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Review Article

LncRNA MALAT1 in Keratinocyte function: A review of recent advances

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ABSTRACT

Keratinocytes, the principal epidermal cells, play a vital role in maintaining the structural integrity and functionality of the skin. Beyond their protective role, keratinocytes are key contributors to the process of wound healing, as they migrate to injury sites, proliferate, and generate new layers of epidermis, facilitating tissue repair and remodeling. Moreover, keratinocytes actively participate in the skin's immune responses, expressing pattern recognition receptors (PRRs) to detect microbial components and interact with immune cells to influence adaptive immunity. Keratinocytes express a diverse repertoire of signaling pathways, transcription factors, and epigenetic regulators to regulate their growth, differentiation, and response to environmental cues. Among these regulatory elements, long non-coding RNAs (lncRNAs) have emerged as essential players in keratinocyte biology. LncRNAs, including MALAT1, play diverse roles in gene regulation and cellular processes, influencing keratinocyte proliferation, differentiation, migration, and response to environmental stimuli. Dysregulation of specific lncRNAs such as MALAT1 can disrupt keratinocyte homeostasis, leading to impaired differentiation, compromised barrier integrity, and contributing to the pathogenesis of various skin disorders. Understanding the intricate interplay between lncRNAs and keratinocytes offers promising insights into the molecular underpinnings of skin health and disease, with potential implications for targeted therapies and advancements in dermatological research. Hence, our objective is to provide a comprehensive summary of the available knowledge concerning keratinocytes and their intricate relationship with MALAT1.

1. Introduction

Keratinocytes, as the principal epidermal cells, play a pivotal role in maintaining the structural integrity and resilience of the skin through their ability to synthesize and accumulate the fibrous structural protein known as keratin [1]. Accounting for a substantial 90 % of the stratified flat epithelium, these cells derive their name from their distinctive capacity to accumulate keratin during their maturation process [2]. Through the production and organization of proteins, including keratins, they establish a robust barrier that defends the body against pathogens, chemicals, and harmful UV radiation [3]. Additionally, keratinocytes are key contributors to the process of wound healing [4]. When an injury occurs, they migrate to the site of the wound, proliferate, and generate a new layer of epidermis, facilitating tissue repair and remodeling [5]. The secretion of growth factors, cytokines, and extracellular matrix components by keratinocytes further supports the healing process. In terms of immune responses, keratinocytes actively participate in the skin's defense mechanisms [6]. They express PRRs that detect microbial components, triggering innate immune responses. Moreover, they interact with immune cells, influencing adaptive immune responses in the skin [7]. In certain inflammatory skin disorders such as psoriasis, atopic dermatitis, and eczema, dysregulated signaling pathways in keratinocytes contribute to the inflammatory processes [8,9]. This leads to the characteristic skin manifestations observed in these conditions. Furthermore, accumulated DNA damage and mutations, often caused by exposure to UV radiation may cause genetic alterations in keratinocyte-related genes which increase the susceptibility that can lead to uncontrolled cell growth and the formation of tumors and to skin

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cancers, including squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) [10,11]. Beyond their role as the skin's structural guardians, keratinocytes exhibit a fascinating array of molecular mechanisms that regulate their growth, differentiation, and response to environmental cues. These intricate processes are tightly orchestrated by various signaling pathways, transcription factors, and epigenetic regulators [12,13]. In recent years, emerging evidence has shed light on the involvement of lncRNAs in keratinocyte biology [14,15]. LncRNAs are transcripts that do not code for proteins of >200 pb in length, once considered transcriptional "noise," are now recognized as key players in gene regulation and have garnered attention for their potential implication in diverse cellular processes [16,17]. Dysregulation of specific lncRNAs can disrupt this balance, leading to abnormal keratinocyte proliferation, impaired differentiation, and compromised barrier integrity, contributing to the pathogenesis of skin disorders such as psoriasis, atopic dermatitis, and skin cancers [18]. In this sense, lncRNA MALAT1 has emerged as a crucial player in various cellular processes, including cell proliferation, differentiation, and migration [19]. Its regulatory influence extends to epigenetic modulation and gene expression, making it an intriguing candidate in the context of keratinocyte biology. MALAT1 expression levels have been found to vary during keratinocyte differentiation, suggesting its potential role in orchestrating the intricate process of keratinocyte maturation and keratinization [20]. Furthermore, MALAT1 appears to be involved in the regulation of key cytokines and growth factors, including epidermal growth factor (EGF) and transforming growth factor (TGF), which are critical in guiding keratinocyte development and response to environmental stimuli. Despite the wide range of information about MALAT1, their specific role in keratinocyte biology still is poorly understood, therefore the purpose of this review is to summarize all the existent information about keratinocytes and MALAT1.

2. lncRNA MALAT1

MALAT-1 also known as nuclear-enriched abundant transcript 2 (NEAT2), HCN, LINC00047, NCRN00047, and PRO1073, is one of the most studied lncRNAs around the world. MALAT1 is transcribed from the MALAT1 gene located on chromosome 11q13 Fig. 1a. It is recognized as one of the longest non-coding RNAs known to date, spanning over 8000 nucleotides [21]. Given its considerable length, MALAT1 exhibits a complex secondary structure, which has been predicted using various bioinformatic algorithms Fig. 1b [22,23]. An intriguing aspect of MALAT1 biogenesis lies in its atypical 3′ end formation. Unlike the polyadenylation process commonly observed in many RNAs, MALAT1 does not possess a poly(A) tail. Instead, the tRNA biogenesis machinery generates its mature 3′ end. Notably, MALAT1's stability is ensured by highly conserved triple helical structures, which accumulate to significant levels in the nucleus Fig. 1c,d and e [24].

MALAT-1 is one of the most abundantly expressed lncRNAs, comparable with some housekeeping genes such as B-actin or GAPDH [28]. MALAT1 primarily localizes to the nucleus, specifically to nuclear speckles, which are subnuclear compartments involved in RNA processing and splicing, this localization implies that MALAT1 likely plays a role in regulating RNA processing and splicing events, including alternative splicing, furthermore, it may interact with other proteins or RNA molecules within nuclear speckles, influencing the splicing machinery and modulating gene expression. In addition, MALAT1's presence in nuclear speckles suggests its involvement in nuclear organization, gene expression control, and potentially in disease processes, particularly those related to dysregulated RNA processing and splicing [29]. On the other hand, MALAT1 can regulate gene expression at different levels, for instance; it has been shown to interact with transcription factors, chromatin modifiers, and RNA-binding proteins, influencing transcriptional regulation, epigenetic modifications, and post-transcriptional processing of target genes. It can act as a scaffold, bringing together

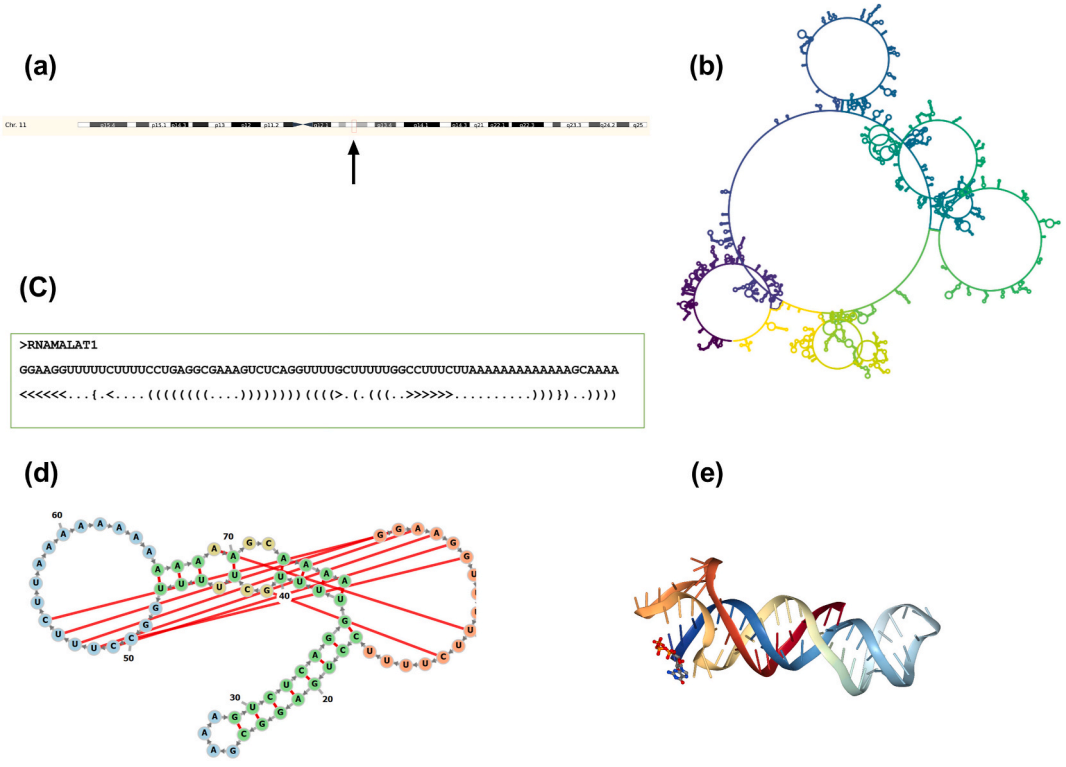

Fig. 1. (a) Chromosomic localization of MALAT1 gene obtained from http://www.ensembl.org/index.html [25]. (b) Secondary structure of MALAT1 predicted through bioinformatics image was sourced from a public repository (https://github.com/sinc-lab/lncRNA-folding) generously provided by by Bugnon and colleagues [22]. (c) Sequence of triple-helical stability element at the 3′ end of MALAT1 extracted from https://www.rcsb.org/ [26]. (d and e) Secondary and tertiary structure of triple-helical stability element at the 3′ end of MALAT1 respectively obtained through https://yanglab.qd.sdu.edu.cn/trRosettaRNA/ [27].

multiple proteins involved in gene regulation [30]. Dysregulation of MALAT1 expression has been observed in several skin disorders, including psoriasis, atopic dermatitis, and systemic lupus erythematosus (SLE), through regulation of different cellular processes Fig. 2 [31–33].

3. Cellular and molecular functions of lncRNA Malat1 in keratinocytes

3.1. MALAT1-miRNA interactions in Keratinocyte biology

Recent research has shed light on the intricate crosstalk between lncRNAs and miRNAs, where lncRNAs act as competitive endogenous RNAs (ceRNAs) or miRNA sponges, pulling miRNAs away from their target mRNAs and thereby modulating the expression of target genes [34,35]. The MALAT1 lncRNA has been found to interact with various miRNAs through complementary base pairing and has been implicated in regulating several cellular processes by affecting miRNA-mediated gene regulation [36,37]. In the context of keratinocyte biology, some researchers have investigated the molecular role of MALAT1 and their association with diverse miRNAs. For instance, Lin He and collaborators carried out an experimental study in which they examined the role of exosomes from adipose-derived stem cells (ADSCS-Exos) on cultured HaCaT keratinocyte cell line simulated a skin lesion model with H2O2. The researchers found that elevated MALAT1 expression in extracellular vesicles from adipose-derived stem cells (ADSC-Exos) was linked to favorable effects on cell proliferation, migration, and apoptosis in HaCaT keratinocytes. Notably, when MALAT1 was depleted in ADSC-Exos, these positive effects were reversed. Bioinformatics analysis and luciferase activity assays further confirmed the direct targeting of miR-124 by MALAT1. Knocking down MALAT1 resulted in an increased expression of miR-124. Investigating the involvement of the Wnt/β-catenin pathway in wound healing, the authors discovered a regulatory association among MALAT1, miR-124, and the Wnt/β-catenin pathway. This intricate network suggests that MALAT1 may modulate keratinocyte behavior through interactions with miR-124 and the Wnt/β-catenin pathway, impacting cellular processes crucial for wound healing and skin biology [38]. On the other hand, Liwen Kuang and colleagues investigated the role of macrophages in wound healing and how human exosomes derived from keratinocytes (KCs) carrying MALAT1 could regulate the expression of miR-1914-3p and MFGE8 in macrophages. First, they found that inhibition of miR-1914-3p increased MFGE8 expression, promoting macrophage phagocytosis, reducing apoptosis, and shifting macrophage polarization towards the M2 type. Additionally, through bioinformatics, the authors found MALAT1 as an lncRNA candidate in regulating the miR-1914-3p/MFGE8 axis. Therefore, they explored the role of MALAT1 as a competitive endogenous RNA (ceRNA) in regulating miR-1914-3p and MFGE8. MALAT1 expression was found reduced in macrophages cultured in a high glucose environment and in the peri-wound skin tissues of diabetic mice. They demonstrated that MALAT1 could competitively bind to miR-1914-3p and regulate MFGE8 expression. The changes in miR-1914-3p and MFGE8 expression influenced macrophage phagocytosis, apoptosis, and polarization through the TGFB1/SMAD3 signaling pathway. Finally, the authors confirmed that exosomes derived from KCs carrying MALAT1 could regulate the expression of miR-1914-3p and MFGE8 in macrophages [39]. In another study, Li-Wen Kuang and collaborators aimed to investigate the possible

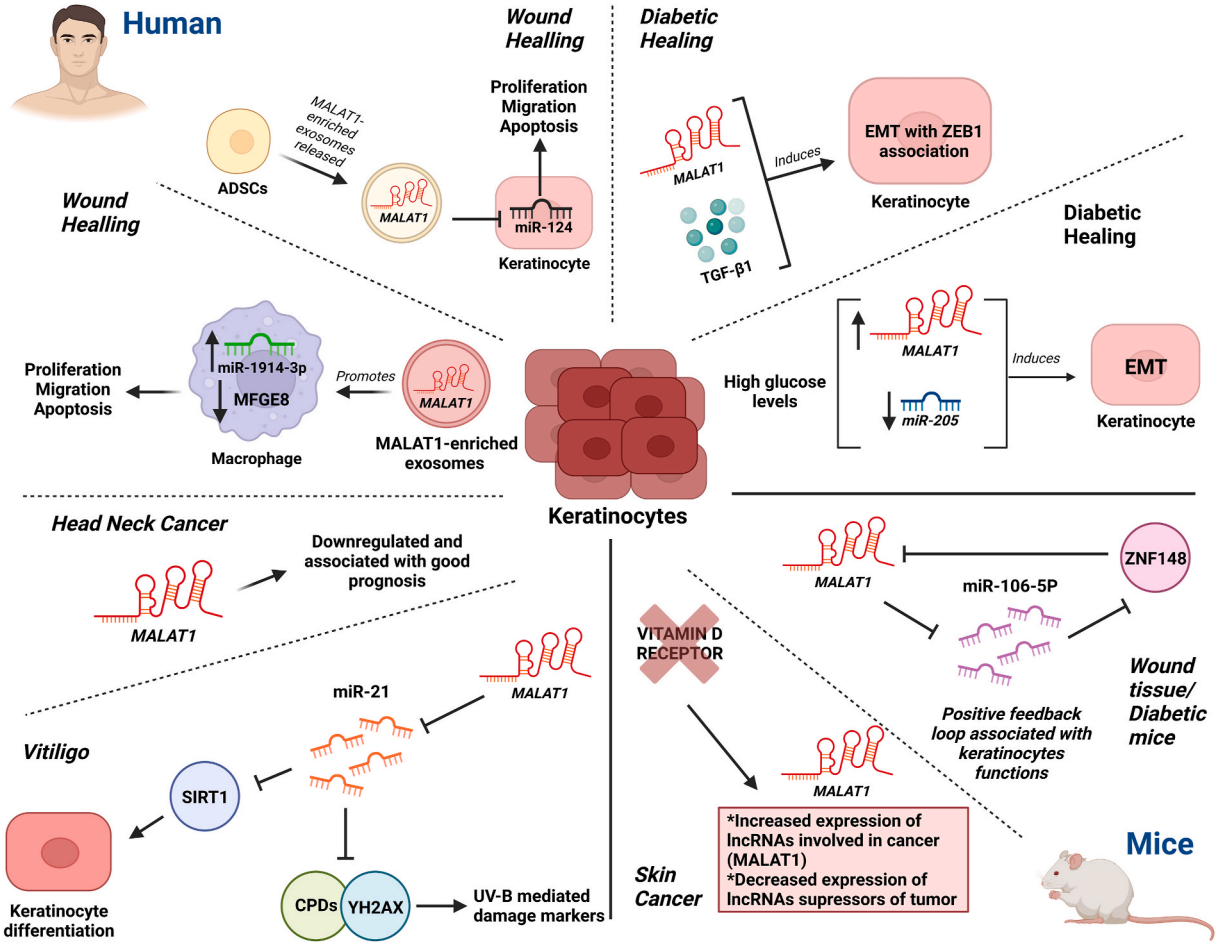

Fig. 2. MALAT1, a long non-coding RNA, intricately modulates keratinocyte biology through diverse mechanisms. It engages in intricate crosstalk with multiple miRNAs, acting as a competitive endogenous RNA (ceRNA) or miRNA sponge, influencing processes like cell proliferation, migration, and apoptosis.

positive feedback loops involving lncRNAs in diabetic wound healing through mice and an *in vitro* keratinocyte model. The researchers observed that MALAT1 expression was reduced in the wound tissue of diabetic mice. They further demonstrated that MALAT1 could promote several biological functions of keratinocytes, which are crucial for wound healing. Furthermore, they also uncovered a regulatory mechanism involving MALAT1, miR-106a-5p, and ZNF148. Specifically, MALAT1 was found to bind to miR-106a-5p, thereby modulating the expression of ZNF148, which is a target gene of miR-106a-5p. This interaction between MALAT1 and miR-106a-5p influenced the expression of ZNF148. Interestingly, the researchers made an unexpected discovery that ZNF148 can bind to a specific region in the MALAT1 promoter. Overall, the study concludes that ZNF148-activated MALAT1 contributes to an amplification mechanism. By competitively binding miR-106a-5p, ZNF148 increases the expression of MALAT1, which in turn enhances ZNF148 expression. This forms a positive feedback loop that ultimately enhances the biological functions of keratinocytes [20]. In another study, Brahmbhatt and collaborators made several important findings regarding the relationship between SIRT1, miR-211, keratinocyte differentiation, and DNA damage in vitiligo. Firstly, they discovered that miR-211, which is the most significantly downregulated microRNA in the lesional epidermis, directly targets SIRT1. This suggests that miR-211 plays a role in regulating SIRT1 expression in vitiligo. The researchers also found that inhibiting SIRT1 using a compound called EX-527 resulted in the downregulation of two proteins called keratin 10 and involucrin. This suggests that SIRT1 promotes the differentiation of keratinocytes, which are the predominant cells in the epidermis. Moreover, the study showed that overexpressing a mimic of miR-211 led to increased levels of γ-H2AX, a marker of DNA damage, and the formation of cyclobutane pyrimidine dimers (CPDs), which are another indicator of UVB-induced DNA damage. These results suggest that miR-211 is involved in the DNA damage response in vitiligo. Interestingly, the researchers found that the effects of miR-211 overexpression on DNA damage could be mitigated by the addition of resveratrol, a SIRT1 activator. This implies that SIRT1 activation may protect against UVB-induced DNA damage in vitiligo. Furthermore, the study identified a long noncoding RNA called MALAT1 as a negative regulator of miR-211. Overexpression of MALAT1 resulted in increased SIRT1 expression and a subsequent reduction in UVB-induced CPDs in primary keratinocytes. This suggests that MALAT1 acts upstream of miR-211 and influences the expression of SIRT1, potentially contributing to the protection of "amelanotic" keratinocytes in vitiligo. Overall, these findings unveil a novel signaling pathway involving MALAT1, miR-211, and SIRT1, which appears to play a role in keratinocyte differentiation, DNA damage response, and potential protection against UVB-induced damage in vitiligo [40]. Finally, Zhou Y. and colleagues investigated the role of the lncRNA MALAT-1 in the pathogenesis of psoriasis, a chronic autoimmune disorder characterized by abnormal keratinocyte proliferation. They examined how MALAT-1 influences keratinocyte proliferation, inflammation, and apoptosis in psoriasis. To do this, they established a psoriasis cell model by treating HaCaT keratinocytes with the inflammatory factor IL-22 and observed upregulation of both MALAT-1 and S100A7 levels, indicating their potential involvement in psoriasis. Silencing MALAT-1 in IL-22-treated HaCaT cells reversed the IL-22-stimulated promotion of keratinocyte proliferation and changes in certain protein levels. Furthermore, MALAT-1 deficiency also reversed the upregulation of pro-inflammatory cytokines and the suppression of cell apoptosis. Through bioinformatics analysis, the researchers identified miR-330-5p as a miRNA that binds to both MALAT-1 and S100A7. They demonstrated that MALAT-1 functions as a competing endogenous RNA (ceRNA), sequestering miR-330-5p and preventing it from inhibiting S100A7 expression, thus forming the miR-330-5p/S100A7 axis. The study highlighted the negative correlation between miR-330-5p and MALAT-1 (or S100A7) expression in psoriatic lesion tissues, supporting the regulatory role of MALAT-1 in psoriasis. Silencing miR-330-5p in response to IL-22 treatment eliminated the effects of MALAT-1 knockdown in HaCaT cells, confirming the functional significance of the miR-330-5p/S100A7 axis in psoriasis-related changes [41]. Overall, the collected evidence from various studies suggests that MALAT1 interacts with and regulates the expression of multiple miRNAs, including miR-124, miR-205, miR-1914-3p, miR-106a-5p, and miR-330-5p. These interactions have implications in various cellular processes and disease contexts. MALAT1 appears to act as a critical regulator of miRNA-mediated gene expression, affecting cell proliferation, migration, apoptosis, inflammation, and differentiation in different biological systems See Table 1 and Fig. 2.

3.2. lncRNA MALAT1's role in Keratinocyte epithelial to mesenchymal transition

The inherent plasticity of the epithelial phenotype is demonstrated by the capacity of epithelial cells to undergo transitions between epithelial and mesenchymal states, partially or fully [42]. During the process known as Epithelial-Mesenchymal Transition (EMT), epithelial cells undergo significant changes: they lose their junctions and apical-basal polarity, reorganize their cytoskeleton, alter signaling pathways that define cell shape, and undergo gene expression reprogramming [43]. These changes increase the motility of individual cells and facilitate the development of an invasive phenotype [44]. EMT plays

Table 1
Cellular and Molecular functions of MALAT1 in keratinocytes.

	Main Finding	Cellular function	Ref
miRNA interaction	Direct targeting of **miR-124** by MALAT1.	Regulation of cell proliferation, migration and apoptosis through the Wnt/β-catenin Pathway	37
	MALAT1 as a competitive endogenous RNA (ceRNA) in regulating **miR-1914-3p** and MFGE8	Regulation of macrophage phagocytosis, reducing apoptosis, and shifting macrophage polarization towards the M2 type	38
	Positive feedback loop of regulation between MALAT1, **miR-106a-5p**, and ZNF148.	Regulation of biological functions of keratinocytes, which are crucial for wound healing.	20
	Discovering a novel signaling pathway involving MALAT1, **miR-211**, and SIRT1.	Keratinocyte differentiation, DNA damage response, and potential protection against UVB-induced damage	39
	MALAT1 as a ceRNA, sequestering **miR-330-5p** and thereby affecting the expression of S100A7.	Modulating cellular responses in psoriasis.	40
Epithelial to Mesenchymal transition	MALAT1 reduces ZEB1 expression.	Regulation of expression levels mesenchymal markers and morphological changes.	31
	MALAT1 affects KRT10, ACTA2 and MMP9 expression.	Regulation of morphological changes associated with EMT.	48
Cancer	MALAT1 downregulated	Linked to good prognosis in HNC.	54
	VDR regulating the expression of MALAT1	Possible association with cancer development and progression.	55
	MALAT1 associated with KTN1 and EGFR	Association with cutaneous squamous cell carcinoma progression	56
	Increased levels of MALAT1 in keratinocytes with deleted Vitamin D receptor (VDR)	VDR are associated with the regulation of several oncogenic and tumor suppressors including MALAT1.	57

a crucial role in development, and the mechanisms involved in this process are reactivated during wound healing, fibrosis, and the progression of cancer. In the context of keratinocytes, EMT is involved in various biological processes, including wound healing, tissue repair, and skin regeneration [45]. During wound healing, keratinocytes at the wound edge undergo EMT to acquire a more migratory and invasive phenotype, allowing them to move into the wound site and contribute to tissue repair [46]. This transition is essential for the re-epithelialization of the wound and the restoration of the skin barrier [47]. In the context of EMT and MALAT1, few studies have investigated both fields. For instance, one study led by Liping Zhang and colleagues examined the involvement of MALAT1 in TGF-β1-induced Epithelial to Mesenchymal Transition in HaCaT cells and its potential relevance to diabetic wounds. They observed that MALAT1 and TGF-β1 expression were significantly increased in diabetic wounds compared to controls. The researchers induced EMT in HaCaT cells by treating them with TGF-β1 and measured the expression levels of specific markers. They found that down-regulated CDH1, an epithelial marker, and up-regulated CDH2, KRT10, and ACTA2, which are mesenchymal markers, were associated with EMT. By knocking down MALAT1, they observed a decrease in TGF-β1-induced EMT, characterized by reduced expression levels of mesenchymal markers and prevention of morphological changes in the cells. Furthermore, they investigated the impact of MALAT1 on the expression levels of the transcription factor ZEB1, known to be involved in EMT. Knocking down MALAT1 reduced ZEB1 expression while overexpressing MALAT1 increased ZEB1 expression [31]. Dysregulation of CDH2, KRT10, and ACTA2 within the MALAT1/TGFB axis in keratinocytes disrupts normal cell behavior, compromising essential aspects like adhesion, structure, and cytoskeletal dynamics critical for maintaining skin function [48]. Then, a further study guided by the same research team investigated the role of MALAT1 and miR-205 in diabetic wounds. They found that MALAT1 expression was increased, while miR-205 expression was decreased in diabetic wounds compared to non-diabetic wounds. Moreover, they found that high glucose levels upregulated MALAT1 and downregulated miR-205 in HaCaT cells, leading to EMT characterized by morphological changes and altered expression of CDH1, CDH2, ACTA2, KRT10, and MMP9. Knocking down MALAT1 attenuated high-glucose-induced upregulation of KRT10 and ACTA2 and prevented EMT-associated morphological changes. Overexpressing miR-205 inhibited high-glucose-induced EMT by increasing CDH1 expression and decreasing CDH2, TAGLN, ACTA2, KRT10, and ZEB1 expression. This study provides insight into the MALAT1/miR-205 pathway in the regulation of EMT of keratinocytes in hyperglycemic conditions [49]. Understanding the association between MALAT1 and EMT in keratinocytes provides valuable insights into the molecular mechanisms governing keratinocyte biology, with potential implications for therapeutic interventions targeting EMT-related processes in skin diseases such skin cancer. However, further research is needed to unravel the complete functional significance of MALAT1's association with EMT in keratinocytes and its potential role as a therapeutic target for various skin-related disorders.

3.3. MALAT1 in keratinocytes and their association with skin cancer

Originally identified as a prognostic marker for metastasis in lung cancer, MALAT1 has since been found to be dysregulated in numerous other cancer types [50,51]. Accumulating evidence suggests that MALAT1 plays multifaceted roles in cancer, including promoting tumor cell proliferation, invasion, and metastasis, as well as affecting tumor microenvironment and therapy resistance [52]. In this sense, Skin cancer is one of the most prevalent forms of cancer worldwide, with increasing incidence rates [53]. In addition, MALAT1 has been found to be dysregulated in various skin cancer types, in which keratinocytes are key actors such squamous cell carcinoma [54]. For instance, Shang-Ju Tang and collaborators aimed to explore the role of long non-coding RNAs in head and neck cancer (HNC). They conducted a comparison of 84 cancer-related lncRNAs using a PCR array in three HNC cell lines (SAS, OECM1, and FaDu) and two normal keratinocyte lines (CGHNK2 and CGHNK6). The findings indicated the involvement of dysregulated lncRNAs in HNC development and progression. Specifically, they identified 27 dysregulated lncRNAs and further assessed their expression levels and prognostic significance in HNC patients. Among these transcripts, nine lncRNAs (TERC, LINC01234, CCAT1, XIST, GACAT1, WT1-AS, CCAT2, HOXA11-AS, and TSIX) were upregulated and associated with poor prognosis, while six (NEAT1, MALAT1, CDKN2B-AS1, CBR3-AS1, IPW, and AIRN) were downregulated and linked to good prognosis. The validation of their findings was performed with only XIST one of the dysregulated lncRNAs using RNA-seq data and RT-qPCR expression analysis. In conclusion, the researchers emphasized that their panel of dysregulated lncRNAs, including MALAT1, holds promise as valuable biomarkers for predicting prognosis in HNC [55]. In addition, Yan J. Jiang and colleagues aimed to profile the expression of 90 well-annotated mouse lncRNAs in cultured mouse keratinocytes. They compared keratinocytes with a deleted vitamin D receptor (VDR) to control cells, utilizing a lncRNA array analysis. The results of the analysis revealed significant alterations in the expression levels of various lncRNAs in VDR-deleted keratinocytes compared to control cells. Several well-known oncogenes, such as H19, HOTTIP, and Nespas, exhibited a substantial increase in expression. Conversely, tumor suppressors like Kcnq1ot1 and lincRNA-p21 showed a decrease in expression in VDR-deleted keratinocytes. To further support these findings, the researchers examined the lncRNA profile in the epidermis of mice with a specific deletion of VDR in the skin, controlled by the K14 promoter and tamoxifen regulation. Consistently, a similar pattern of lncRNA expression was observed in these mice, with increased levels of oncogenes such as HOTAIR, MALAT1, and SRA, and decreased levels of tumor suppressors including Foxn2-as, Gtl2-as, and H19-as the researchers highlighted the crucial role of VDR in regulating the expression of specific lncRNAs involved in skin cancer development. The dysregulation of oncogenic and tumor-suppressing lncRNAs in the absence of VDR underscores the importance of VDR in maintaining the proper balance of these lncRNAs for skin cancer prevention [56]. In another study, Ying Zhang and colleagues aimed to elucidate the role of MALAT1 in cutaneous squamous cell carcinoma (cSCC) and its potential regulatory mechanisms on EGFR expression in diverse cell lines including HaCaT keratinocyte cell line. They observed that MALAT1 loss resulted in the inhibition of EGFR protein expression without affecting EGFR mRNA levels. Investigating potential indirect regulatory mechanisms, they proposed cancer-specific pathways involving miRNAs or HIF-2α. Transcriptomic sequencing revealed KTN1 as a critical mediator in the MALAT1-KTN1-EGFR axis. KTN1 downregulation significantly reduced EGFR protein expression, pointing to its role in promoting cSCC progression. Moreover, the study identified c-MYC as a key interacting partner of MALAT1, suggesting its involvement in both epigenetic transactivation of MALAT1 and a direct interaction to enhance KTN1 expression, ultimately contributing to cSCC development. The findings unveil a novel regulatory axis, MALAT1-KTN1-EGFR, providing potential therapeutic targets for anti-cSCC therapy [57].

Finally, in another study guided by Yan Jiang delved into the protective role of vitamin D signaling against chemical and UVR-induced skin cancer, an area where the mechanistic understanding is limited. Recognizing the significance of long non-coding RNAs in cancer, the study focused on profiling 90 well-annotated mouse lncRNAs in keratinocytes with a deleted vitamin D receptor (VDR) compared to control cells. The results unveiled a dysregulation in the balance of oncogenic and tumor-suppressing lncRNAs in VDR-deleted keratinocytes, marked by a substantial increase in oncogenes (H19, HOTTIP, Nespas, and MALAT1) and a decrease in tumor suppressors (Kcnq1ot1, lincRNA-p21). This pattern was consistent in the epidermis of VDR-null mice. Notably, the study identified a novel mechanism whereby VDR protects against skin cancer formation by maintaining the equilibrium of oncogenic and tumor-suppressing lncRNAs. The disturbance of this balance

in VDR-deficient conditions, leading to increased oncogene expression and decreased tumor suppressors, provides insights into the predisposition of VDR-deficient mice to skin cancer. The authors utilized lncRNA array analysis and real-time PCR to substantiate their findings, shedding light on the intricate role of lncRNAs in the protective mechanisms of vitamin D signaling in skin cancer [58].

By elucidating the specific roles of MALAT1 in skin cancer progression, including its impact on cell proliferation, invasion, metastasis, and therapy resistance, researchers can identify potential therapeutic targets and biomarkers that hold promise for more effective and personalized cancer treatments. Additionally, further exploration of MALAT1's association with skin cancer could lead to the development of non-invasive diagnostic tools, improving early detection and prognosis assessment.

3.4. lncRNA MALAT1 in the clinical trial landscape

Clinical trials, integral to exploring novel biomarkers and therapeutic targets, increasingly acknowledge the pivotal role of lncRNAs in physiological and pathological processes. These trials, assessing intervention efficacy and safety, unravel the regulatory functions of non-coding RNAs in gene expression across diverse disorders [59,60]. Within this landscape, the lncRNA MALAT1 stands out, highlighted in one published and two ongoing studies. Xihao Du study on air pollution impact reveals 55 differentially expressed lncRNAs, including MALAT1, providing insights into the cardiovascular effects of air pollution [61]. Notably, two clinicalTrials.gov studies focus on MALAT1. The completed study (NCT05708209) evaluated MALAT1's diagnostic accuracy in oral squamous cell carcinoma (OSCC) through salivary biomarkers. Saliva samples from OSCC patients and healthy controls were quantitatively analyzed. Another ongoing study (NCT05995067) explores MALAT1's association with epithelial-mesenchymal transition in periodontitis, assessing lncRNA expression and EMT-related genes in healthy and diseased periodontal tissues. Despite these trials are not focused on Keratinocytes and skin diseases, they offer valuable contributions to understanding MALAT1's implications in various disorders. These trials contribute to a comprehensive understanding of MALAT1 in skin disorders, offering potential for innovative therapeutic interventions, personalized treatment strategies, and non-invasive diagnostic tools. As MALAT1's intricacies continue to be unraveled through clinical trials, the future of skin disorders medicine holds the promise of targeted, effective, and personalized approaches for improved patient outcomes.

3.5. Future perspectives

The investigation of the long non-coding RNA, MALAT1, has shed light on its potential pivotal roles in the complex biology of keratinocytes. Researchers are delving into this captivating realm of scientific inquiry, uncovering an intriguing interplay between MALAT1 and keratinocytes. The concept of personalized medicine, driven by the identification of unique RNA profiles, offers promising prospects for tailored treatments with enhanced precision and minimized side effects. Moreover, the interplay between MALAT1 and environmental factors, such as UV radiation, holds significant potential in unraveling the mysteries of skin aging and the genesis of skin cancers. As MALAT1 harmonizes with an array of lncRNAs, a comprehensive portrait of skin biology and the development of diverse skin disorders emerges. Within this intricate landscape, exosomes stand out as pivotal messengers, paving the way for precise therapeutic delivery. Furthermore, the integration of multi-omics approaches weaves a compelling narrative, illuminating the intricate complexities of keratinocyte biology, lncRNAs, and cutaneous health. To advance the field, further studies should focus on unraveling the intricate molecular mechanisms of MALAT1 in the realm of dermatology, holding the promise of advancing personalized medicine and therapeutic strategies.

4. Conclusions

In conclusion, this review on MALAT1 and keratinocytes presents a captivating journey into the intricate world of long non-coding RNAs and their role in skin biology. Through the exploration of MALAT1, researchers have uncovered its potential key roles in regulating keratinocyte function. The newfound knowledge provides a foundation for future investigations, aiming to unlock new therapeutic avenues and enhance our understanding of skin disorders, wound healing, and skin cancer development. With this wealth of information, researchers are empowered to pave the way for innovative advancements in dermatology, benefitting patients with improved clinical outcomes and personalized care.

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Credit authorship contribution statement

Yaneli Juárez-Vicuña: Conceptualization, Writing – original draft, Writing – review & editing. **Dayanara Ruiz-Ojeda:** Writing – original draft, Writing – review & editing, Investigation. **Javier González-Ramírez:** Conceptualization, Writing – original draft, Supervision. **Ximena Flores-Balderas:** Writing – original draft, Writing – review & editing, Investigation. **Rashidi Springall:** Supervision, Writing – review & editing, Investigation. **Fausto Sánchez-Muñoz:** Investigation, Supervision, Writing – review & editing. **Carlos A. Guzmán-Martín:** Conceptualization, Investigation, Supervision, Writing – review & editing.

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During the preparation of this work the author(s) used OpenAI ChatGPT 3.5 in order to improve language. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

Declaration of competing interest

The authors declare that they have no conflicts of interest.

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