blood flow. This results in the establishment of a mature environment devoid of blood vessels and cellular activity. Despite healing, the restored skin typically only reaches approximately 80 % of its original tensile strength [151–154].

4. Advances in multi-omics technologies

Following the publication of the full human genome, research related to macro and micro molecules witnessed a significant transformation in the biomedical field [155]. The development and crossover applications of various high-throughput screening technologies with large-scale data-rich biology have led to the introduction of multi-omics or integrative omics. Several omics-based technologies have been playing a key role in exploring the genetics, epigenetics, and molecular basis of various diseases by exploiting the micro and macromolecules such as protein, DNA, RNA, and metabolites [156,157]. By combining data from these different omics layers, researchers can obtain a holistic view of the molecular and cellular mechanisms that regulate wound healing.

While each omic layer, such as genomics, transcriptomics, proteomics, and metabolomics offers individual insights, the integration of multiple omics technologies provides a more nuanced and comprehensive view of the biological processes involved in tissue repair. For example, metabolomics helps in assessing the metabolic changes that occur during tissue repair, such as increased glycolysis and oxidative stress, which can be further elucidated when metabolomic data is integrated with transcriptomic and proteomic findings [27,58]. The joint analysis of these omics layers allows for a more accurate mapping of the complex interactions between genes, proteins, and metabolites during wound healing. By integrating proteomics, it can be identified which proteins are being produced in response to gene expression and their role in the cellular repair process [27,83]. Moreover, this integration allows for the identification of novel biomarkers that are relevant at multiple levels-genetic, transcriptomic, proteomic, and metabolic. Multi-omics approaches also enable the discovery of new therapeutic targets by providing insights into how signaling pathways, metabolic networks, and protein interactions coalesce to regulate tissue regeneration [155].

Multi-omics studies have helped identify metabolic pathways involved in inflammation resolution, providing potential targets for therapeutic intervention [52–54]. A study by Mascharak et al. (2022) investigated the molecular events driving skin wound cells toward scarring or regenerative fates [18]. By using a multi-omics approach, they performed single-cell RNA sequencing to capture transcriptional profiles, timsTOF proteomics to analyze protein expression, and extracellular matrix ultrastructural analysis to assess tissue-level changes. Through the integration of these data, they identified distinct molecular trajectories of fibrotic and regenerative healing. The study revealed that inhibiting YAP mechanotransduction, a key signaling pathway, triggered regenerative repair processes in fibroblasts by activating Trps1 and Wnt signaling.

Another study used single-cell RNA sequencing (RNA-seq) and ATAC sequencing (ATAC-seq) to investigate the early wound response in the mouse corneal epithelium. By integrating these omics layers, the researchers were able to capture both transcriptional and epigenetic changes during the healing process [158]. They found that early wound healing led to a reduction in cell type-specific genes and an increase in common transcriptional responses. Additionally, chromatin accessibility changed significantly across all epithelial cell types, with wound-induced open regions showing enrichment for Fosl1/AP-1 binding sites. However, the study also revealed that only a small subset of wound-induced genes showed a high correlation with chromatin accessibility, highlighting the complexity of gene regulation during healing. This multi-omic approach provided a more detailed landscape of wound response, demonstrating how transcriptomic and epigenetic data can be integrated to improve our understanding of tissue repair mechanisms [158].

Another study by Kim et al. (2025) [19] used a high-resolution spatial multi-omics method, integrating spatial transcriptomics and single-cell RNA sequencing, to investigate fibroblast populations during skin wound healing. They identified nine genes potentially involved in inflammation-related scarring, including integrin beta-like 1 (Itgbl1), which was found to be crucial for granulation tissue formation and fibrogenesis. They also detected a minority population of Acta2high-expressing myofibroblasts that contributed to scarring, alongside Itgbl1 expression. The study revealed that IL-1β signaling inhibited Itgbl1 expression in TGF-β1-treated fibroblasts, showing how inflammatory signals regulate fibroblast activity. By integrating spatial transcriptomics and scRNA-Seq, the study provided new insights into fibroblast–inflammatory cell interactions, offering a better understanding of the mechanisms driving wound scarring [19].

Groten et al. (2023) [27] used a multi-omics approach to dissect the molecular mechanisms of endothelial cell (EC) inflammatory responses. They applied an unbiased cytokine library and found that TNFα and IFNγ induced the most significant EC response, resulting in distinct proteomic inflammatory signatures. Notably, combining TNFα and IFNγ stimulation created an additional synergistic inflammatory signature. The study integrated phospho-proteomics, transcriptomics, and secretomics to investigate these inflammatory states, revealing a wide range of altered immune-modulating processes, such as complement proteins, MHC complexes, and cytokines. The synergy between TNFα and IFNγ led to the cooperative activation of transcript induction, illustrating the complexity of endothelial inflammation [27].

A multi-omics investigation by Zeng et al. (2024) [71] explored the proteomic and metabolomic changes in chronic wound (CW) tissue from

13 non-diabetic patients. The study identified 82 differentially expressed proteins (DEPs) and 214 differentially expressed metabolites (DEMs), revealing significant alterations in wound tissue compared to the surrounding tissue. The DEPs were primarily enriched in focal adhesion (FA), extracellular matrix–receptor interaction (ERI), and PI3K-Akt signaling (PA) pathways, which are key in cellular interactions and survival. On the metabolomic side, DEMs were enriched in pathways related to amino sugar and nucleotide sugar metabolism, which play a critical role in cell wall biosynthesis and tissue remodeling. Correlation analysis uncovered that PA signaling, along with its associated pathways, co-enriched several DEPs and DEMs, suggesting a close interplay between these molecular pathways in the wound healing process. Notably, FBLN1, FBLN5, and EFEMP1 proteins were found to be elevated in wound tissue, which may impair vascular and skin cell proliferation, degrade the extracellular matrix, and contribute to the pathogenesis of chronic wounds [71].

These studies show that multi-omics approaches provide a more comprehensive understanding of the molecular mechanisms involved in tissue repair and regeneration. By integrating genomics, transcriptomics, proteomics, and metabolomics, researchers can uncover the complex interactions between genes, proteins, and metabolites that regulate wound healing. This integration allows for a more accurate mapping of the biological processes driving tissue regeneration and scarring, revealing critical insights into inflammatory responses, signaling pathways, and cellular interactions. Moreover, multi-omics technologies help identify novel biomarkers and therapeutic targets, ultimately contributing to more effective treatments for chronic wounds and improving our ability to modulate tissue repair processes.

4.1. Proteomics

In the field of biomedicine, a range of advanced and high-throughput technologies have been used to unravel remarkable discoveries in therapeutic interventions, disease diagnosis, and drug discovery. Proteomics, consisting of expression, structural, and functional proteomics, plays a pivotal role in understanding the complexities of biological systems. Employing various advanced techniques such as polyacrylamide gel electrophoresis, mass spectrometry analysis, NMR spectroscopy, protein microarray, X-ray crystallography, and Edman sequencing, proteomics enables comprehensive exploration of proteins and their functions [158–163].

A study by Liu et al. (2023) employed multi-omics analysis to elucidate the mechanism of a herbal extract mixture promoting diabetic wound healing in rats. The study utilized ultra-high-performance liquid chromatography-quadrupole-exactive high-resolution mass spectrometry (UHPLC-QE-MS) to identify the chemical composition of the herbal extract and integrated proteomic and transcriptomic data to uncover the molecular pathways involved in wound healing [83]. Another study investigated novel wound healing pathways in diabetic foot ulcers (DFU) using proteomics and network pharmacology. It identified 509 differentially expressed proteins (DEPs) in DFU tissues and analyzed associated pathways using GO and KEGG. Key targets, including MMP9, FABP5, and ITGAM, were found to play crucial roles in DFU-related signaling pathways. The research also highlighted *Staphylococcus aureus* infection and leukocyte transendothelial migration as significant pathways in DFU. The findings provide new insights into the molecular mechanisms underlying DFU and may inform future therapeutic strategies [164].

Proteomics provides a more nuanced comprehension of an organism's structure and function compared to genomics, notwithstanding its heightened intricacy. It examines protein structures, functions, expressions, and interactions in a particular cell, tissue, or body. This superiority stems from the dynamic nature of protein expression, which evolves over time and in response to environmental cues [165]. Manchanda et al. combined transcriptomics and metabolomics to explore metabolic changes in acute and chronic wounds. It found upregulation of glycolysis, the tricarboxylic acid cycle, glutaminolysis, and β-oxidation during wound healing. Modulating glycolysis and glutaminolysis had a significantly greater impact on wound healing than manipulating oxidative phosphorylation and β-oxidation [166].

Relying solely on genomic studies proves insufficient for acquiring diverse sets of information. For instance, unraveling the mechanisms underlying disease progression, aging, and the impacts of environmental stimuli remains unattainable solely through genome investigations. Additionally, the identification of drug targets and the characterization of protein modifications necessitate scrutiny of proteins [167–172]. A study investigated the molecular differences between normal and non-healing human skin wounds by using proteomic analysis of wound exudates. The research identified 149 proteins, revealing that healing wounds contained mediators characteristic of tissue formation, while nonhealing wounds exhibited proteins associated with persistent inflammation and tissue destruction. This comparative proteome analysis provided an explanation for the molecular pathophysiology of chronic wounds and identified potential biomarkers for better understanding and monitoring disease progression [173].

In the last 20 years, the approaches through which proteomics has been studied have changed. For instance, the time-consuming gel-based proteomics and immunoassays have been replaced by more robust techniques such as liquid chromatography-tandem mass spectrometry (LC-MS/MS)-based proteomics [174]. As shown in Fig. 5, these approaches could be top-down, bottom-up, and middle-down proteomics. In top-down proteomics, the separation of proteins is carried out while keeping the proteins intact. Subsequently, the analysis is performed using LC-MS/MS, and the proteoforms are quantified for studying post-translational modifications, splicing, and other genetic variations at the protein level [175–179]. The bottom-up proteomics approach is one of the most widely used options in which the proteins are digested into thousands of peptides using enzymatic proteolysis procedures. The resulting peptides are then separated and analyzed [180–184].

In tissue repair and wound healing, proteomics can play a very important role in identifying key biomarkers, regulatory processes, protein integrations, and post-translational modifications in the process of tissue repair. In a study, Aiba-Kojima et al. studied proteomics in post-surgical wounds. They concluded that the expression of TGF-beta, EGF, PDGF, and VEGF was significantly higher in platelet-rich plasma than in platelet-poor plasma [185]. In another study, it was revealed that the healing of leg ulcers did not change the protein level of IL-6, while IL-1 significantly changed as the wound healed [186]. Lobman et al. conducted a study in which they used gelatin zymography in diabetic patients with chronic wounds and concluded that Pro-MMP-2 was three times higher, while the MMP-2 active form was 6 times higher in chronic wounds [187].

Immunohistochemistry is a technique in which the protein in a cell is labeled with antibodies against specific antigens. This technique helps researchers to locate the protein in wounded tissue during the healing phases. In a study, Galkowski et al. studied the tissues of a diabetic foot patient and analyzed the protein expressions of IL-10, EGF, TGF-beta, CXCR1, IL-8, and MCP-1 in the isolated keratinocytes. They found increased expression of GM-CSF, TGF-beta1, and EGF in Keratinocytes isolated from diabetic foot [188]. Stojadinovic and colleagues conducted a comparative analysis involving normal skin samples from reduction mammoplasty, debrided tissue, and punch biopsies. They observed the presence of C-myc and beta-catenin in the nuclei of cells located at the non-healing edge of chronic wounds, contrasting with the acute wound edges. The researchers posited that this observation might signify delayed healing processes [189]. This finding underscores the importance of molecular markers in discerning between different stages of wound healing, offering valuable insights into the underlying mechanisms of tissue repair. Such discoveries not only enhance our understanding of wound biology but also hold promise for the development of targeted therapeutic interventions to promote effective wound healing.

In conclusion, proteomics is a vital tool for unraveling the complex

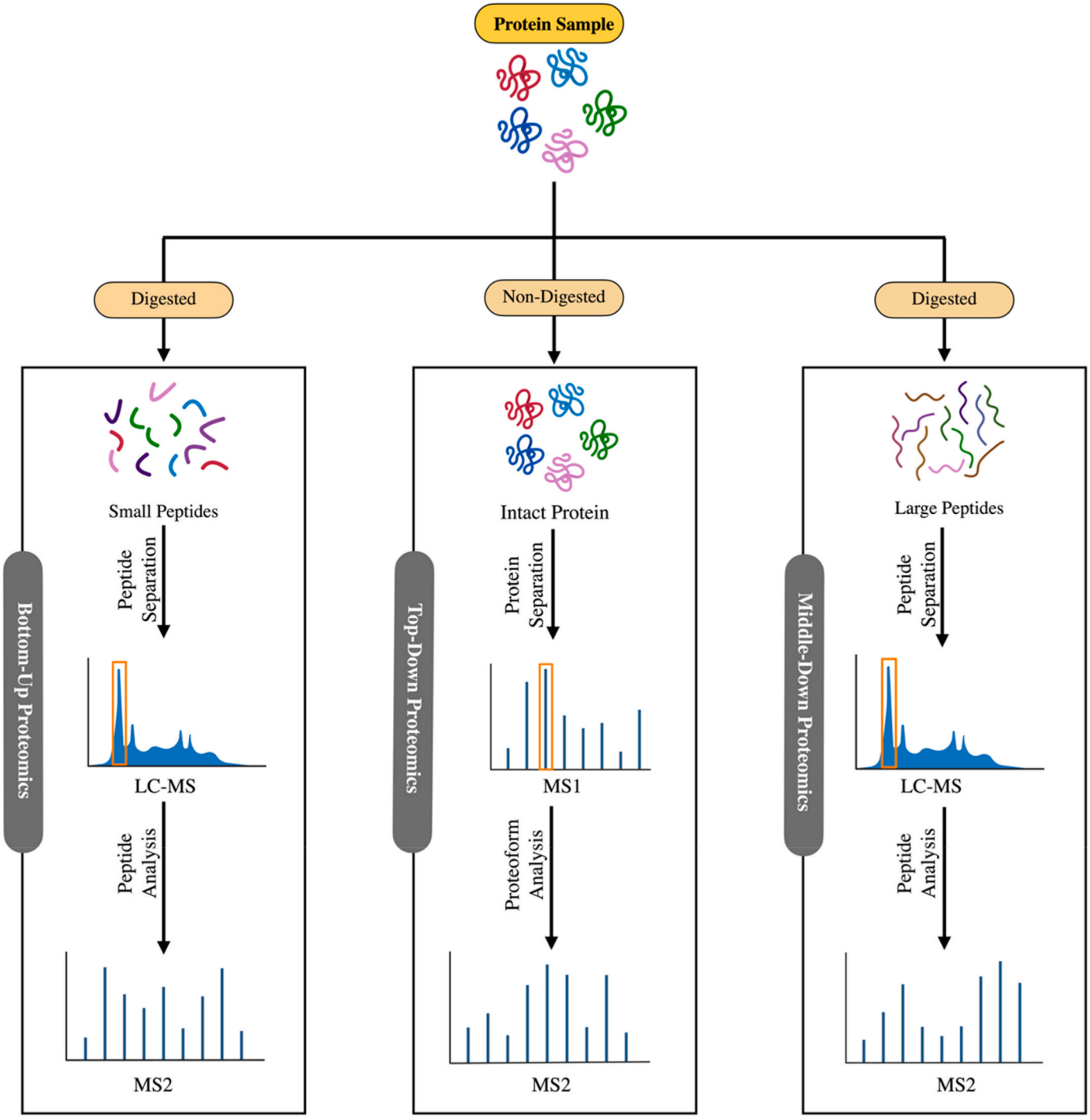

Fig. 5. A visual depiction illustrating various essential types of protein digestion, protein separations, and analysis.

biological mechanisms involved in tissue repair. By identifying key proteins and their modifications, it provides a deeper understanding of the molecular changes during wound healing and the development of chronic wounds. The integration of proteomics with other omics technologies, such as transcriptomics and metabolomics, enhances our ability to identify novel therapeutic targets and biomarkers. As proteomics technologies continue to evolve, they hold significant promise for improving wound healing outcomes and developing targeted treatments for various tissue repair challenges.

4.2. Transcriptomics

Transcriptomics, such as studies related to mRNA, RNA, micro-RNA, and non-coding RNA, plays an important role in the understanding of various transitions and molecular mechanisms that are involved during tissue repair. For instance, the expression profiles of various genes during the different phases of wound repair can be instrumental in identifying the expression trends in various pathways [190,191]. In a study, Zhu et al. studied gene expression profiles in 37 biopsies obtained from patients with split-thickness skin grafts. In their results, they identified 85 upregulated and 164 downregulated genes in the inflammatory and proliferation phases. In the remodeling phase, they

identified a total of 170 differentially expressed genes [192].

Transcriptomics allows for the identification of gene expression changes during tissue repair, offering critical understanding into how genes are regulated in response to injury. For example, a study by Sherrill et al. explored the effects of ablative fractional laser treatment on skin rejuvenation using transcriptomics. Skin biopsies from 14 women were collected at multiple time points before and after treatment. The analysis revealed significant changes in gene expression, particularly in inflammatory, epidermal, and dermal genes, with dermal remodeling observed at later stages. The study showed that fractional laser treatment reversed age-related gene expression changes and that multiple treatments further enhanced dermal remodeling, highlighting the need for repeated treatments to achieve optimal skin rejuvenation [193].

St. Laurent III et al. used cutting-edge single-molecule sequencing (SMS) technology for RNA (RNA-seq) to generate a detailed map of the mouse transcriptome throughout the process of wound healing. This comprehensive map was then utilized to delineate alterations induced by treatment with Tr14. RNA-seq-based transcript profiling offers an advanced and unbiased perspective of the transcriptome, enabling the identification of potential networks for assessing the effects of drugs and biological targets [194]. In their results, they not only reported differential expression but also varied influx of several cells in response to a wound. They postulated that lymphocytes and macrophages were modulating the expression of genes, cell death, and paracrine signaling in different phases of wound repair [194]. This highlights how RNA-seq allows researchers to observe the temporal and spatial distribution of gene expression during wound healing, furthering our understanding of the immune system's contribution to tissue repair.

Sass et al., conducted a comprehensive study using different organisms such as mice, rats, and human beings and different organs including the liver, skin, spinal cord, heart, and bones. In their results, the transcriptomics observed revealed less consistency in hemostasis, inflammation, and remodeling phases. They also observed the differential regulation of various transcriptomics in all phases of wound healing and organs [195]. Some of the key transcriptomics they reported included ANXA1, CCL2, TIMP1, SERPINA3, CD44, ICAM1, LGALS3, SPP1, ANXA2 and TIMP1 [190]. The transcriptomics analysis performed by Hoffmann et al. also reported that SERPINA3 demonstration could improve chronic wounds in diabetic mice [196]. It is also reported that the CCL2 deletion leads to reduced angiogenesis and impaired re-epithelisation in the skin repair process [197]. These studies emphasize the paramount importance of transcriptomics in unraveling the complexities of tissue repair and wound healing. By delving into the dynamic changes in gene expression patterns during the healing process, transcriptomic analyses provide invaluable insights into the intricate molecular mechanisms underlying tissue regeneration.

In conclusion, transcriptomics has become an indispensable tool in understanding the molecular dynamics of tissue repair. By examining gene expression during different stages of wound healing it reveals the key regulatory processes that govern tissue regeneration and the immune response. The application of advanced techniques like RNA-seq has enabled researchers to map gene expression profiles and identify critical biomarkers involved in tissue repair. Studies have highlighted the significant roles of genes such as CCL2, SERPINA3, and TIMP1 in regulating inflammation, angiogenesis, and ECM remodeling.

4.3. Metabolomics

Metabolomics is one of the fields that is rapidly evolving with strong analytical techniques and procedures in different biomedical conditions [198]. It refers to the collection or a fraction of metabolites present in a cell, tissue, organ, or organism [199]. Metabolites are biomolecules with a low molecular weight (<1500 Da) that are instrumental in metabolic reactions. They are produced as downstream products during gene transcriptions and are highly dependent on internal physiological conditions such as the process of tissue repair [200,201]. Recent advancements in metabolomics have enabled a deeper understanding of how metabolic shifts during tissue repair are crucial for healing. For example, mass spectrometry (MS), liquid chromatography (LC), imaging mass spectrometry (IMS), and metabolic flux analysis (MFA) are now widely used in the study of tissue repair and regeneration, providing high-throughput and detailed analyses of metabolic pathways [202–207].

Tissue repair and regeneration is a complex and metabolically demanding process that needs a continuous balance of phospholipids, adenosine triphosphate, and other intracellular metabolites [208]. In the skin, metabolites can be produced by various cellular resources such as fibroblasts, keratinocytes, and melanocytes, and therefore may serve as important biomarkers for therapeutic interventions, diagnosis, and prognosis [209]. For instance, amino acids play an important role in water retention and acid-base balance, which consequently impacts tissue repair and wound healing [210]. Moraes et al. studied the skin cells and reported toluene and 4-Hydroxy-4-methylpentan-2-one as biomarkers. Similarly, another study investigated serum metabolites in patients with psoriasis and reported several biomarkers for wound management [211,212].

In a study, Ashrafi et al. profiled the skin microbiome and metabolome to understand wound healing. Eleven volunteers were analyzed at five time points, with metabolites collected and microbial communities sequenced. The study found significant changes in the wound metabolome over time, identifying key metabolites linked to healing. A reciprocal relationship between *Staphylococcus* and *Propionibacterium* was observed, with correlations to collagen. The findings suggested that the wound metabolome and microbiome could serve as novel biomarkers for wound healing, though further studies are needed to confirm these results [213]. Similarly, another study used 1H NMR spectroscopy and multivariate data analysis to profile the metabolites of oil palm leaflets (OPLs) and assess their antioxidant and wound healing properties. Four solvent extracts were analyzed, with polar extracts showing higher phytochemical content. Compounds like (+)-catechin and (−)-epicatechin were strongly correlated with antioxidant activities and wound healing, demonstrating the potential of OPLs as natural agents for promoting wound healing [214].

In a recent study, Hellmann et al. found omega-3 fatty acid-based D-series resolvins to be associated with tissue repair and regeneration in animal models, which was later proposed as a topical intervention [215]. Various other studies have also explored the impact of diabetes on the healing process of skin wounds. Notably, Sood and colleagues found that diabetic skin exhibits significant impairments in collagen synthesis, nitric oxide production, inflammation, and fibroblast proliferation [216]. Furthermore, the metabolic influences of a Chinese herbal remedy, the Huiyang Shengji formula, on non-healing wounds in diabetic skin were investigated using a rat model of diabetic skin ulcers. This investigation revealed potential enhancements in glucose and branched-chain amino acid metabolism, alongside improved antioxidant and pro-angiogenic properties within diabetes-related wounds [217].

Metabolomics plays a critical role in understanding the metabolic changes involved in tissue repair. By profiling metabolites, it helps reveal how metabolic pathways regulate wound healing, inflammation, and tissue remodeling. Studies have shown that metabolites such as amino acids, fatty acids, and glycolytic intermediates are essential for tissue repair processes. As metabolomic technologies continue to advance, they provide valuable opportunities for identifying biomarkers and developing targeted therapies to enhance wound healing, particularly in conditions like diabetes, where metabolic dysfunction hampers recovery.

4.4. Epigenomics and metagenomics

Both epigenomics and metagenomics play important roles in the

understanding of molecular mechanisms implicated in tissue repair and wound regeneration. Epigenetics refers to the alteration of DNA and chromatin without changing the sequence of DNA or proteins. At the same time, metagenomics is the process of directly analyzing the genetics of genomes in an environment [218,219]. Over the past couple of decades, the methodologies and techniques for exploring epigenomics and metagenomics have undergone significant improvements. These techniques have been employed in studies to detect DNA and chromatin at various dimensions from single loci to genome-wide sequencing [220].

Epigenomics is particularly important in tissue repair because it helps researchers understand how gene expression is regulated during wound healing through modifications to chromatin, DNA, and histones. For instance, an epigenetics study by Ludwig-Slomczynska et al. [221] investigated the effect of negative pressure wound therapy (NPWT) on DNA methylation in patients with neuropathic diabetic foot ulcers (DFUs). The study analyzed tissue samples before and after treatment, revealing significant changes in DNA methylation patterns, particularly on chromosomes 6 and 20, which are linked to DNA repair and autocrine signaling. The results suggested that NPWT may influence DFUs through epigenetic modifications, specifically inhibiting complement system activation [221].

The advanced technologies that have been used in epigenomics studies include chromatin functional assays, high-throughput sequencing technologies, high-quality antibodies, and various imaging tools [217]. On the other hand, advanced technologies such as next-generation sequencing, shotgun sequencing, and third-generation sequencing have been employed to study metagenomics [222]. Advanced sequencing technologies of the third generation enable extended sequence reads, presenting promising avenues for investigating various base modifications, including 5 mC, 6 mA, and 4 mC, without the need for bisulfite treatment [223]. The specific antibody-directed chromatin immunoprecipitation (ChIP) assay stands as a particularly valuable technique for examining DNA-protein interactions, enabling the analysis of chromatin structure surrounding a particular DNA sequence [224].

In treating wounds on extremities, the identification of microbial bioburden is conventionally conducted through standard bacterial culture methods. However, these culture-based analyses often underestimate both the diversity and burden of microbes present. Research on chronic wounds has demonstrated that a thorough comprehension of bioburden is paramount for accurately interpreting healing responses [225–227]. Metagenomic sequencing is a reliable method that can comprehensively analyze microbial composition, with a direct amplicon-based approach using 16S rRNA gene regions of bacteria [228].

In a study, microarray profiling was carried out in non-healing wounds and reported enrichment of inflammatory response and fibrogenetic pathways [229], which corresponded to the findings of disorganized ECM, chronic inflammation, and fibrosis [230–232]. Radiation-induced injury is typically characterized by various endpoints, including telangiectasia, atrophy, and notably, fibrosis, which not only compromises function but also diminishes quality of life. Genome-wide association studies (GWAS) have identified polymorphisms in TGFB1, as well as XRCC1, which encodes a protein involved in DNA base excision repair, as factors associated with an increased risk of radiation-induced fibrosis [233,234]. Numerous genome-wide association studies (GWAS) have been undertaken in patients with non-alcoholic fatty liver disease (NAFLD). One such study conducted in a Japanese cohort identified a single-nucleotide polymorphism (SNP) in PNPLA3 as significantly associated with NAFLD [235].

Understanding the genetic factors that influence tissue repair and wound healing holds significant implications for the advancement of therapeutic strategies. Recent studies have underscored the importance of specific mutations in genes of the TGF-β family in altering the dynamics of wound healing. For instance, there is a growing body of evidence linking certain gene mutations to an increased risk of developing keloid formation and hypertrophic wound scarring during tissue repair [236,237].

Epigenetic regulatory mechanisms play a vital role in maintaining skin homeostasis and are integral to the processes of wound healing. Within the nucleus, gene expression is orchestrated through distinct chromatin structural states and their remodeling, facilitated by epigenetic mechanisms. These include DNA methylation and hydroxymethylation, post-translational histone modifications, ATP-dependent chromatin remodeling, higher-order chromatin structure, and 3D genome organization. Such mechanisms ensure precise regulation of gene expression patterns critical for skin health and effective wound repair [238].

In recent years, epigenetic regulators have emerged as crucial components capable of transiently rewiring the cell's transcriptional program to facilitate the ongoing regeneration of the mouse epidermis [239,240]. This mode of gene regulation operates at multiple levels, encompassing histone and DNA modifications, chromatin remodeling, and the activity of various subtypes of RNA species, including non-coding RNAs and microRNAs (miRNAs) [241,242]. These epigenetic mechanisms can profoundly influence the transcriptional landscape of the cell, playing a pivotal role in the transient activation or repression of approximately 1000 genes necessary for wound closure [243].

4.5. *Integrative omics in wound repair and regeneration*

Integrative omics is transforming the understanding of wound repair and regeneration by offering a multi-dimensional view of the complex biological processes involved in healing. By combining genomics, transcriptomics, proteomics, metabolomics, and microbiomics, researchers can investigate the molecular and cellular events that regulate tissue repair, inflammation, and regeneration [244].

Genomics provides insights into genetic predispositions and mutations that may impair healing [245], while transcriptomics uncovers the gene expression changes during different phases of wound healing [246]. Proteomics identifies critical proteins involved in cell signaling, extracellular matrix formation, and tissue remodeling, while metabolomics reveals metabolic shifts that support cell proliferation and migration. Microbiomics further elucidates the role of microbial communities in wound healing, highlighting how the presence of certain bacteria can either promote or hinder the regeneration process [247].

The integration of these diverse omics technologies has led to significant advancements in wound repair research. For instance, Wilkinson et al. investigated the role of endogenous metals in wound healing using ICP-MS and RNA sequencing in mice. It found elevated levels of calcium, magnesium, iron, copper, and manganese at 7 days post-wounding, with additional increases in metals at 14 days. Metal-regulated genes were enriched in wound-induced pathways, and specific metals were linked to distinct healing processes. The study also identified TNF as a potential regulator in calcium-induced epidermal differentiation, highlighting the important roles metals play in wound repair and suggesting avenues for further research [248].

Ashrafi et al. [213] conducted an exploratory temporal profiling study to clarify the wound healing process by analyzing the skin microbiome and metabolome using non-invasive methods. Through gas chromatography-mass spectrometry (GC–MS) for metabolites and 16sRNA sequencing for microbiome analysis, they revealed the dynamic and temporal nature of the metabolome and wound microbiome. These findings provide insights into identifying a potential signature of the microbiome and metabolome across different phases of skin healing, offering the possibility of detecting biomarkers associated with various stages of tissue repair. This approach exemplifies the power of integrative omics in understanding complex biological processes like wound healing. Similarly, in another study, integrative omics was used to analyze microRNAs (miRs) in human tissue samples from acute wounds

and chronic venous ulcers (VUs). They identified 17 miRs with abnormal expression in VUs, including miR-34a, miR-424, and miR-516, which suppressed keratinocyte migration and promoted inflammation. These findings suggest that targeting specific miRs could offer new therapeutic strategies to enhance wound healing in chronic wounds [249].

In a recent study, the mechanisms behind age-related differences in wound healing using extracellular matrix (ECM) scaffold membranes were explored through an integrated approach combining single-cell RNA sequencing (scRNA-Seq) with spatial transcriptomics. The study identified six distinct macrophage and lymphocyte groups surrounding the ECM scaffolds, revealing that the dysfunction of Spp1+ macrophages in aged mice impaired the type II immune response, thereby hindering the activation of epidermal cells and fibroblasts. This research underscores the importance of precision-based biomaterials tailored for aged individuals, offering valuable insights into the application of integrative omics for improving wound healing strategies [250]. The study exemplifies the potential of omics technologies to uncover the complex biological interactions in tissue repair, paving the way for more effective, personalized therapeutic approaches in regenerative medicine.

5. Omics-based diagnosis and biomarker discovery in tissue repair and regeneration

A biomarker refers to a substance or molecule that is quantifiable and helps assess a condition as an indicator of a normal or abnormal physiological condition [251]. In the realm of tissue repair and wound regeneration, biomarker identification involves establishing a clinically relevant process followed by validation in patients or cell and animal models. A number of omics-based high-throughput approaches have been used to understand the mechanisms of tissue repair that may lead to the discovery of potential biomarkers [252–254].

In the process of tissue repair and wound healing, the important sources of specimens are normally wound fluid, serum, or tissue specimens. Wound fluids are normally collected to assess proteins and inflammation-associated cells [254,255]. Wound swabs are collected to assess the diversity of infections and study proteomics, such as specific proteases during wound healing. Wound tissue is normally employed in studying diagnostic evaluation, biomarker studies, and other micro-based quantitative and qualitative investigations. Blood and serum are used to identify spectrum biomarkers in the tissue repair process [256–258].

In a study, Stojadinovic et al. investigated wound healing in venous ulcers using omics, specifically microarray analysis, to identify gene expression changes at the nonhealing edges. The study found suppressed BMPR, GATA3, and ID2/ID4, along with activation of the Wnt pathway, indicated by increased β-catenin and c-myc expression. The downregulation of LRIG1 and absence of keratin 15 (K15) suggested depletion of epidermal stem cells (ESCs), contributing to the hyperproliferative, nonmigratory wound edges that hinder healing. These findings highlight potential biomarkers for assessing and targeting the dysfunction of ESCs in chronic wound healing [259].

The MMPs, or matrix metalloproteinase enzymes, along with their regulators, tissue inhibitors of matrix metalloproteinases (TIMPs), play a significant role in wound healing. Metalloproteinases encompass a group of endopeptidases that can be broadly categorized based on their primary catalytic substrate into collagenases, gelatinases, stromelysins, matrilysins, and membrane-type MMPs [260,261]. Clinical trials are currently investigating the use of quantitative assessments of MMPs as diagnostic biomarkers to predict wounds with poor healing potential. In one study, authors utilized wound fluid collected from pressure ulcers (PUs) to assess the MMP-9/MMP-1 ratio. They found that the average MMP-9/MMP-1 ratio decreased significantly in healing wounds and was notably lower at the time of collection in wounds that took longer than 36 days to heal. These findings suggest that the MMP-9/MMP-1 ratio may serve as a predictive biomarker for pressure ulcer healing [262]. Moreover, elevated levels of various cytokines and growth factors have been observed in the wound fluid of venous leg ulcers (VLUs) with impaired healing [263].

In another study, Harsha et al. investigated the role of A disintegrin and metalloprotease 12 (ADAM12) in wound healing and found it to be fivefold upregulated in the nonhealing edges of chronic wounds compared to healthy skin. Using transcriptomics, the study confirmed increased ADAM12 expression in chronic wounds. Experiments with ADAM12-deficient mice showed enhanced keratinocyte migration, suggesting that ADAM12 inhibits migration [264]. These findings indicate that ADAM12 may impair wound healing, and its inhibition could be a potential therapeutic approach for chronic wounds. Additionally, ADAM12's upregulation in chronic ulcers suggests it could serve as a valuable biomarker for diagnosing impaired wound healing and monitoring treatment efficacy.

Gazel and colleagues conducted a transcriptomic-based study in which they compared the transcriptomes obtained from human skin with other types of cells. By large oligonucleotide microarray technology, they identified genes with differential expression. Their results further revealed the presence of a large number of receptors and transcription factors that were instrumental in tissue repair and wound healing [265]. In another omics-based study, genes associated with tissue repair were studied using circulating proteomic signatures in fibrotic liver. They identified 20 upregulated proteins that are normally active in tissue repair and wound healing pathways. These proteins predominantly represent immune activation and tissue repair pathways, encompassing responses like the TNF response and aminopeptidase activity. Notably, there were associations between plasma peptides and factors such as visceral fat content and $CD4^+$ T-cell count [266].

Zhang et al. (2015) investigated the therapeutic potential of exosomes derived from human induced pluripotent stem cell-derived mesenchymal stem cells (hiPSC-MSCs) in cutaneous wound healing. Their research demonstrated that these exosomes facilitated wound closure by promoting collagen synthesis and angiogenesis. In vitro analyses revealed that hiPSC-MSC-exosomes enhanced the proliferation and migration of human dermal fibroblasts and human umbilical vein endothelial cells (HUVECs). Additionally, they increased the secretion of Type I and III collagen and elastin by fibroblasts and promoted capillary tube formation by HUVECs. Histological examination of wound sites in a rat model showed accelerated re-epithelialization, reduced scar formation, and improved collagen maturation following treatment with hiPSC-MSC-exosomes. These findings suggest that exosomes from hiPSC-MSCs can effectively promote cutaneous wound healing by enhancing both collagen synthesis and angiogenesis [267]. Similarly, Hédou et al. introduced Stabl, a machine learning method that identifies reliable biomarkers by integrating noise injection and a signal-to-noise threshold into predictive modeling. Evaluated on synthetic and clinical datasets, Stabl improved biomarker sparsity and reliability while maintaining predictive performance. It successfully identified biomarkers for labor onset, pre-term birth, and post-surgical infections, demonstrating its potential for clinical diagnostics and multi-omic integration [268].

A recent multi-omics study by Zeng et al. investigated non-diabetic wounds while combining proteomics and metabolomics. Their results revealed a total of 82 differentially expressed proteins, of which 38 were up-regulated and 44 were down-regulated. The study concluded FBLN1, EFEMP1, FBLN5, and EFEMP2 as potential biomarkers in tissue repair and wound regeneration phases [71,269]. In another multi-omic study, stojadinovic et al. investigated the molecular changes that take place during keratinocyte activation in tissue repair. They used Affymetrix chip technology in non-healing edges obtained from venous ulcers. In their results, they found biomarkers related to the differentiation and activation of keratinocytes. They reported the upregulation of differentiation-related markers such as transgultaminase 1 and involucrin. According to their results, the late differentiation markers such as filaggrin were downregulated in the tissue repair phase as compared to

normal tissues [270]. These studies highlight the pivotal contribution of multi-omics methodologies in pinpointing genes as biomarkers and diagnostics for tissue repair.

Biomarker discovery plays a critical role in the diagnosis, prognosis, and monitoring of tissue repair and regeneration. Omics technologies, such as proteomics, genomics, and metabolomics, provide a comprehensive view of the molecular processes involved in wound healing. However, current biomarker research is limited by several challenges, including the difficulty in validating biomarkers across diverse patient populations, inconsistencies in biomarker reproducibility, and the complexity of integrating data from multiple omics layers [271].

While proteomics, genomics, and metabolomics have each individually contributed to the identification of biomarkers like MMPs and TGF-β1 for wound healing, these biomarkers often need further validation in clinical settings to ensure their accuracy and relevance. Additionally, a lack of standardized protocols for biomarker discovery across studies can result in inconsistencies and prevent the widespread adoption of biomarkers for clinical use [272].

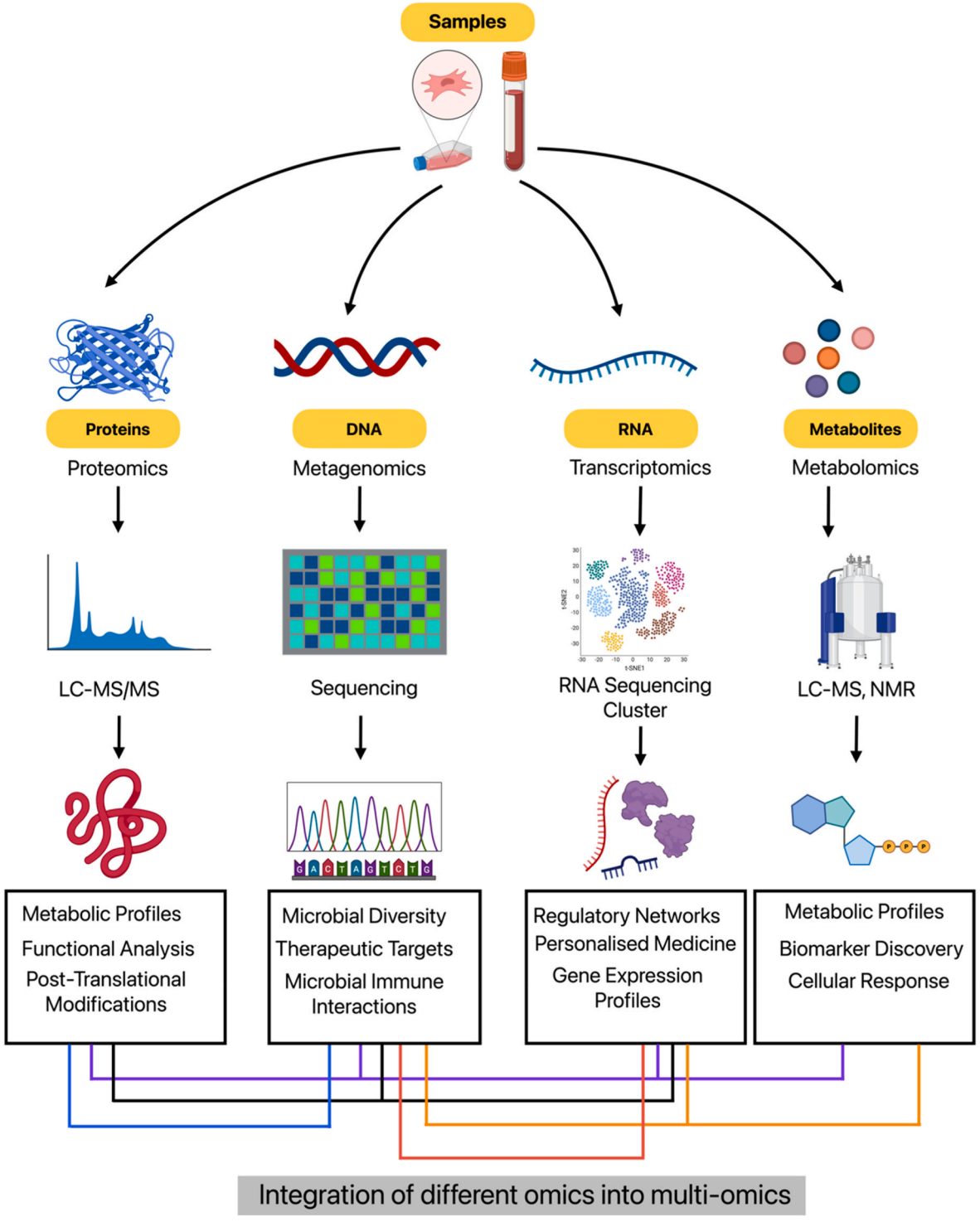

Fig. 6. Shows how individual omics such as proteomics, genomics, transcriptomics, and metabolomics could be integrated into multi-omics with a better understanding and outcome.

To overcome these limitations, future research should focus on enhancing biomarker identification through the integration of multi-omics approaches and the application of artificial intelligence (AI) and machine learning (ML) techniques. AI and ML can facilitate the processing and analysis of large, complex multi-omics datasets, enabling more accurate identification of biomarkers that predict tissue repair outcomes. In addition, AI-based predictive models could aid in developing personalized treatment strategies by integrating multi-omics data to tailor therapies to individual patient profiles [273].

6. Monitoring and therapeutic implications of multi-omics in tissue repair and regeneration

As technological interventions are on the rise, the world is witnessing a paradigm shift from "one-size-fits-all" strategies to more robust and multi-faceted approaches. Over time, the steady rise in high-throughput technologies has gradually led to the development of multi-omics approaches in which multiple biological layers are integrated for a range of applications in healthcare and precision medicine. The utilization of this unified approach is garnering attention across various diseases and health-related conditions, including cancer, metabolic, and cardiometabolic diseases [274,275]. Individual Omics have played a significant role in identifying biomarkers, facilitating diagnosis, and effective treatment modalities for various diseases [276,277]; however, the use of a single omics approach cannot capture the complexities and diverse molecular events in a specific disease or condition [277]. If the approach is integrative omics, such as combining proteomics with transcriptomics or metabolomics, it can capture the complexities that may entail an advanced understanding of the molecular interplay that takes place during a disease or medical condition [278] (Fig. 6).

Recent advancements in multi-omics have improved the monitoring of tissue repair processes. Foster et al. presented a multimodal-omics platform to study cell populations in complex tissue during wound healing. Using a stented wound model and Rainbow transgenic lines to track fibroblast fate, the study integrated single-cell chromatin landscapes and gene expression with spatial transcriptomics. This approach revealed mechanisms controlling fibroblast migration, proliferation, and differentiation, providing new insights into the phases of wound healing. These findings highlight the potential of multi-omics approaches for monitoring and offering therapeutic implications in tissue repair and regeneration, enabling targeted strategies for improving healing outcomes [279]. Similarly, Yu et al., applied multi-omics techniques to study bone tissue repair, integrating genomics, epigenomics, transcriptomics, proteomics, glycomics, and lipidomics. The study highlighted genetic and epigenetic factors in cellular responses to injury and the role of RNA, protein expression, and metabolism in the repair process. This approach offers valuable monitoring and therapeutic implications, advancing strategies for tissue repair and regeneration [280].

Zeng and colleagues conducted a multi-omics study in which they sought to investigate proteomics and metabolomics-related changes in chronic wound tissues obtained from 13 patients with non-diabetic wounds. The study reported differentially regulated upstream and downstream mediators of the PI3K-Akt pathway, which were significantly associated with the development of chronic wounds. Their results also demonstrated the increased expression of FBLN1, 3, and 5 proteins, which inhibited the proliferation of cells that led to delayed wound healing [71]. Ulcerative colitis (UC) is characterized by chronic inflammation of the colon and rectum, leading to the development of ulcers or sores in the affected areas [281–285]. Janker and colleagues employed a multi-omics-empowered deep phenotyping approach using human tissues obtained from different colon locations. Tissue proteome profiling revealed colitis-associated activation of various immune cells such as neutrophils, macrophages, B- and T-cells, along with fibroblasts, endothelial cells, and platelets. Additionally, the findings indicated hypoxic stress and a general downregulation of mitochondrial proteins, alongside apparent wound healing–promoting activities, including scar formation [286].

The kidney demonstrates remarkable regenerative capacity, particularly in response to ischemic or toxic injury, where proximal tubule cells can proliferate to rebuild damaged tubules and restore kidney function. However, in cases of severe acute kidney injury (AKI) or recurrent AKI events, this regenerative process may become maladaptive, leading to disease progression from AKI to chronic kidney disease (CKD) [287–292]. In an attempt to get novel insights into the kidney-related tissue repair process, Zhang et al. conducted a multi-omics study targeting proteomics and transcriptomics metabolomics. They identified differentially expressed genes and proteins, many of which may serve as potential biomarkers in the kidney repair process. They demonstrated Cyp4a10, Hmgcs2, and Cyp4a14, the key players implicated in kidney tissue repair [293]. Other than this, several studies focusing on proteomics, genomics, transcriptomics, and epigenomics have reported differential modulation in kidney injury and tissue repair processes [294,295].

Exposure to high-dose radiation induces acute radiation syndrome, characterized by hematopoietic, gastrointestinal, cerebrovascular, and other organ-specific injuries. Alterations in genomic variations, gene expression, metabolite concentrations, and microbiota profiles in blood plasma or tissue samples indicate whole-body radiation injuries. Consequently, multi-omics profiles obtained from high-resolution omics platforms provide a comprehensive approach to identifying reliable biomarkers for predicting radiation-induced injuries to organs and tissues from radiation exposure [296]. A study investigated the radiation effect on the multi-omics of radiation-induced injuries in human tissue. The study concluded that high-dose radiation impaired differentiation while low-dose radiation was associated with comparatively improved tissue repair in the healing process [296]. Similarly, a systematic review reported various differentially expressed genes, including GADD45A, MYC, TNFSF4, ZMAT3, and TNFSF4 in the radiation-induced injury and injury repair [297].

To understand the variability in stem cell reprogramming, Mahmoudi et al. carried out a multi-omics study and revealed that the old mice had activated fibroblasts, which corresponded with the reprogramming efficacy of pluripotent stem cells (iPSC) [298]. Certain antibiotics have been implicated in causing liver injury, leading to hepatotoxicity, which can range from mild liver enzyme elevations to severe liver damage, including hepatitis and liver failure [299–302]. A study in which multi-omics analyses were performed found 21 proteins that were significantly associated with the tissue repair process in the tissue microenvironment [301]. To find candidate biomarkers for antibiotic-induced liver injury, Lee et al. leveraged a multi-omics approach using 32 healthy subjects. In their findings, they observed changes such as increased liver enzyme activity, increased lymphocyte proliferation, and increased miR-122 levels in the wound repair phases [302].

All these multi-omics studies highlight the importance of integrative omics in elucidating the intricate cellular and molecular processes that are involved in tissue repair and regeneration. These studies have demonstrated valuable insights into the understanding of developing potential therapeutic interventions and strategies for discovering new biomarkers and facilitating early diagnosis. Overall, it may lead to a better management of tissue repair and wound healing.

By combining proteomics, genomics, and metabolomics, researchers can track dynamic changes in gene expression, protein activity, and metabolic shifts during wound healing. However, therapeutic monitoring faces challenges in integrating data from various omics platforms. Current multi-omics approaches often encounter data overload, making it difficult to extract meaningful patterns from large datasets. The future of monitoring tissue repair will benefit from leveraging artificial intelligence (AI) and machine learning (ML) to improve multi-omics data analysis. These technologies can help automate the integration of proteomics, genomics, and metabolomics data, enabling real-time identification of the most relevant biomarkers and pathways for tissue

regeneration.

7. Conclusion

A wound refers to an injury to a biological tissue, such as skin or other tissue, that damages and disrupts the normal anatomical structures in the body. Research in biomedicine has been revolutionized with the advent of advanced multi-omics techniques and high-throughput technologies. The studies included in this review article have demonstrated the great potential of multi-omics approaches in elucidating the complex biological, cellular, and molecular mechanisms implicated in the process of tissue repair, biomarker identification, and diagnosis procedures. While the potential of multi-omics in tissue repair and regeneration is clear, there are several limitations and challenges that must be addressed for its broader application. First, the current methods for integrating data from different omics layers, such as genomics, transcriptomics, proteomics, and metabolomics, are still in the early stages. The complexity of multi-omics data and the lack of standardized frameworks for data analysis present significant barriers to widespread clinical adoption. In biomarker discovery, for instance, while multi-omics offers a more comprehensive view of the molecular processes, the lack of cross-platform integration and difficulty in validating findings across different patient cohorts remains a major challenge. Moreover, the application of multi-omics in prognosis and treatment monitoring is hampered by the sheer volume of data and the need for specialized computational tools to interpret the results effectively. The reliance on manual annotation and the inconsistency of protocols across platforms often leads to data fragmentation, making it harder to draw clear conclusions or predictions. To make multi-omics more clinically applicable, there is a need for universal analytical tools and standardized protocols that can improve the reliability of results and facilitate their widespread use in medical practice. Looking ahead, the clinical translational value of multi-omics can be enhanced by integrating AI and machine learning (ML) technologies. These advancements will improve the efficiency of analyzing complex multi-omics data, enabling clinicians to predict patient-specific outcomes and tailor personalized treatment plans. With the right tools and technologies, multi-omics can play a transformative role in advancing personalized medicine and improving clinical decision-making in tissue repair and regeneration.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors did not use AI-assisted technologies.

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Declaration of competing interest

The authors declare that there are no conflicts of interest.

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