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Role of miRNAs in amino acid metabolism: Model of ER stress in human dermal fibroblasts

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Endoplasmic reticulum (ER) stress is a key cellular event that disrupts protein folding and homeostasis and is implicated in the pathogenesis of various metabolic and degenerative diseases. Despite extensive research on ER stress, the precise mechanisms linking ER stress-induced metabolic alterations and post-transcriptional regulation by microRNAs remain inadequately understood. Given the central role of amino acid metabolism in stress adaptation and the emerging importance of miRNAs in fine-tuning gene expression under stress conditions, this study was undertaken to explore the interplay between ER stress, amino acid metabolism, and microRNA regulation. In this study, ER stress was induced in human dermal fibroblast cell line CCD-1135Sk using tunicamycin, a potent inhibitor of N-linked glycosylation. Amino acid profiles were analyzed using liquid chromatography-mass spectrometry, and differentially expressed miRNAs associated with metabolic shifts were identified through real-time PCR. Our findings demonstrate that ER stress significantly alters amino acid metabolism, and these changes correlate with differential expression of specific miRNAs that may orchestrate cellular stress responses and metabolic adaptations. This integrated analysis provides novel insights into how cells modulate metabolic networks and gene regulation under ER stress conditions, which could have implications for understanding disease mechanisms and developing targeted interventions.

Keywords: Unfolded protein response, Tunicamycin, Metabolic adaptation, Non-coding RNA, Human skin cells

Dermal fibroblasts are connective tissue cells located in the dermis layer of the skin, primarily responsible for producing extracellular matrix (ECM) components such as collagen, elastin, and hyaluronic acid[1]. These cells play essential roles in maintaining dermal structure, skin elasticity, and wound healing[2]. Under physiological conditions, fibroblasts respond to cellular stress or damage such as abnormal protein accumulation or external insults, by activating internal mechanisms that help preserve cellular function and prevent damage[3]. Their ability to synthesize ECM proteins and facilitate tissue remodeling makes them central to skin repair. Due to their high protein production capacity, fibroblasts are particularly susceptible to endoplasmic reticulum (ER) stress[4,5]. ER stress arises when misfolded or unfolded proteins accumulate within the ER lumen, often due to environmental stressors or cellular dysfunction. This accumulation overwhelms the ER′s protein-folding machinery, especially chaperone proteins, and triggers an adaptive signaling cascade known as the unfolded protein response (UPR)[6]. The UPR aims to restore ER homeostasis by halting protein translation, promoting the degradation of misfolded proteins, and increasing the production of molecular chaperones[7]. However, if ER stress is prolonged or unresolved, it can lead to apoptosis. In fibroblasts, chronic ER stress can impair essential functions such as collagen production, migration, and proliferation, all of which are critical for effective wound healing and tissue repair[8]. Reduced fibroblast function due to ER stress has been linked to delayed wound healing and the pathogenesis of skin-related disorders. ER stress disrupts normal protein processing and can compromise cellular function, leading to insufficient ECM production and weakened skin structure[9]. Moreover, fibroblasts exposed to persistent stress exhibit reduced motility and impaired response to injury, further hindering the repair process. Chronic ER stress has also been associated with premature skin ageing and dermal degeneration due to loss of collagen integrity[10]. One of the common experimental inducers of ER stress is tunicamycin, a naturally occurring antibiotic that inhibits N-linked glycosylation, thereby promoting the accumulation of misfolded glycoproteins within the ER. Tunicamycin has been widely used to study ER stress in various cell types, including fibroblasts, as it effectively simulates stress conditions by impairing protein folding[11]. It provides a reliable model to investigate how fibroblasts respond to stress at molecular and metabolic levels, and how these responses could be harnessed for therapeutic strategies in skin diseases. ER stress not only impacts protein folding but also has significant effects on amino acid metabolism. Amino acids are essential for maintaining protein synthesis, energy balance, and redox homeostasis, especially under stress conditions.

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Recent research suggests that ER stress alters intracellular amino acid profiles, reflecting adaptive mechanisms to maintain cellular homeostasis. These metabolic shifts include changes in the synthesis, uptake, and utilization of key amino acids such as glutamine and serine[12]. Glutamine is particularly important in this context due to its role in supporting protein synthesis, nucleotide biosynthesis, and antioxidant defense. Under ER stress, increased glutamine uptake and utilization have been observed, likely reflecting a cellular attempt to meet the heightened demand for protein synthesis and stress adaptation[13]. Zhang *et al*. demonstrated that ER stress leads to enhanced glutamine metabolism, which in turn supports protein folding and cellular recovery mechanisms. Elevated glutamine levels may also aid in mitigating oxidative stress, thereby enhancing cell survival[13]. Similarly, serine is another amino acid significantly affected by ER stress. It serves as a precursor for phospholipid synthesis and plays a role in maintaining membrane integrity and protein homeostasis. Alterations in serine metabolism may indicate ER stress-induced shifts in lipid metabolism and biosynthetic capacity[14]. Changes in levels of methionine, another amino acid involved in methylation and antioxidant pathways, have also been noted during ER stress, suggesting a broader metabolic reprogramming that extends beyond glutamine and serine[12]. These findings collectively point to a critical interplay between ER stress and amino acid metabolism in dermal fibroblasts. Disruptions in amino acid homeostasis may exacerbate the effects of ER stress, while specific amino acid responses may serve as compensatory mechanisms to alleviate stress. Understanding how fibroblasts modulate their metabolic pathways in response to ER stress is essential for deciphering their role in tissue repair and could inform the development of therapeutic interventions for skin diseases.

Materials and Methods

Cultivation of cells

The human dermal fibroblast cell line CCD-1135Sk (adult skin origin) was obtained from the Ankara ŞAP Institute collection. Recent literature confirms that CCD-1135Sk cells are routinely cultured in Dulbecco′s Modified Eagle Medium (DMEM) supplemented with 10% fetal bovine serum (FBS) at 37 °C in a humidified 5% CO_2 atmosphere, reflecting standard practice in fibroblast-based studies[15].

Application of tunicamycin

The human dermal fibroblast cell line CCD-1135Sk was seeded into well culture plates at a density of approximately 5×10^5 cells per well. After 24 hours of adhesion under standard culture conditions (DMEM with 10% FBS and 1% penicillin–streptomycin at 37 °C and 5% CO_2), the medium was replaced with fresh DMEM containing tunicamycin at a final concentration of 5 µg/mL. Cells were then incubated for two time points, 6 and 24 hours, to induce ER stress. This protocol aligns with established methodologies for tunicamycin-induced ER stress in fibroblast cultures, where tunicamycin treatment effectively triggers markers such as GRP78 and CHOP within similar incubation periods[16].

Analysis of miRNAs by real-time PCR

Total RNA was extracted from both control and tunicamycin-treated CCD-1135Sk fibroblasts (5 µg/mL) using an Invitrogen total RNA isolation kit, following the manufacturer′s protocol. cDNA synthesis and real-time PCR were performed using Power SYBR™ Green PCR Master Mix on an Applied Biosystems QuantStudio 6 Flex system, in line with recent fibroblast studies demonstrating reliable UPR gene expression quantification under ER stress conditions[17].

Amino acid profiling with LC-MS/MS instrument

After the incubation periods, control and tunicamycin-treated CCD-1135Sk cells (5 µg/mL) were harvested using trypsinization and centrifuged at 2,500 × g for 2.5 minutes to pellet cells and remove supernatant. Then, 20 mL of extraction solvent (ultrapure water with 1% formic acid) was added, vortexed for 5 seconds, and centrifuged at 9,000 rpm for 5 minutes. For derivatisation, 50 µL of sample, 50 µL internal standard and 700 µL of amino acid reagent were mixed in Eppendorf tubes. After centrifugation at 1,350 rpm for 5 minutes, the clear supernatant was transferred into glass vials for LC-MS/MS analysis. Amino acid profiling was conducted using an Agilent 1260 Infinity LC coupled to an Agilent 6460 Triple Quadrupole MS/MS (Jet Stream ESI source), following validated protocols for high-throughput amino acid quantification in complex biological matrices[18,19].

Statistical analysis

All data are expressed as mean Standard deviation (SD). Differences between groups were statistically analyzed using two- way ANOVA DUNCAN test

using SPSS 21. $p < 0.05$ were considered statistically significant.

Results and Discussion

Under tunicamycin-induced ER stress, both miRNA and amino acid profiling were observed in CCD-1135SK cells, revealing various changes. In such analyses, amino acid levels and miRNA gene expression provide valuable data for understanding how cellular processes and genetic/regulatory pathways associated with ER stress are affected. These profiles can help identify key molecular players involved in the stress response and offer insights into potential adaptive mechanisms that cells may activate to cope with ER stress. By integrating both types of profiling, researchers can gain a more comprehensive understanding of how cellular metabolism and gene regulation are intertwined in response to stress conditions.

Amino acid results

Endoplasmic reticulum (ER) stress was induced in CCD-1135SK cells by treating them with 5 µg/mL tunicamycin for 6 and 24 hours. Amino acid profiling revealed significant metabolic changes in response to ER stress. Taurine levels increased significantly at both time points, suggesting a role in the cellular stress response. Gamma-aminobutyric acid (GABA) was elevated after 6 hours, while L-glutamic acid increased at both 6 and 24 hours, likely supporting protein folding and neurotransmitter functions. β-alanine showed a variable pattern, increasing at 6 hours but decreasing at 24 hours, indicating its involvement in short-term stress adaptation. L-aspartic acid rose only after 6 hours, reflecting rapid metabolic adjustments. L-alanine and L-glycine were consistently elevated at both durations, possibly aiding intracellular metabolism and stress modulation. Trans-4-hydroxy L-proline was low at 6 hours but increased at 24 hours, highlighting adaptations to prolonged stress. L-asparagine was higher at 6 hours, while L-proline decreased at 24 hours after an initial increase at 6 hours, suggesting dynamic amino acid utilization for protein folding. L-citrulline was elevated throughout the treatment, whereas essential amino acids such as L-isoleucine, L-leucine, L-arginine, and L-cystine were reduced at both times compared to controls. Similarly, L-glutamine and other amino acids (L-lysine, L-threonine, L-methionine, L-tyrosine, L-phenylalanine) decreased, possibly reflecting metabolic resource optimization under ER stress. Lastly, trans-hydroxyproline showed a pattern similar to trans-4-hydroxy L-proline, indicating fibroblast regulation of collagen metabolism during prolonged ER stress. Overall, these amino acid changes demonstrate a comprehensive metabolic reprogramming aimed at maintaining cellular homeostasis and adapting to ER stress. Detailed results are provided in Table 1.

Real-time PCR results

The effects of tunicamycin-induced ER stress on gene expression in CCD-1135SK cells were examined after 6 and 24 hours of treatment with 5 µg/mL tunicamycin. Real-time PCR results showed significant changes in multiple miRNAs and genes. miR127 levels remained similar to controls at 6 hours but increased significantly at 24 hours, suggesting a role in long-term stress response. miR199b and miR124a1 were consistently downregulated at both time points, indicating possible suppression of functions related to stress adaptation and neurological control. miR106b was upregulated at both durations, implying a protective role during ER stress. miR126, miR124a2, miR181a1, and miR125a showed decreased expression throughout, reflecting stress-induced inhibition. miR128 decreased at 6 hours but rose at 24 hours, pointing to activation during prolonged stress, while miR10b exhibited a dynamic pattern with decreased expression early and increased expression later, indicating adaptive regulation over time. Among inflammatory markers, IL-6 expression was reduced, suggesting suppressed inflammation. TLR-4 showed a biphasic response, with lower expression at 6 hours and increased levels at 24 hours, reflecting its role in different phases of ER stress. IL-β was strongly upregulated at 6 hours but returned to control levels by 24 hours, indicating an acute early response. CD14 expression increased only at 24 hours, implying involvement in later immune modulation. CDKN3, a cell cycle regulator, was downregulated at both time points, suggesting impaired cell proliferation under stress. ETR1 expression decreased at 6 hours but increased at 24 hours, highlighting its potential role in cellular adaptation during prolonged ER stress. Overall, as illustrated in Fig. 1, tunicamycin-induced ER stress caused significant shifts in genes related to amino acid metabolism and immune regulation. These findings deepen our understanding of cellular molecular responses to ER stress and may guide future therapeutic approaches.

Table 1 — Amino acid results among groups

Amino acids	Control	± std	Tuni-6	± std	Tuni-24	± std
L- Tryptophan	30,202	0.191	28,802	1,094	29,435	1,093
Taurine	14,548	0.208	61,135	6,462	20,241	1,553
L- Phenylalanine	167,101	3,921	150,052	5,094	158,621	7,497
L- Tyrosine	95,216	8,826	80,373	0.267	77,296	5,082
L- Leucine	228,690	1,372	205,416	3,822	189,677	4,841
L- isoleucine	172,583	9,355	153,138	4,717	144,471	5,837
L- Methionine	69,687	0.277	57,477	1,341	60,582	1,893
Gamma-aminobutyric acid	0.437	0.020	0.860	0.008	0.440	0.022
L-Valine	195,305	27,081	163,959	2,339	206,466	16,377
L- Glutamic acid	177,548	2,057	254,854	3,632	237,569	3,112
Ethanolamine	2,127	0.398	2,199	0.172	2,330	0.206
Beta- Alanine	1,871	0.290	3,798	0.350	1,314	0.105
L- Aspartic acid	54,623	2,481	64,613	3,861	57,594	6,739
L- Threonine	325,059	8,180	304,362	6,588	298,726	4,205
L-Serine	174,094	7,686	192,606	1,639	186,755	3,148
L- Alanine	127,488	6,433	171,347	7,514	148,649	3,044
L- Glycine	205,957	4,382	264,164	4,724	252,855	2,698
Trans-4-hydroxy L- proline	7,500	0.415	6,603	0.373	7,570	0.326
L- asparagine	53,428	2,183	59,756	1,258	53,672	0.812
L- Proline	103,659	5,057	108,574	2,697	96,620	2,997
L-Glutamine	1326,330	4,264	1119,762	2,677	1184,677	1,310
L- Citrulline	7,874	1,429	11,244	0.503	10,647	2,052
L- Cystine	63,315	1,341	45,401	1,609	47,945	1,821
L-Histidine	132,722	10,422	126,124	9,158	126,645	6,773
L- Arginine	452,074	5,748	382,233	1,631	390,411	5,103
L- ornithine	27,278	2,715	25,912	0.568	28,461	0.880
L- Lysine	309,744	5,176	260,941	8,474	268,068	5,927
3-Methyl-L-Histidine	0.902	0.088	0.740	0.106	0.976	0.089

[n=3, mean±std]

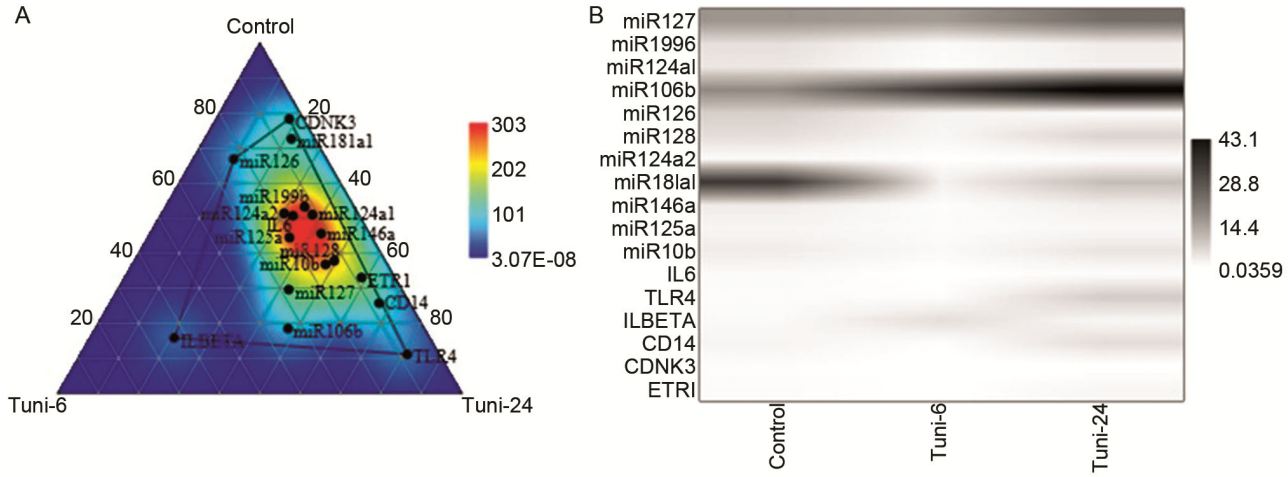

Fig. 1 — Ternary plot representing the distribution and density of gene expression shifts across three key metabolic regulators under ER stress conditions. Density mapping highlights clusters of co-expressed transcripts (A). Data are based on three independent experiments. (B)Heatmap showing relative expression levels of selected miRNAs and genes involved in amino acid metabolism and ER stress in human dermal fibroblasts treated with tunicamycin. Colour intensity indicates upregulation (black) or downregulation (white) relative to control cells, normalized to internal reference genes.

Endoplasmic reticulum (ER) stress significantly impairs protein folding and intracellular homeostasis, resulting in cellular dysfunction. Dermal fibroblasts, which are critical for extracellular matrix synthesis, collagen deposition, and tissue repair, are particularly vulnerable to this stress. When ER stress disrupts protein folding in fibroblasts, their ability to maintain skin integrity and promote healing is weakened, potentially contributing to conditions such as fibrosis, chronic wounds, and scarring. Understanding how ER stress affects fibroblast biology is therefore essential for devising novel therapies for skin disorders. Compounds that target ER stress pathways such as inhibitors of PERK or IRE1α offer promising avenues to restore fibroblast function and enhance tissue repair[20]. Recent studies have shown that ER stress can drive fibroblast differentiation into myofibroblasts, which are central to wound contraction and ECM remodeling. For example, tunicamycin-induced ER stress activates α-SMA and collagen I expression via PERK- and IRE1-dependent signaling, suggesting that ER stress modulation may be harnessed to promote controlled fibroblast activation[21]. Additionally, ER stress has been implicated in impairing fibroblast migration, a critical process in wound closure; tunicamycin and thapsigargin delay fibroblast motility, which can be reversed by chemical chaperones promoting ER homeostasis[16]. Further, ER stress intersects with oxidative stress pathways, leading to ROS accumulation and activation of NF-κB and JNK signaling, which reinforces fibrotic and inflammatory responses. These cascades impair both fibroblast proliferation and migration, further compromising wound repair. Amino acid metabolism appears to modulate these stress responses particularly glutamine and serine by supporting antioxidant defence, protein refolding, and energy balance under stress conditions. Therapeutically, agents that alleviate ER stress such as small molecule chaperones or miRNA modulators targeting UPR effectors could improve fibroblast resilience and tissue regeneration. By restoring proper protein folding, migration, and collagen synthesis, these strategies could enhance healing outcomes in chronic wounds and fibrotic skin diseases. Future research should focus on evaluating such compounds in primary human dermal fibroblasts and *in vivo* skin models to validate translational potential.

Investigating the impact of ER stress on fibroblast function offers new opportunities to enhance the healing capacity of these cells and develop therapeutic approaches. Additionally, the relationship between ER stress and amino acid metabolism plays a critical role in modulating cellular responses. Amino acids such as glutamine and serine are essential for maintaining cellular homeostasis. Understanding how ER stress affects the metabolism of these amino acids allows for a better comprehension of cellular adaptation and metabolic changes[22,23]. This knowledge can aid in the development of potential strategies for treating various diseases, including skin disorders, cancer, and metabolic diseases[24].Heindryckx *et al*. demonstrated that ER stress plays an important role in the pathogenesis of fibrosis and that components of the ER stress pathway can serve as therapeutic targets[19]. In their study, inhibiting the IRE1α signaling pathway prevented myofibroblast activation and reversed the fibrotic phenotype. These findings highlight the role of ER stress in fibrosis development and potential therapeutic targets. Similarly, Dai *et al*. explored the effects of miR-199a-5p in modulating ER stress and showed that this miRNA plays a protective role against ER stress in hepatocytes[25]. These types of miRNAs could be promising therapeutic tools for treating diseases associated with ER stress. A 2023 study showed that ER stress affects miRNAs related to inflammation and embryo implantation, particularly miR-17-5p, miR-21-5p, and miR-193b-3p, which regulate pathways associated with ER stress and inflammation[26]. *In silico* analyses also examined the effects of these miRNAs on embryo implantation and inflammatory responses. These findings shed light on how ER stress modulates cellular functions by affecting inflammation-related gene expression. Hardin *et al*. examined the relationship between ER stress, amino acid starvation, oxidative stress, and protein folding processes and explained how eIF2α phosphorylation regulates cellular stress responses[27]. The phosphorylation of eukaryotic initiation factor 2 alpha (eIF2α) constitutes a pivotal adaptive mechanism that restricts global protein synthesis under endoplasmic reticulum (ER) stress, thus alleviating the folding burden on the ER and promoting cell survival. When ER stress is triggered, the PERK arm of the UPR rapidly phosphorylates eIF2α on Ser51, leading to a general inhibition of cap-dependent translation. This translation attenuation reduces the influx of nascent proteins into the stressed ER, allowing time for the

restoration of folding homeostasis. Concurrently, this mechanism facilitates the selective translation of stress-responsive mRNAs such as ATF4, which drives the expression of genes involved in redox balance, amino acid metabolism, autophagy, and antioxidative defense[28,29]. Phospho-eIF2α–ATF4 signaling also regulates transcriptional programs that support mitochondrial function and antioxidant homeostasis. Recent studies reported that without proper eIF2α phosphorylation, cells suffer from depletion of GSH and NADPH pools, leading to ferroptosis and apoptosis conditions mitigated by ATF4 overexpression or supplementation with antioxidants[30]. Notably, this axis is critical not only in maintaining proteostasis but also in coordinating metabolic adaptations essential for survival under chronic stress. In addition to translational reprogramming, eIF2α phosphorylation engages mitochondrial respiration and bioenergetics by promoting the formation of respiratory supercomplexes, regulated via ATF4, to meet elevated energy demands during ER stress[31]. Crosstalk between ER and mitochondrial UPR pathways further supports adaptive responses; inter-organellar signaling helps maintain ATP and redox equilibrium under proteotoxic load. Therapeutically, targeting the ISR offers promising avenues. Small molecules such as ISRIB, which reverse the effects of eIF2α phosphorylation, or chemical chaperones that reduce ER burden, can restore protein turnover and prevent maladaptive outcomes. Additionally, modulating downstream targets such as ATF4 or Nrf2 may improve metabolic resilience and redox balance in disease contexts involving chronic ER stress[32]. A comprehensive understanding of these mechanisms can inform the development of interventions that preserve cell viability during ER stress and improve cellular metabolic adaptation. Thus, exploring eIF2α–ATF4 signaling in depth provides a robust framework for identifying novel therapeutic targets. In our study, tunicamycin-induced ER stress in dermal fibroblasts led to pronounced alterations in amino acid metabolism and miRNA expression specifically, elevated levels of taurine, GABA, L-glutamic acid, and L-alanine, as well as upregulation of miR-106b. These changes likely reflect orchestrated cellular defence mechanisms to maintain proteostasis and metabolic balance. Recent evidence indicates that miR-106b and related miRNAs regulate amino acid transporter expression, such as the SLC family, modulating intracellular amino acid concentrations during stress conditions[33]. For example, miR-106b-5p modulates ER stress propagation in exosomal signaling, influencing target cells through effects on ER-associated proteins like ATL3[33]. Meanwhile, miRNA clusters including miR-23a/27a/24-2 modulate ER mitochondrial crosstalk by influencing ROS levels and UPR activation, suggesting miRNAs can indirectly regulate oxidative metabolism and amino acid usage under ER stress[34]. Moreover, ER stress affects inflammatory gene expression: miR-4734 has been shown to suppress the ATF4–IRE1 axis and downstream proinflammatory cytokines (IL-6, TLR-4, CD14) in fibroblast-like cells under metabolic stress, providing insights into how early inflammatory responses may be dampened[35]. This aligns with your observation of initial IL-6 downregulation followed by dynamic changes over time. The interplay between miRNAs and amino acid metabolism extends to metabolic enzymes: miR-23a~27a cluster influences serine/glycine metabolism and redox balance via regulation of related enzymes[36]. Collectively, these findings suggest that miRNAs serve as central regulators in the amino acid inflammation ER stress nexus, influencing both metabolic adaptation and gene expression regulation.

Our investigation revealed that tunicamycin-induced ER stress significantly remodels amino acid metabolism and miRNA expression in dermal fibroblasts, with elevations in taurine, GABA, L-glutamic acid, L-alanine, and upregulation of miR-106b. This pattern strongly suggests that miRNAs orchestrate adaptive metabolic responses, particularly by regulating amino acid transporters and metabolic enzymes under stress[37]. Supporting studies confirm that ER stress responsive miRNAs fine-tune nutrient transporter expression and UPR signaling. For instance, miR-106b-5p propagated ER stress signals via ATL3 modulation in exosomal pathways, influencing recipient cells[38,39]. Other miRNAs (e.g. miR-30c-2-3p, miR-455) modulate UPR sensors like IRE1α and ATF6α to impact inflammatory gene expression[40]. Additionally, amino acids such as alanine and glutamate are known to act as key signal molecules regulating redox and UPR gene expression[41]. Proteomic studies in fibroblasts have demonstrated that cancer-secreted miRNAs (miR-105, miR-204) alter translation and metabolic pathways via modulation of mTORC1 signaling[38]. Our study

provides novel evidence linking miRNA-mediated amino acid regulation to ER stress adaptation in dermal fibroblasts a finding with significant implications for therapeutic targeting of chronic skin pathologies.

Conclusion

Dermal fibroblasts are cells that play a critical role in the production of matrix structures in the dermis, tissue repair, and healing processes. These cells respond quickly and effectively to environmental stimuli, trauma, and pathological changes. ER stress can disrupt protein folding and post-translational modification processes in fibroblasts, which may affect cellular homeostasis. The ER is an organelle that ensures proteins are correctly folded and functional, which is essential for maintaining the fibroblasts' important functions, such as tissue repair and wound healing. Fibroblasts constantly produce large amounts of protein, and these proteins need to be correctly folded and functional. However, disruptions in this process, such as excessive protein production or accumulation of misfolded proteins, can trigger ER stress. ER stress results in the accumulation of misfolded proteins within the cell, which can overwhelm the cellular quality control mechanisms. In response, fibroblasts activate a mechanism called the unfolded protein response (UPR) as a stress response. The UPR aims to maintain proteostasis, and when the capacity of the ER is exceeded, broader molecular responses are initiated within the cell. These responses involve defence mechanisms such as correcting protein folding and degrading misfolded proteins. However, these responses have limitations, and if ER stress becomes chronic, the function of the cells may be impaired. Chronic ER stress is believed to impede fibroblast proliferation, diminish matrix synthesis and tissue remodelling, and ultimately contribute to the progression of skin fibrosis. This is directly related to the pathogenesis of skin diseases, and the sensitivity of dermal fibroblasts to these stresses could be linked to tissue damage and impaired wound healing. Furthermore, gaining a better understanding of the molecular mechanisms associated with ER stress in fibroblasts is crucial for developing potential therapeutic strategies for the treatment of skin diseases. Detailed studies on how chemical compounds such as tunicamycin affect cellular processes disrupted by ER stress could provide important insights. Tunicamycin, a compound known to induce ER stress, promotes protein folding defects and ER stress in fibroblasts. Such studies could aid in the development of new treatment strategies for diseases associated with ER stress. In conclusion, dermal fibroblasts are sensitive cells that play a critical role in tissue repair. Understanding how ER stress affects fibroblast function is essential for developing new approaches to the treatment of skin diseases. Research on ER stress provides deeper insights into the pathogenesis and treatment of skin diseases, and the modulation of these mechanisms could reveal new therapeutic targets.

Conflict of interest

The authors declare no conflicts of interest.

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