



# The Impact of Proteomic Investigations on the Development and Improvement of Skin Laser Therapy: A Review Article

Shabnam Shahrokh<sup>1</sup>, Zahra Razzaghi<sup>2</sup>, Vahid Mansouri<sup>3\*</sup>, Nayebali Ahmadi<sup>3</sup>

<sup>1</sup>Gastroenterology and Liver Diseases Research Center, Research Institute for Gastroenterology and Liver Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran

<sup>2</sup>Laser Application in Medical Sciences Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

<sup>3</sup>Proteomics Research Center, Faculty of Paramedical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran

## \*Correspondence to

Vahid Mansouri, Proteomics Research Center (PRC), Darband St., Qods Sq., Tehran, Iran.  
Tel: +982122714248;  
Email: vm1343@yahoo.com

Published online December 1, 2019



## Abstract

**Introduction:** Different molecular approaches have contributed to finding various responses of skin to external and internal tensions such as laser irradiation and many important mediators of skin disease have been identified through these approaches. However, different essential signals of skin biomarker pathways and proteins are partially detected or completely unknown. In the present study, the impact of proteomics on the evaluation of laser therapy for the treatment of skin diseases is investigated.

**Methods:** The keywords of "Proteomics", "Laser therapy", "Skin", and "Skin disease" were searched in Google Scholar, Scopus and PubMed search engines. After screening, 53 documents were included in the study.

**Results:** The global assessments revealed that different proteins in different signaling pathways of skin metabolism in terms of health or illness after laser therapy are expressed differentially. The results indicated that the application of proteomics is a useful method for promoting the results of laser interventions.

**Conclusion:** This kind of research dealt with the practical proteomics of skin diseases and skin laser therapy.

**Keywords:** Protein, Skin diseases, Proteomics, Laser therapy

## Introduction

The use of a low-power laser (LPL) to reduce infection, pain and edema, wound healing, plus superficial nerve repair has been known for many years.<sup>1-3</sup> The LPL usage in dermatology has attracted the attention of many researchers recently.<sup>4,5</sup>

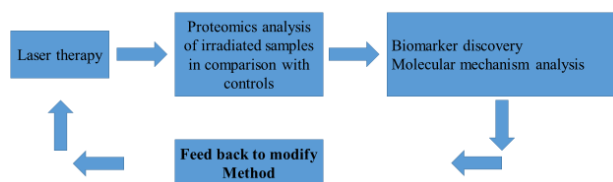
This article reviews the molecular mechanisms that LPLs perform on the skin and various skin diseases. In this regard, the database of comprehensive proteomic studies concerning altered proteins in the skin laser therapy has been reviewed. This paper presents what advances have been made in the application of proteomics in introducing molecular interactions between proteins in different cellular and molecular cycles after laser application in the treatment of skin diseases. However, there is a large capacity for performing a wide range of investigations in the field of proteomics and laser therapy. In Figure 1, the schematic relationship between proteomic investigations and laser therapy improvement is presented.

## Methods

The search engines of Google Scholar, Scopus, and PubMed were used to search such keywords as "Proteomics", "Laser therapy", "Skin", and "Skin disease". The identified titles in English were studied and the relevant ones were selected for more assessment. The abstracts of 150 documents were investigated that led to select 97 full texts. Among 97 articles, 53 documents were suitable to include in the study.

## Laser Devices and Properties

A laser is a device that typically generates electromagnetic radiation. The ruby laser, as described in 1960, is uniform in the wavelength, phase, and polarization.<sup>6</sup> The laser beam has both light and radiation energy.<sup>7</sup> Biological systems could be affected by the LPL as a non-thermal kind.<sup>8</sup> Mester et al started to investigate about the LPL in 1967 as the non-thermal effects of lasers on the growth of mouse hair.<sup>9</sup> As Posten et al reported, low-level lasers



**Figure 1.** The Schematic Relationship Between Proteomics Studies and Laser Therapy Improvement.

(LLS) have these properties: the power output of lasers is ranged between 0.001 and 0.1; the wavelength is in the range of 300-10600 nm; pulse rate from 0 to 5000 Hz (cycles per second); and the intensity is 0.01-10 W/cm<sup>2</sup> with a dose of 0.01 to 100 J/cm<sup>2</sup>.<sup>10</sup> Popular methods in the administration of LLL radiation include ruby (694 nm), Ar (514 and 488 nm), He-Ne (632.8 nm), Ga-Al-As (650 or 805 nm), and Krypton (521, 530, 568, and 647 nm).<sup>11</sup> Basically, the use of light for improving healing, reducing infection and relieving pain in biological systems can be considered as the application of a LPL. Unlike other medical laser techniques, LPLs do not have ablative or thermal effects, but the photochemical effects have been reported. The photochemical effect refers to the absorption of light by skin and chemical changes.<sup>12</sup> Other kinds of laser therapy for ablation and cutting tissues and thermal tissue coagulation are not comparable to an LPL.<sup>13</sup>

### Laser Impact on Cell Biology

The reason for LLL therapy usage is the low-density delivery of energy.<sup>14</sup> Several kinds of studied samples in this article are tabulated in Table 1. Some molecular photo-acceptors named chromophores in target tissues could absorb photons by their electronic absorption bands treated by LLL therapy.<sup>14</sup> Recent researches have shown that LLL affects mitochondria and cytochrome C.<sup>12</sup>

Cytochrome c oxidase (Cox) is the primary photo acceptor for the red-NIR range in mammalian cells.<sup>15</sup> Excited electrons in Cox lead to more electron transportation, leading to more ATP production.<sup>16</sup> On the other hand, Cox activity is inhibited by nitric oxide.<sup>17</sup> Investigations indicate that inhibition caused by NO binding to Cox could be reversed by the LPL or LPL in separated mitochondria or inside cells.<sup>18</sup> The LPL shifts the cell reactions to greater oxidations<sup>19</sup> and increases ROS generation.<sup>20</sup> The effect of LPL on gene expression alteration, cell proliferation and remodeling, synthesis and DNA repair, and ion channels and membrane potential has been reported.<sup>21</sup> The LPL has beneficial effects on wrinkles, acne scars, hypertrophic scars, and the healing of burns in dermatology.<sup>4</sup> The effects of laser therapy on neuropathic pain were analyzed in rats.<sup>22</sup> Orringer et al quantified the molecular changes resulted from micro ablative resurfacing by the erbium: yttrium aluminium garnet (Er:YAG) laser. They found the up-regulation of keratin 16, IL-1B, and IL-8. In this research, the up-

**Table 1.** Several Types of Studied Samples in This Article

Studied Sample or Affected Target	Ref.
Mitochondria and cytochrome C	12
Cytochrome c oxidase	15
Wrinkles, acne scars, hypertrophic scars, and healing of burns	4
Neuropathic pain	22
Extracellular matrix	23
Skin incisions	24
Photo-damaged face and neck skin	25
Different layers of the skin	26,27
Foot and breast skin	28
Keratinocytes	30
Human epidermis stem cells and transit amplifying cells	32
Cytokeratin	40-42
Rho GDP-dissociation inhibitor1	43
Human arm skin	52
Human gingival fibroblasts	53

regulation of MMP-1 and MMP-3 of the extracellular matrix (ECM) was also remarkable. They concluded that after laser peeling by Er-YAG; collagen build-up process is increased and a wrinkles are decreased.<sup>23</sup> On the other hand, the application of the PIRL laser to skin incisions indicates that the following events happen: minimal ablation of tissue, less damage to surrounding tissue resulting in the reduced activation of  $\beta$ -catenin and TGF- $\beta$  signaling, more cell viability, decrease of cell proliferation, collagen deposition sooner in the scar, and thus an accelerated healing response.<sup>24</sup> The CO<sub>2</sub> laser resurfacing photo-damaged face and neck skin demonstrated the up-regulation of MMPs 1, 3, 9, and 13 as well as MMP-10 and MMP-11.<sup>25</sup>

### Proteomics and Skin

Proteomics is a large-scale study of proteins and proteome is the entire set of proteins produced or modified by a system or a cell. Proteomics could cover the exploration of proteomes from the overall level of protein composition, structure, and activity in skin. Conventional methods have shown the presence of collagen type I, III, VII, IV and reticular and elastin fibers along with laminin, nidogen, entactin, and heparin sulfate proteoglycans in different layers of the skin.<sup>26,27</sup> Since proteomic techniques do not have limitations like dyeing techniques and immuno-histochemistry, they can be used to introduce various proteins in the skin. For example, in a study that investigated foot skin proteins compared to the breast skin, fifty common and more prominent proteins in the skin of both regions were found as collagen, creatine and ECM proteins such as lumacan, cDNA highly similar to mimecan, periostin, biglycan, decorin, prolargin, and elastin. However, in the breast skin, only tenascin-x and other uncharacterized protein were found and in

the leg skin, only serum amyloid P-component vice versa was found.<sup>28</sup> Another study that investigated the functional aspects of the skin proteomics revealed the comprehensive proteomic profiling of the rats' skin.<sup>29</sup> Thousands of protein spots were digested by enzymes to identify thousands of proteins. Matching algorithms for isolated peptides accompanied by bioinformatics analysis performed as other global assessments have been done.

To understand the skin and keratinocytes responses to injuries, the oligonucleotide microarray technique is suitable.<sup>30</sup> The microarray has enabled the analysis of large numbers of genes. However, this technique could not supply data about the transitional regulation of protein expression. One of the disadvantages of this technique is the lack of access to the conformational and steady state information of proteins along with the post-translational alterations or modifications of proteins in steady levels such as glycosylation and phosphorylation. Therefore, proteomics could manage to profile most proteins and their isoforms which are expressed in glycosylation and phosphorylation as post-translational modification and proteolytic cleavages. Interferon-g-induced polypeptides are up-regulated in old patients, revealed by proteomic profiling of epidermis in the skin; therefore, the p85b subunit of phosphatidylinositol 3-kinase and manganese-superoxide dismutase could be induced.<sup>31</sup> Proteomics techniques can compare the stem cells of human epidermis with transit amplifying cells (their differentiated daughter cells). Based on this finding, epidermal fatty acid binding proteins (PA-FABP) along with annexin II, and other keratin related proteins were deregulated in the transit amplifying cells.<sup>32</sup> They suggest that PA-FABP is a novel marker for transit amplifying cells. Seven new human epidermal protein markers were identified for skin irritation via proteomics. HSP27 was identified as the most prominently up-regulated protein among these 7 proteins. They suggested HSP27 as a skin irritation sensitive marker.<sup>33</sup> To understand the global protein pattern of skin, an effort for identifying the expression of proteins in the murine skin has been initiated. Huang et al constructed a map for reference proteins of BALB/c murine abdominal skin via proteomics. They used PDQuest software (Bio-Rad, Hercules, CA) to detect more than 500 protein spots. 44 of those spots corresponded to 28 different proteins. They could be distinguished by using laser mass spectrometry (MALDI-TOF MS) and a suitable algorithm of probability-based database-searching subsequently.<sup>34</sup>

Proteomic analysis of laser microdissected melanoma cells of skin revealed that proteins such as tenascin-C, fibronectin and  $\alpha$ -actinin-4 are up-regulated in melanoma cells to increase invading characters of melanoma cells in the culture.<sup>11</sup>

Rezaei-Tavirani et al represented critical proteins as GAPDH, RHOA, DCTN2, PDIA3, AKT1, PRNP, RPSA, TPT1, HSPB1, and TP53. They play important roles when skin is exposed to laser irradiation. They believed

that there is a balance between cancer promotion and skin treatment with Laser irradiation.<sup>35</sup>

### Skin and Laser Therapy

Skin aging has some problems such as tissue elasticity reduction, wrinkling, telangiectasia, and dyspigmentation. Other features like the reduction of collagen and the fragmentation of collagen fibers in company with the degeneration of elastic fibers, tortuous dermal vessel appearance, and the up-regulation of matrix metalloproteinases 1 & 2 (MMPs) are significant with epidermal atrophy in aged skin.<sup>36</sup> Such factors as time and environment could influence skin normal aging; however, UV skin photo damaging is the most effective factor responsible for skin aging.<sup>37</sup>

Laser resurfacing is a treatment for reducing facial wrinkles and skin deformities such as blemishes or acne scars. The technique shoots concentrated pulsating beams of light at irregular skin to remove skin layer by layer. Laser therapy has some risks, including bleeding, infection, pain, scarring, and changes in skin color, but people also tend to be healed faster with laser operations. In a research study, using the erbium-YAG laser to assess the damages and changes to mouse skin revealed a significant increase in trans-epidermal water loss and erythema with the skin pH at 4 after 24-hour laser therapy. These effects decreased to a baseline after 96 hours. Following exposure to the laser, p21 and p53 proteins were up-regulated significantly in the cells of skin. This up-regulation means p53 protein supports DNA repair to survive skin.<sup>38</sup> Another crucial role of laser irradiation is reported during the responses to stress as arrest of G<sub>1</sub> phase of cell cycle.<sup>39</sup> However, by low fluence-laser therapy (7.5 J/cm<sup>2</sup>), the nuclear antigen belongs to proliferation down-regulated as the cytokeratin expressions. The see-saw apoptosis and proliferative mechanisms occur by skin laser irritation. Coagulation, necrosis and scars correspond to the Er:YAG laser.<sup>40</sup> The expression of cytokeratin remarkably decreases following laser treatment.<sup>41</sup> Cytokeratin down-regulation leads to changes in blistering and vacuolization.<sup>42</sup> Researchers reported that one of the members of molecular chaperones (Rho GDP-dissociation inhibitor1 or Rho GDI 1) in metastatic carcinoma was overexpressed.<sup>43</sup> However, Rho GDI 1 expression was down-regulated after laser therapy in proteomics assays. Rho GDI 1 down-regulation is equal to the modulation of Rho protein activities. This led to the disruption of the actin cytoskeleton which was associated with new keratinocytes moving to replace those keratinocytes killed by the laser.<sup>40</sup> The concentration of Heat shock protein or HSP25 changed according to the place of keratinocytes. HSP25 increased in the upper keratinocytes from the basal layer as the extent of keratinization was also higher in surface keratinocytes.<sup>44</sup> Laser therapy could damage the skin cells according to HSP26 reduction 24 hours after treatments.<sup>40</sup> Laser irradiation can cause epidermal cell death and loss

of vital cells.<sup>45</sup> It may be consistent with post-apoptotic necrosis.<sup>46</sup> PCNA is a marker to provide further insights into laser-tissue interactions. Polymerase D is a marker for cell proliferation and PCNA is reported as an auxiliary protein or cyclin for polymerase D.<sup>46</sup> P21 DNA damage-induced cell cycle arrested by inhibiting PCNA leads to the up-regulation of P21.<sup>47</sup>

Recently network analysis has been applied to the evaluation of proteomic findings from the studies into diseases. In this method, a large number of proteins interact to construct an interactome. Network analysis

**Table 2.** Five Classes of Biological Terms Related to the Deregulated Genes in the Arm Skin After CO<sub>2</sub> Laser Therapy

Cluster	R	Biological Term
1	1	Cytokine-mediated signaling pathway
2	1	Interferon gamma signaling
	2	Response to interferon-gamma
	3	Cellular response to interferon-gamma
	4	Interferon-gamma-mediated signaling pathway
3	1	Hepatitis C
	2	Measles
	3	Influenza A
	4	Herpes simplex virus 1 infection
	5	Epstein-Barr virus infection
4	1	Hepatitis C
	2	Measles
	3	Influenza A
	4	Herpes simplex virus 1 infection
	5	Antiviral mechanism by IFN-stimulated genes
	6	Interferon alpha/beta signaling
	7	Interferon Signaling
	8	Response to type I interferon
	9	Negative regulation of the viral process
	10	Regulation of the viral process
	11	Cellular response to type I interferon
	12	Type I interferon signaling pathway
5	1	Hepatitis C
	2	Antiviral mechanism by IFN-stimulated genes
	3	Cytokine Signaling in the Immune system
	4	Interferon alpha/beta signaling
	5	Interferon Signaling
	6	Regulation of the multi-organism process
	7	Negative regulation of the multi-organism process
	8	Regulation of symbiosis, encompassing mutualism through parasitism
	9	Response to virus
	10	Defense response to other organisms
	11	Response to type I interferon
	12	Negative regulation of the viral process
	13	Regulation of the viral process
	14	Defense response to the virus
15	Viral life cycle	
16	Viral genome replication	
17	Cellular response to type I interferon	
18	Regulation of the viral life cycle	
19	Negative regulation of the viral life cycle	
20	Type I interferon signaling pathway	
21	Negative regulation of viral genome replication	

leads to introducing the critical ones that play crucial roles in the diseases.<sup>48-50</sup> Using protein-protein interaction network analysis, researchers analyzed proteomics and large-scale data after laser irradiation in skin and diabetic retinopathy.<sup>51,52</sup> They reported that 43 biological terms (see Table 2) clustered in five groups were related to the critical genes which were dysregulated in the arm skin after CO<sub>2</sub> laser therapy.

Ogita et al reported that the protein expression of human gingival fibroblasts which were exposed to low-level Er:YAG laser irradiation one day after exposure changed. Based on their documents, 59 proteins were up-regulated and 15 ones were down-regulated. Galectin-7 that is known as an important factor in wound healing was included in the up-regulated proteins. This experiment revealed that laser irradiation was associated with cell proliferation increment in human gingival fibroblast.<sup>53</sup>

### Conclusion

As it was mentioned above, many proteins are associated with laser therapy, especially in skin treatment. However, several of them have been detected and recognized and there are large numbers of proteins that have not been determined. Proteomics is a useful method which in cooperation with the other large-scale methods and bioinformatics is able to analyze the large and varied data available on various skin investigations. It seems that many proteins, whose roles have not yet been determined, can be identified by proteomic investigations in the near future.

### Ethical Considerations

Not applicable.

### Conflict of Interests

The authors declare no conflict of interest.

### Acknowledgment

Laser Application in Medical Sciences Research Center of Shahid Beheshti University of Medical Sciences supported this research.

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