BURNS 49 (2023) 1525–1533

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/burns

Review

Systematic review of molecular pathways in burn wound healing

Annika S. Walter [a], *Elias Volkmer* [a,b], *Gerd Gauglitz* [c], *Wolfgang Böcker* [a], *Maximilian M. Saller* [a,*]

[a] *Musculoskeletal University Center Munich (MUM), Department of Orthopeadics and Trauma Surgery, Ludwig-Maximilians-University (LMU), Fraunhoferstraße 20, 82152 Martinsried, Germany*

[b] *Division of Hand Surgery, Helios Klinikum München West, Steinerweg 5, 81241 Munich, Germany*

[c] *Department of Dermatology and Allergy, Ludwig-Maximillians-University (LMU), Frauenlobstraße 9-11, 80337 Munich, Germany*

ARTICLE INFO

Article history:
Accepted 7 March 2023

Keywords:
Wound healing
Burn wound healing
Molecular pathway
Skin scar
Scar formation

ABSTRACT

Depending on extent and depth, burn injuries and resulting scars may be challenging and expensive to treat and above all heavily impact the patients' lives. This systematic review represents the current state of knowledge on molecular pathways activated during burn wound healing. All currently known molecular information about gene expression and molecular interactions in mammals has been summarized. An ample interaction of regenerative cytokines, growth factors, ECM-regenerative molecules and proinflammatory immune response became apparent. We identified three molecules to be most often involved in the pathways: TGFB1, ACTA1 and COL1A1. Yet, other factors including FLII, AKT1 and miR-145 were shown to play pivotal roles in burn wound healing as well. This systematic review helps to explain the fundamental molecular proceedings participating in burn wound healing. A number of new molecular interactions and functional connections were identified yielding intriguing new research targets. An interactive version of the first network about molecular pathways and interactions during burn wound healing is provided in the online edition and on WikiPathways.

© 2023 Elsevier Ltd and ISBI. All rights reserved.

Contents

* Corresponding author.
E-mail address: maximilian.saller@med.uni-muenchen.de (M.M. Saller).

https://doi.org/10.1016/j.burns.2023.03.006
0305-4179/© 2023 Elsevier Ltd and ISBI. All rights reserved.

Descargado para Anonymous User (n/a) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en noviembre 16, 2023.
Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2023. Elsevier Inc. Todos los derechos reservados.

1. Introduction

Healing of burn wounds is a complex spatiotemporal process which is accompanied by acute and long-term consequences including continuing psychological and physiological problems for affected patients. Especially patients with high degree burn wounds need intensive care in special burn trauma centers as well as extensive surgery. This may even include multiple skin transplants. After months of acute and rehabilitative care, these patients often suffer from pathological scar formations, such as hypertrophic scars or atrophic contractions, which mostly result in some degree of impaired mobility as well as aesthetic claims [1,2].

Burn injured casualties are patients with a very high need for intensive medical care. In Germany, 1088 adult and 2129 adolescent burn patients were officially registered in burn care centers in the year 2019 [3]. In 2019, 39 German hospitals specializing in burns were part of the official burn register of the German Association of Burn Treatment. The number of registered burn patients treated in these special burn centers decreased over the years. On average, 13.9% of the body surface area was affected in adults with burn wounds. Data of the German Association of Burn Treatment shows that the intensive care for burn patients costs around 4600 € per percent of the burned total body surface area (TBSA). Thus, the cost for acute and life-saving treatment of burn patients costs 64,000 € per case on average. However, the costs of rehabilitation are significantly higher and long-term care phases after acute hospitalization phases can take several months up to years [4].

Burn wounds differ in type, depending on the temperature and the duration of the exposure to the heat source. The pressure applied by the heat source as well as its aggregate state also influence the type of burn wound [1,5]. Pathophysiologically, it is known that heat of 69 °C for one second on the epidermis is enough to produce necrotic skin processes [6]. Necrosis induces a general inflammatory reaction in the affected tissues. The inflammatory process along with the necrosis damage skin tissue, including small capillaries, which are essential for nutrition and oxygen supply of the skin [7]. This thermally induced destruction enables fluids to pass the damaged endothelial cells of skin capillaries and starts a release of proinflammatory cytokines [8–10]. This ultimately results in the formation of local oedema in the burned area and induces systemic reactions such as hypovolaemia-associated shock symptoms, including potential life-threatening cardiac complications [9,11]. In order to prevent massive oedema and shock symptoms, protein-rich fluid substitution is necessary [6,7].

Wound healing consists of complex molecular mechanisms and interactions and can be delineated into three distinct wound healing phases independent of the type of skin injury: Inflammatory phase, proliferation phase and remodeling phase [12]. The time span for wound healing in humans after an acute trauma is mentioned in the literature at 48–72 h for the inflammation phase, 5–10 days for the proliferation phase and about 3 weeks for the remodeling phase [13,14]. Each wound healing phase shows a smooth, individual transition, which makes it difficult to specifically distinguish the different phases. There are many different types of wounds such as sharp cuts, blunt crush wounds and burn wounds. On the one hand, all types hurt skin and tissue, cause bleedings and initiate the inflammation phase [13]. On the other hand, burn wounds differ from cut wounds especially in the extent of the affected area as well as varying degrees of severity. In particular, third-degree burns with extensive affected areas and penetration of multiple skin layers correlate with the risk of a systemic inflammatory reaction which can cause a severe loss of fluids in particular. Hypovolemia and burn shock are some of the most important factors specifically caused by with widespread third-degree burns. Especially the increased capillary permeability and decreased interstitial fluid pressure lead to subsequent detrimental therapeutic consequences in patients with burn wounding [13,15]. Burn wound healing is even more individual and therefore more difficult to differentiate the individual phases. Even if wound healing follows this general pattern, each patient with deep burn wounds differs to another. Individual factors like age, sex, pre-existing conditions, type of accident, depth of wound, temperature of applied

Descargado para Anonymous User (n/a) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en noviembre 16, 2023.
Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2023. Elsevier Inc. Todos los derechos reservados.

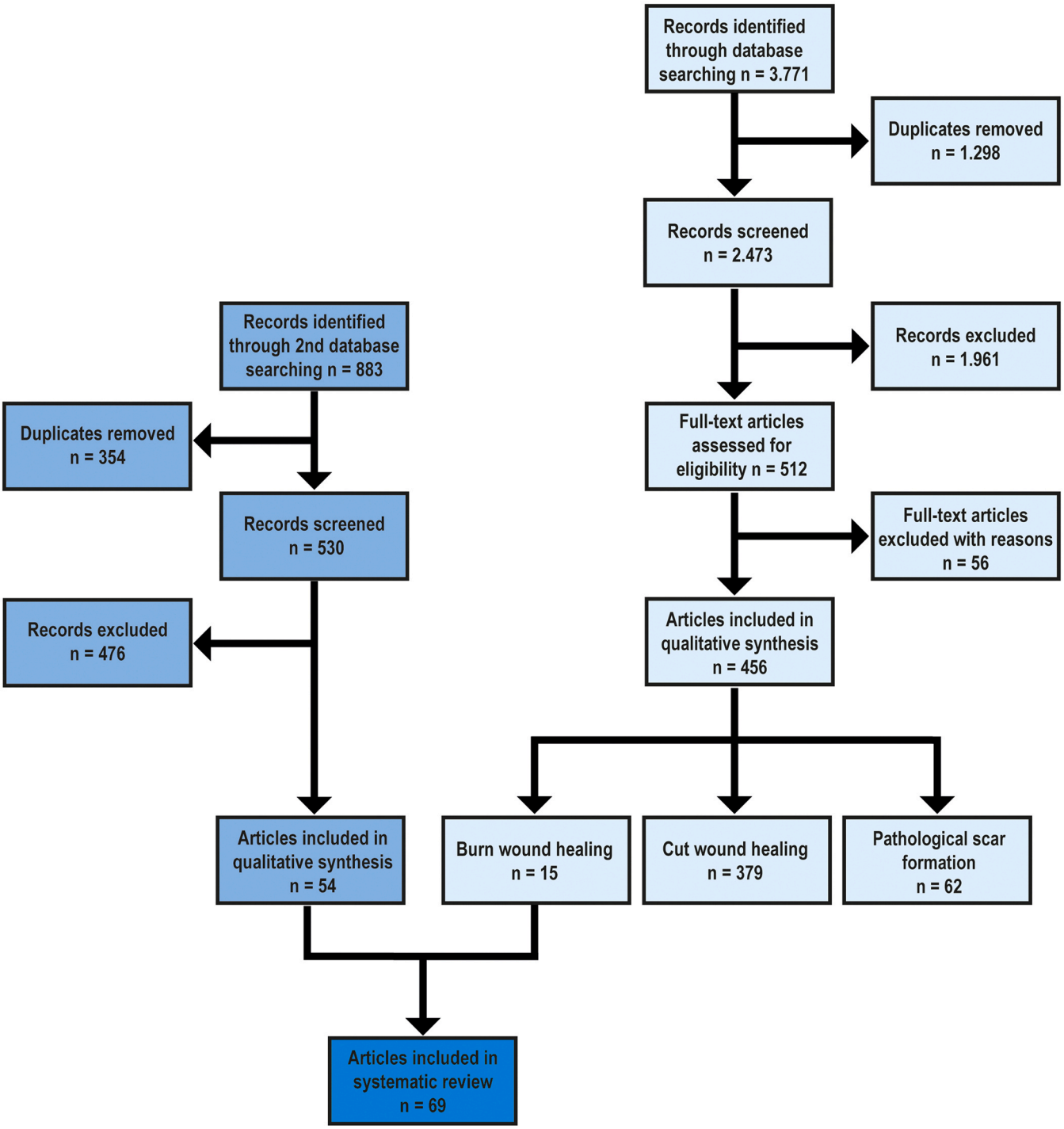

Fig. 1 – : *Flow-chart of systematic literature search about burn wound healing.* Following the PRISMA guidelines, after searching with all key word combinations, we counted 3771 articles in the first search round (right arm). After eliminating duplicates and screening the remaining articles, we excluded articles according to the exclusion criteria. The included articles were separated into three main categories: burn wound healing, cut wound healing, pathological scar formation. Despite the high rate of new publications about wound healing, we only gathered 15 articles matching our inclusion criteria for the systematic review. We thus performed a second check with more detailed key words focused on thermal injuries (left arm). Both search procedures followed the same inclusion and exclusion criteria. In the end, 69 articles were included in this systematic review.

Descargado para Anonymous User (n/a) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en noviembre 16, 2023.
Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2023. Elsevier Inc. Todos los derechos reservados.

heat, wound infection etc. make it difficult to determine a fixed time frame for individual wound healing phases. Wound Healing in humans is different to wound healing in an experimental setting with mice or rats [16]. The environment, rate of cell proliferation, skin contractions and structure of skin appendages differs compared to wound healing in humans [16]. In addition, it is technically challenging to represent time factors visually. The detailed molecular mechanism of wound healing, especially after thermal injuries, is currently not well understood.

The profibrotic, potent cytokine transforming growth factor 1 (TGFB1) leads to an upregulation of many molecular factors like alpha smooth muscle actin (ACTA1) [17], heat shock protein 47 (SERPINH1) [18] or collagen type 1 (COL1A1) [18]. ACTA1 positive myofibroblasts can stimulate re-epithelization, matrix deposition and are involved in contraction during wound closure and scar formation [19,20].

In contrast, interferon alpha 2 (IFNA2) has antifibrotic properties by decreasing the production of fibronectin and different collagens during wound healing [21–23]. Various molecular factors and different types of interactions are involved in the regulation of wound healing. The correct balance between spatiotemporal stimulation and suppression of specific pathways is pivotal in obtaining optimal wound healing results. Up to now, no systemic summary of molecular biological influences on burn wound healing has been available. The aim of this systematic literature review was to collect all involved molecular players and to visualize the essential pathways in burn wound healing. It serves as a starting point for a systematical, biological view of molecular interactions in burn wound healing to enable prospective new research approaches. The major molecular key players for burn wound healing are discussed.

2. Methods

This systematic literature review was registered in December 2019 on the International prospective register of systematic reviews PROSPERO (Registration-ID: CRD42019150478) and follows the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) protocol. Two reviewers per screening phase worked independently of each other to avoid bias. To maintain equivocality, discrepancies in individual studies were discussed with specialists.

2.1. Search strategy

We started our general database PubMed search with the following keywords and their combinations: (“myofibroblast” OR “myofibroblasts” OR “epithelial cell” OR “epithelial cells” OR “keratin cell” OR “keratin cells” OR “fat cell” OR “fat cells” OR “fibroblast” OR “fibroblasts”) AND (“skin”) AND (“defect” OR “lesion” OR “injury” OR “healing” OR “scar” OR “contraction” OR “mechanical tension”) AND (“lesion” OR “injury” OR “epithelial cell” OR “scar AND wound” OR “contractile” OR “mechanotransduction”). After getting an overview of the current research point to the topic “wound healing”, more detailed and burn associated wound healing articles were necessary. In order to specify the literature search on burn wound healing, a second database PubMed search with more specific molecular burn wound healing associated key words and combinations was conducted: (“burn wound” OR “burn wounds” OR “burns” OR “thermal injury”) AND (“skin”) AND (“scar” OR “healing”) AND (“gene” OR “expression” OR “pathway” OR “molecular biology” OR “DNA” OR “miR” OR “RNA” OR “protein”). In both search sections special signs “* ” as well as “#” were used in our literature search in order to receive all applicable articles and possible MESH terms. A complete summary of all used key words and key word combinations as well as the number of articles found on PubMed can be viewed in the attachment (Supplementary Table 1). The number of articles received with these keyword combinations was recorded and evaluated (Fig. 1).

2.2. Inclusion and exclusion criteria

After downloading the obtained publication lists to a reference manager (Mendeley, Elsevier, USA), duplicates were removed automatically and residual manuscripts were screened for inclusion and exclusion criteria via title and abstract. As inclusion criteria, we determined English language, experimental studies (in vivo and in vitro from mammals, including humans) that included physiological molecular pathways. We excluded non-English language, review articles, case reports, animals other than mammals, synthetic grafts, skin diseases, tissue engineering studies, genetic animal studies without control group, extrinsic treatment or interventional studies, pathological skin diseases and clinical studies. Due to the missing histological analysis of the same patients over a longer time period, clinical studies were excluded. This review offers a qualitative description of burn wound healing as a snapshot to one point in time (April 2022) and enables participation of others in the design process thanks to its free access.

2.3. Data extraction

Initial data extraction started after all articles relevant for the molecular pathways had been analyzed with the data being collected in tables. Information about humans or type of animal, in vivo or in vitro studies, cell types, genes, proteins, type of injury and PubMed-ID were collected. Each extraction of information was checked by team members working independently.

2.4. Data analysis and quality appraisal

All qualitative data was transferred to PathVisio (Version 3.3.0, Department of Bioinformatics, Maastricht University, Netherlands) for the creation of molecular interactions and pathways separated by species and published on WikiPathways (Homo sapiens, Mus musculus, Rattus norvegicus, Sus scrofa domesticus). A merged pathway with all included single species separated pathways created via Cytoscape can be seen in Fig. 2. Depending on the number of mentions and of interactions, the round protein symbols were colored from light- to dark-colored. Supplementary table 2 represents all descriptive genes which have no experimentally validated regulatory function. It might be

Descargado para Anonymous User (n/a) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en noviembre 16, 2023.
Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2023. Elsevier Inc. Todos los derechos reservados.

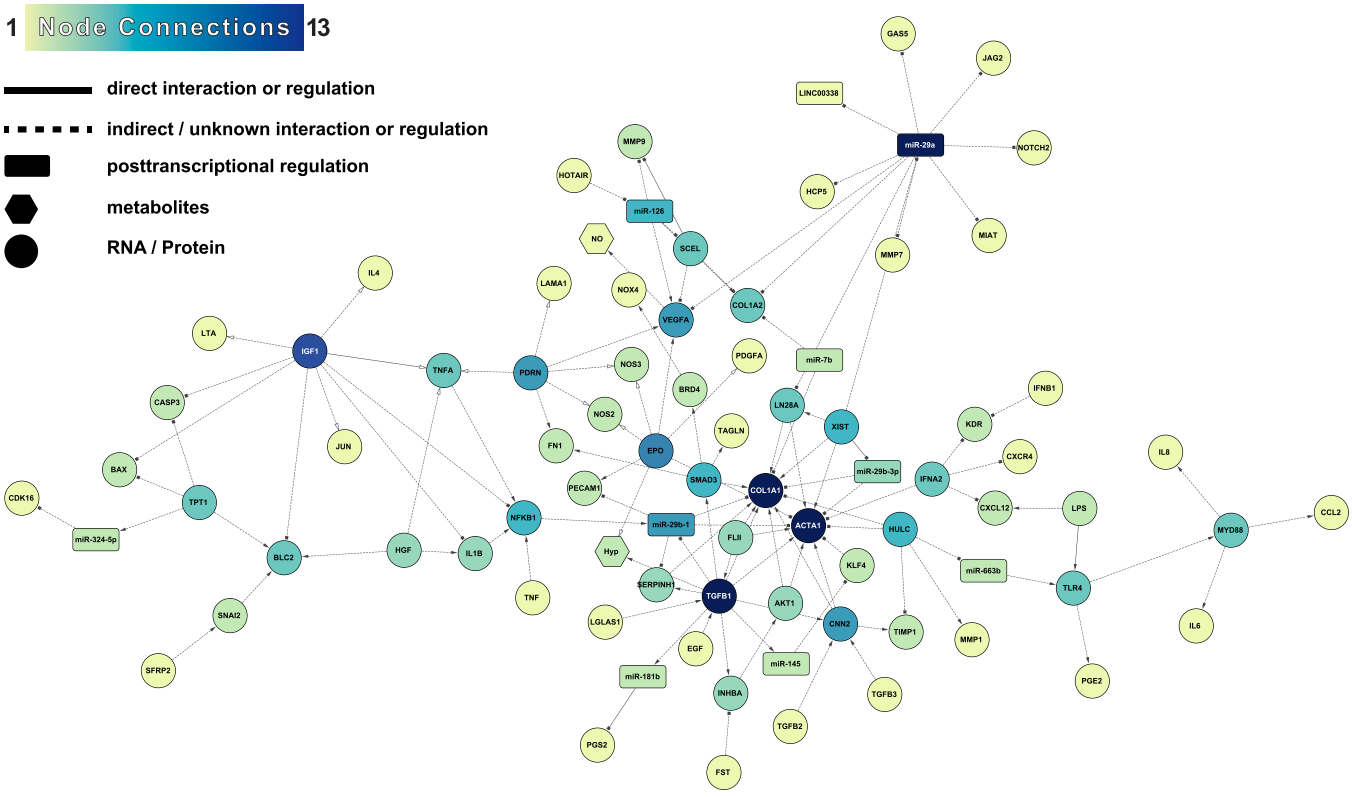

Fig. 2 – : *Network formation via Cytoscape*. This network includes and merges all created pathways, designed in PathVisio, of all included species. It shows new molecular interactions and gives an overview of the current state of knowledge on molecular proceedings during burn wound healing. Colour represents the frequency of their occurrence during the merge of all pathways. Round circles symbolize proteins. Post-transcriptional regulations are visualized as rectangular symbols. Metabolites like Nitric oxide and Hydroxyproline are marked as hexagonal symbols. Solid lines: direct regulations; dashed lines: indirect regulations; arrowheads: activation, t-bars: inhibition.

possible that these genes play a part in similar pathways, but there is no specific experimental evidence for involvement in burn wound healing. Thus, all descriptive genes were excluded from the final merged network. For network formation and analysis, the individual species pathways of humans, mice and rats were merged via Cytoscape version 3.8.1 [24].

3. Results

After defining key words and key word combinations, we started the literature search and sorting process. In Fig. 1, our step-by-step process is visualized. After sorting all relevant articles according to our defined inclusion and exclusion criteria, only 15 articles were included in our systematic review about burn wound healing. Thus, a second literature search with new, extended key words was carried out (Fig. 1, left arm). Finally, 61 articles about burn wound healing were included in this systematic review.

After extraction of data, creation of molecular pathways via PathVisio and merging them via Cytoscape, new molecular interactions and clusters were found (Fig. 2). This network represents the current state of molecular research on burn wound healing and shows new potential research points. In the final network, in vivo as well as in vitro studies were included. Of course the data presented here is derived from a systematic review of the literature and not from actual experiments, thus care must be taken for the interpretation of the results. Due to the technical limitations and a lack of content, no visualization of single gene expression to a time line or correlation to the three wound healing phases was possible. An extensive and interactive version of the molecular network is published on WikiPathways and in the online edition. The online edition contains additional information on the temporal expression of the most important genes involved in wound healing.

3.1. *Molecular reviews as an asset for future research*

In the last years, three essential key players for burn wound healing have been identified. *TGFB1*, *ACTA1* and *COL1A1* are the central molecular factors during wound healing. For each molecular key factor numerous single pathways are known, but overlapping interactions are missing. This systematic review focuses on molecular connections between these well-known key factors and their known single pathways to fill in the knowledge gaps in-between and to form a common pathway which uncovers small molecular intricacies. The synthesis of all known pathways offers as opportunity for future research. Single molecular factors such as *Flii*, *Act1* and

Descargado para Anonymous User (n/a) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en noviembre 16, 2023.
Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2023. Elsevier Inc. Todos los derechos reservados.

miR-145, among others, which earlier appeared to be less important, receive more attention. This review serves as an introduction to the complexity of molecular pathways during burn wound healing and gives the opportunity to create new research hypothesis.

3.2. *Rarely mentioned molecular factors in the center of attention*

3.2.1. *Top named genes in pathway*

Molecular network formation forms the basis of systems biology. Fig. 2 represents the current state of research on gene expression and molecular interactions during burn wound healing. Solid lines show direct stimulation / inhibition which have been verified experimentally. Dotted lines show indirect stimulation / inhibition due to a lack of evidence for direct influence. The top three most investigated nodes are *TGFB1*, *ACTA1* and *COL1A1* (colored dark blue) which make up the key factors. Especially often contemplated genes are *IGF1*, *EPO*, *CNN2*, *PDRN*, *miR-29-b1*, *miR-29a*, *VEGFA*, *SMAD3*, *miR-126* and *XIST* (colored middle blue, dark green). There are also some genes that are mentioned several times like *TNFA*, *NFKB*, *IFNA2*, *BCL2*, *HGF*, *IL1B*, *SERPINH*, *AKT1*, *INHBA*, *FLII*, *COL1A2* and *TLR4 among others* (colored middle green). Following genes belong to the rarest mentioned genes: *JUN*, *BAX*, *TAGLIN*, *EGF*, *TIMP1*, *FST*, *PDGFA*, *CXCR4*, *IFNB1* and *LAMA1* (colored yellow). In this systematic analysis, one group of molecular factors went unnoticed. Light green colored genes are genes which are mentioned twice such as *SNAI2*, *BRD4*, *FN1*, *PECAM1*, *NOS2*, *NOS3*, *KLF4*, *MMP9*, *KDR* and *CXCL12*. *They* are important to finally connect the known single pathways around the top three genes *TGFB1*, *ACTA1* and *COL1A1* and to fill in the gaps.

3.2.2. *Top counted interactions in pathway*

Looking at most interactions, *TGFB1* and *COL1A1* lead with 12 each, followed by *ACTA1* with eleven interactions to differential factors. *IGF1* has nine interaction partners, CNN2, PDRN, *miR-29b-1*, *miR-29a* all have six known molecular interactions during burn wound healing. *XIST* and *VEGFA* built up the network with five connections for each, followed by *IFNA2*, *MYD88*, *SCEL*, *TNFA* and *NFKB1* with four interactions each.

4. Discussion

4.1. *TGFB1 is currently the key growth factor during burn wound healing*

Growth factors and their interactions play an important role during cell proliferation, cell interactions and tissue regeneration.

Flightless I (Flii) is highly expressed in human burn wounds and hypertrophic scars [25]. As a transcriptional coactivator, Flii leads to an increase in the amount of myofibroblasts by upregulation of transforming growth factor β1 (*Tgfb1*) and alpha-smooth-muscle-actin (*Acta1*) [25,26]. These newly differentiated myofibroblasts deposit high levels of the extracellular matrix protein collagen I (Col1a1) [25,27]. Thus, upregulation of *Flii* during burn wound healing drives the (pathological) thickening of the scar and potentially intensifies scar contractions.

Besides Flii, Epidermal growth factor (EGF) also stimulates the expression of TGFB1 [28]. TGFB1 as a proliferating and profibrotic cytokine acts as a key factor for multiple processes during wound healing. It is involved in differential molecular reactions and is necessary for optimal cell interactions. TGFB1 seems to be species independent and thus forms a central molecular player in burn wound healing. Transcription factor SMAD3 (Mothers against decapentaplegic homolog 3) is activated through phosphorylation by TGFB1 [20]. By building complexes with other SMAD-molecules, SMAD3 is able to stimulate the gene expression of bromodomain-containing protein 4 (BRD4), Fibronectin 1 (FN1) and Transgelin (TAGLN) [20,29]. BRD4 stimulates NADPH oxidase 4 (NOX4), which is part of Proto-oncogene tyrosine-protein kinase ROS (ROS) and necessary for controlling the oxygen level in cells [20,30].

Moreover, TGFB1 stimulates the gene expression of Calponin-2 (CNN2)/Connective tissue growth factor (CTGF) in order to activate cell contractions and mechanical wound closure via ACTA1 after skin injuries [31]. CNN2 can also be activated by TGFB2 and TGFB3 [31]. ACTA1 stimulates profibrotic ECM-remodeling and cell contractions e.g. in myofibroblasts [31]. Acta1 is inhibited by Erythropoietin (Epo) [32] which is an extracellular matrix protein. Furthermore Epo stimulates the expression of other growth factors like platelet-derived growth factor subunit A (Pdgfa) [32] and vascular endothelial growth factor A (Vegfa) [32].

4.2. *Regeneratively and effectively remodeling extracellular matrix molecules during burn wound healing*

After a thermal injury, the damaged tissue is regenerated through rebuilding and remodeling of extracellular matrix (ECM). TGFB1 stimulates the expression of collagen alpha 1 (COL1A1) [18,27,33], which is also stimulated by transcription factors SMAD3 [20] or CNN2 [31]. Collagen 1 is essential in building up extracellular matrix and it interacts with several proteins that support profibrotic tissue remodeling. Transcriptional regulation of collagen 1 can be positively modulated by RAC-alpha serine/threonine-protein kinase (AKT1) [34] or miR-126 [35,36]. Interestingly, miR-126 also leads to increased expression of collagen degrading matrix metalloproteinase-9 (MMP9) [35,37].

However, other extracellular matrix molecules like FN1 [20,38], laminin subunit alpha1 (Lama1) [38] and matrix metalloproteinase inhibitor 1 (Timp1) [39] are also embedded into the molecular network. In order to strike a balance between building and dismantling damaged tissue, inhibiting factors such as miR-29a [40], miR-29b-1 [18] and miR-29b-3p [41] are necessary.

4.3. *Inflammatory molecules as immune response during burn wound healing*

Each injury activates multiple inflammatory reactions. Inflammatory molecules will initially release, to degenerate burned tissue areas and to give the capability for tissue regeneration. Tumor necrosis factor alpha (TNF) is a central

Descargado para Anonymous User (n/a) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en noviembre 16, 2023.
Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2023. Elsevier Inc. Todos los derechos reservados.

wound healing activated cytokine which stimulates the transcriptional expression of nuclear factor NF-kappa-B p105 subunit (NFKB1) [18] as well as Interleukin 1B (IL1B) [18,29]. NFKB1 stimulates the transcription of miR-29b-1 which inhibits extracellular matrix regeneration [18]. These inflammatory molecules attract macrophages and neutrophils which in turn degrade thermally injured tissues. *Tnf* is directly inhibited by Nlrp3 (NLR family pyrin domain containing 3) [38,42] as well as insulin-like growth factor 1 (Igf1) [43]. Hepatocyte growth factor (Hgf) stimulates the expression of Tnf [44], interleukin 1b (Il1b) [44] and apoptosis regulator Bcl-2 (Bcl2) [44]. Bcl-2 is stimulated by Igf1 [45] which activates multiple inflammation reactive molecules e.g. interleukine-4 (Il4) [43], transcription factor AP-1 (Jun) [45] and lymphotoxin-alpha (Lta) [43]. Furthermore, Igf1 inhibits different molecules such as apoptosis regulator Bax (Bax), Nfkb1 [45] and caspase-3 (Casp3) [45,46] in order to hold the baseline between destruction of injured tissue and proliferation as well as regeneration of new matrix.

This review unveiled some unexpected molecular factors which may link the established pathways and key factors.

One unexpected gene product is the profibrotic Protein flightless-1 (FLII) [25]. FLII stimulates the expression of ACTA1 as well as TGFB1 and COL1A1. ACTA1 expression is stimulated by Krueppel-like factor 4 homolog (KLF4) [47] whose expression in turn is stimulated by miR-145 [47]. TGFB1 stimulates the expression of miR-145 [47]. This simple pathway closes the arc between two key factors during burn wound healing. FLII as well as KLF4 are molecular factors which now surprisingly come to the fore. This insight gives new input to international molecular research. Does an inhibition of miR-145 have an antifibrotic effect to burn wound healing while downregulating the expression of KLF4?

FLII as well as SMAD3 stimulate the expression of COL1A1 [20,25]. It is known that SMADs regulate receptors and are activated by TGFB1. More unknown is the connection between SMAD3 and Fibronectin (FN1) [20,29]. FN1 is also stimulated by PDRN. PDRN is able to increase the expression of EPO (Erythropoietin) which is one of the most important inhibitors of the expression of ACTA1 [32,38,48]. This control loop shows the interaction between the key factors COL1A1 and ACTA1. Focused on FN1, PDRN and EPO new hypotheses can be set up. Does the stimulation of EPO help to improve wound healing and reduce scar formation?

Like ACTA1 and COL1A1, TGFB1 is also stimulated by FLII [25]. TGFB1 is able to increase the gene expression of INHBA (Inhibin beta A chain) [34] which leads to increase of AKT1 (RAC-alpha serine/threonine-protein kinase) [34]. AKT1 is a profibrotic kinase which is part of several cell processes and stimulates gene expression of ACTA1 [34]. It forms a link between the key factors TGFB1 and ACTA1. Focusing on the binding element AKT1, new research starting points targeting the support of the wound healing process and the inhibition of scar formation are possible.

FLII is able to stimulate all three key factors and shows negative effects on wound healing and hypertrophic scar formation. Because of its stimulation possibilities, inhibition of FLII could help to reduce wound healing complications and pathological scars. This pathway gives the possibility to increase the molecular importance of single binding elements during burn wound healing. New hypotheses can be generated in order to support the wound healing process while inhibiting pathological scar formation.

5. Conclusion

This systematic review gives a comprehensive overview of molecular interactions and network connections during burn wound healing. It is based on experimentally validated molecular interactions or gene/protein regulations from all included articles. All extracted data about molecular pathways were visualized via PathVisio and published on WikiPathways. Subsequent network analysis via Cytoscape showed new potential molecular interactions across species including humans, mice and rats. However, it has to be pointed out that the presented network is purely based on the gene/protein expression data of the selected literature and thus, the bioinformatics overlay of the individual studies has to be experimentally validated. This network shows a selection of current research and will be published interactively online. Molecular interactions that were previously known and classified as insignificant, are now moving into focus. Single genes like FLII, KLF4, FN1 and AKT1 become more important for further molecular research. Moreover, our manually curated molecular network can be utilized as a hallmark gene set for single-cell-RNA sequencing and Omics data. In summary, this review represents a research snapshot of molecular interactions during burn wound healing. To stay up-to-date, this review is still in progress and can constantly be modulated by researchers worldwide. Systems biology will play an increasingly important role in the future in understanding such complex systems and immense amounts of biological data. Our work facilitates the validation of former hypotheses as well as the generation of new hypotheses regarding the molecular biology of burn wound healing.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgments

We thank the WikiPathway team for continuous help during creation of the species-specific pathways.

Conflict of interest

The authors have declared that no competing interests exist.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.burns.2023.03.006.

Descargado para Anonymous User (n/a) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en noviembre 16, 2023.
Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2023. Elsevier Inc. Todos los derechos reservados.

REFERENCES

[1] Schneider B.M. *Der Nürnberger Handscore: Ein Neues System Zur Erfassung von Verbrennungsfolgen an Der Hand*. 2010.

[2] Ray S, Ju X, Sun H, Finnerty CC, Herndon DN, Brasier AR. The IL-6 trans-signaling-STAT3 pathway mediates ECM and cellular proliferation in fibroblasts from hypertrophic scar. J Invest Dermatol 2013;133(5):1212–20. https://doi.org/10.1038/jid.2012.499

[3]. German Association For Burn Treatment. *Jahresbericht 2020 Für Den Zeitraum Jan.-Dez. 2019*.

[4] Mirastschijski U, Sander JT, Weyand B, Rennekampff HO. Rehabilitation of burn patients: an underestimated socio-economic burden. Burns 2013;39(2):262–8. https://doi.org/10.1016/j.burns.2012.06.009

[5] Zellweger G. *Die Behandl Der Verbrennungen Prakt Hinw Für Diagn, Ther, Rehabili-Tation* Dtsch Ärzteverlag 1985.

[6] Dugan RC, Nance FC. Enzymatic burn wound debridement in conventional and germ-free rats. Surg Forum 1977;28:33–4.

[7] Kamolz LP, Herndorn DN, Jeschke MG. Verbrennungen Diagnose, Therapie Und Rehabilitation Des Thermischen Traumas. Springer,; 2009.

[8] Zeng J, Lin X, Fan H, Li C. Hydrogen sulfide attenuates the inflammatory response in a mouse burn injury model. Mol Med Rep 2013;8(4):1204–8. https://doi.org/10.3892/mmr.2013.1610

[9] Evers LH, Bhavsar D, Mailländer P. The biology of burn injury. Exp Dermatol 2010;19(9):777–83. https://doi.org/10.1111/j.1600-0625.2010.01105.x

[10] Singer AJ, Boyce STBurn Wound Healing. and Tissue Engineering. J Burn care Res: Publ Am Burn Assoc 2017;38(3):e605–13. https://doi.org/10.1097/BCR.0000000000000538

[11] Gurney JM, Kozar RA, Cancio LC. Plasma for burn shock resuscitation: is it time to go back to the future. Transfus (Paris) 2019;59(S2):1578–86. https://doi.org/10.1111/trf.15243

[12] Tiwari VK. Burn wound: How it differs from other wounds. Indian J Plast Surg 2012;45(2):364–73. https://doi.org/10.4103/0970-0358.101319

[13] Tiwari VK. Burn wound: How it differs from other wounds. Indian J Plast Surg 2012;45(2):364–73. https://doi.org/10.4103/0970-0358.101319

[14] Raziyeva K, Kim Y, Zharkinbekov Z, Kassymbek K, Jimi S, Saparov A. Immunology of Acute and Chronic Wound Healing. Biomolecules 2021;11(5). https://doi.org/10.3390/biom11050700

[15] Rowan MP, Cancio LC, Elster EA, et al. Burn wound healing and treatment: review and advancements. Crit Care 2015;19:243. https://doi.org/10.1186/s13054-015-0961-2

[16] Zomer HD, Trentin AG. Skin wound healing in humans and mice: Challenges in translational research. J Dermatol Sci 2018;90(1):3–12. https://doi.org/10.1016/j.jdermsci.2017.12.009

[17] Weber CE, Li NY, Wai PY, Kuo PC. Epithelial-mesenchymal transition, TGF-β, and osteopontin in wound healing and tissue remodeling after injury. J Burn care Res: Publ Am Burn Assoc 2012;33(3):311–8. https://doi.org/10.1097/BCR.0b013e318240541e

[18] Zhu Y, Li Z, Wang Y, et al. Overexpression of miR-29b reduces collagen biosynthesis by inhibiting heat shock protein 47 during skin wound healing. Transl Res 2016;178(38):53.e6. https://doi.org/10.1016/j.trsl.2016.07.001

[19] Darby IA, Zakuan N, Billet F, Desmoulière A. The myofibroblast, a key cell in normal and pathological tissue repair. Cell Mol Life Sci 2016;73(6):1145–57. https://doi.org/10.1007/s00018-015-2110-0

[20] Ijaz T, Jamaluddin M, Zhao Y, et al. Coordinate activities of BRD4 and CDK9 in the transcriptional elongation complex are required for TGFβ-induced Nox4 expression and myofibroblast transdifferentiation. Cell Death Dis 2017;8(2):e2606https://doi.org/10.1038/cddis.2016.434

[21] Jimenez SA, Freundlich B, Rosenbloom J. Selective inhibition of human diploid fibroblast collagen synthesis by interferons. J Clin Invest 1984;74(3):1112–6. https://doi.org/10.1172/JCI111480

[22] Ghahary A, Shen YJ, Scott PG, Tredget EE. Expression of fibronectin messenger RNA in hypertrophic and normal dermal tissues and in vitro regulation by interferon alfa-2b. Wound Repair Regen: Publ Wound Heal Soc Eur Tissue Repair Soc 1993;1(3):166–74. https://doi.org/10.1046/j.1524-475X.1993.10306.x

[23] Nedelec B, Shankowsky H, Scott PG, Ghahary A, Tredget EE. Myofibroblasts and apoptosis in human hypertrophic scars: the effect of interferon-alpha2b. Surgery 2001;130(5):798–808. https://doi.org/10.1067/msy.2001.116453

[24] Shannon P, Markiel A, Ozier O, et al. Cytoscape: a software environment for integrated models of biomolecular interaction networks. Genome Res 2003;13(11):2498–504. https://doi.org/10.1101/gr.1239303

[25] Cameron AM, Turner CT, Adams DH, et al. Flightless I is a key regulator of the fibroproliferative process in hypertrophic scarring and a target for a novel antiscarring therapy. Br J Dermatol 2016;174(4):786–94. https://doi.org/10.1111/bjd.14263

[26] Zhang K, Garner W, Cohen L, Rodriguez J, Phan S. Increased types I and III collagen and transforming growth factor-beta 1 mRNA and protein in hypertrophic burn scar. J Invest Dermatol 1995;104(5):750–4.

[27] Yang L, Chan T, Demare J, et al. Healing of burn wounds in transgenic mice overexpressing transforming growth factor-beta 1 in the epidermis. Am J Pathol 2001;159(6):2147–57. https://doi.org/10.1016/s0002-9440(10)63066-0

[28] Ghahary A, Marcoux Y, Karimi-Busheri F, Tredget EE. Keratinocyte differentiation inversely regulates the expression of involucrin and transforming growth factor beta1. J Cell Biochem 2001;83(2):239–48. https://doi.org/10.1002/jcb.1223

[29] Evdokiou A, Kanisicak O, Gierek S, et al. Characterization of Burn Eschar Pericytes. J Clin Med 2020;9(2). https://doi.org/10.3390/jcm9020606

[30] Hecker L, Vittal R, Jones T, et al. NADPH oxidase-4 mediates myofibroblast activation and fibrogenic responses to lung injury. Nat Med 2009;15(9):1077–81. https://doi.org/10.1038/nm.2005

[31] Colwell AS, Phan TT, Kong W, Longaker MT, Lorenz PH. Hypertrophic scar fibroblasts have increased connective tissue growth factor expression after transforming growth factor-beta stimulation. Plast Reconstr Surg 2005;116(5):1382–7.

[32] Imam RA, Rizk AAE. Efficacy of erythropoietin pretreated mesenchymal stem cells in murine burn wound healing: possible in vivo transdifferentiation into keratinocytes. *Folia Morphol (Warsz)* Publ Online 2019. https://doi.org/10.5603/FM.a2019.0038

[33] Cameron AM, Turner CT, Adams DH, et al. Flightless I is a key regulator of the fibroproliferative process in hypertrophic scarring and a target for a novel antiscarring therapy. Br J Dermatol 2016;174(4):786–94. https://doi.org/10.1111/bjd.14263

[34] Fumagalli M, Musso T, Vermi W, et al. Imbalance between activin A and follistatin drives postburn hypertrophic scar formation in human skin. Exp Dermatol 2007;16(7):600–10. https://doi.org/10.1111/j.1600-0625.2007.00571.x

Descargado para Anonymous User (n/a) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en noviembre 16, 2023.
Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2023. Elsevier Inc. Todos los derechos reservados.

[35] Neely AN, Brown RL, Clendening CE, Orloff MM, Gardner J, Greenhalgh DG. Proteolytic activity in human burn wounds. Wound Repair Regen 1997;5(4):302–9. https://doi.org/10.1046/j.1524-475X.1997.50404.x
[36] Zhou J, Zhang X, Liang P, et al. Protective role of microRNA-29a in denatured dermis and skin fibroblast cells after thermal injury. Biol Open 2016;5(3):211–9. https://doi.org/10.1242/bio.014910
[37] Jiang B, Tang Y, Wang H, et al. Down-regulation of long non-coding RNA HOTAIR promotes angiogenesis via regulating miR-126/SCEL pathways in burn wound healing. Cell Death Dis 2020;11(1):61. https://doi.org/10.1038/s41419-020-2247-0
[38] Bitto A, Galeano M, Squadrito F, et al. Polydeoxyribonucleotide improves angiogenesis and wound healing in experimental thermal injury. Crit Care Med 2008;36(5):1594–602. https://doi.org/10.1097/CCM.0b013e318170ab5c
[39] Castleberry SA, Golberg A, Sharkh MA, et al. Nanolayered siRNA delivery platforms for local silencing of CTGF reduce cutaneous scar contraction in third-degree burns. Biomaterials 2016;95:22–34. https://doi.org/10.1016/j.biomaterials.2016.04.007
[40] Guo L, Huang X, Liang P, et al. Role of XIST/miR-29a/LIN28A pathway in denatured dermis and human skin fibroblasts (HSFs) after thermal injury. J Cell Biochem 2018;119(2):1463–74. https://doi.org/10.1002/jcb.26307
[41] Cao W, Feng Y. LncRNA XIST promotes extracellular matrix synthesis, proliferation and migration by targeting miR-29b-3p/COL1A1 in human skin fibroblasts after thermal injury. Biol Res 2019;52(1):52. https://doi.org/10.1186/s40659-019-0260-5
[42] Vinaik R, Abdullahi A, Barayan D, Jeschke MG. NLRP3 inflammasome activity is required for wound healing after burns. Transl Res 2020;217:47–60. https://doi.org/10.1016/j.trsl.2019.11.002
[43] Spies M, Nesic O, Barrow RE, Perez-Polo JR, Herndon DN. Liposomal IGF-1 gene transfer modulates pro- and anti-inflammatory cytokine mRNA expression in the burn wound. Gene Ther 2001;8(18):1409–15. https://doi.org/10.1038/sj.gt.3301543
[44] Jeschke MG, Bolder U, Finnerty CC, et al. The effect of hepatocyte growth factor on gut mucosal apoptosis and proliferation, and cellular mediators after severe trauma. Surgery 2005;138(3):482–9. https://doi.org/10.1016/j.surg.2005.03.021
[45] Dasu MRK, Herndon DN, Nesic O, Perez-Polo JR. IGF-I gene transfer effects on inflammatory elements present after thermal trauma. Am J Physiol Regul Integr Comp Physiol 2003;285(4):R741–6. https://doi.org/10.1152/ajpregu.00046.2003
[46] Abbas OL, Ozatik O, Terzi YK, Ozatik FY, Nar R, Turna G. The Notch Signaling System Is Involved in the Regulation of Reparative Angiogenesis in the Zone of Stasis. J Burn Care Res 2017;38(6):e923–33. https://doi.org/10.1097/BCR.0000000000000522
[47] Gras C, Ratuszny D, Hadamitzky C, Zhang H, Blasczyk R, Figueiredo C. miR-145 Contributes to Hypertrophic Scarring of the Skin by Inducing Myofibroblast Activity. Mol Med 2015;21:296–304. https://doi.org/10.2119/molmed.2014.00172
[48] Galeano M, Altavilla D, Bitto A, et al. Recombinant human erythropoietin improves angiogenesis and wound healing in experimental burn wounds. Crit Care Med 2006;34(4):1139–46. https://doi.org/10.1097/01.CCM.0000206468.18653.EC

Descargado para Anonymous User (n/a) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en noviembre 16, 2023.
Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2023. Elsevier Inc. Todos los derechos reservados.