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Unlocking the Molecular Canvas: Lasers and Epigenetics

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Aesthetic dermatology had been focusing on anti-aging but there has been a paradigm shift in recent years and the goal is moving towards a "longevity" framework. It is focusing on skin's biological health, resilience and its role as a mirror of internal health. Aging process has been studied extensively and the main factors which have been identified include genomic instability, mitochondrial dysfunction, telomerase shortening, loss of proteostasis, nutrient-sensing system impairment, cellular senescence, decreased ability of self-renewal and epigenetic alterations.[1]

Certain environmental exposomes also impact skin aging. Exposome is a measure of all the environmental exposures in one's lifetime and how they affect our biology. The concept was introduced in 2005 as a complement to the human genome. The genetics give us the blueprint of our health whereas the exposome can trigger or prevent a disease over time. There are internal, specific external and general external exposomes. The environmental exposome includes external drivers such as UV radiation, poor diet and smoking which accelerate the epigenetic clock. Chronic UV exposure also causes DNA hypomethylation leading to collagen breakdown and increased cancer risk.[2]

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Traditional dermatology views genetics as the reason for skin aging. Modern science shows that the heritable but reversible changes in gene expression called "epigenetics" play a far more important role. The concept of plasticity in which the epigenome is defined as dynamic, unlike fixed DNA sequences, influenced by external factors, making skin aging a modifiable and potentially reversible process. There are three core epigenetic mechanisms including DNA methylation, histone modification and non-coding RNAs (miRNAs). In DNA methylation there is addition of methyl groups to DNA which can activate or silence the genes. With age the epigenetic drift leads to inactivation of genes which are responsible for collagen production and antioxidant defense. Histones are proteins around which the DNA is wrapped. The chemical modification in histones makes the chromatins accessible. Open chromatin allows active repair whereas closed chromatin leads to impaired healing and skin thinning. miRNAs regulate gene expression after transcription. Dysregulated miRNAs cause pigmentation, inflammation and scarring.[3] **(Figure 1)**[4].

The biological or epigenetic clocks, such as Hovrath's clock and GrimAge, provide objective biomarkers to measure the result of rejuvenating therapies. These biomarkers use the DNA methylation pattern to measure the person's biological age which can be different from their chronological age. Assessing these clocks can help dermatologists to customize the treatments based on molecular profile rather than age-based guidelines for skin treatments. Lifestyle factors including high-sugar diets and stress further

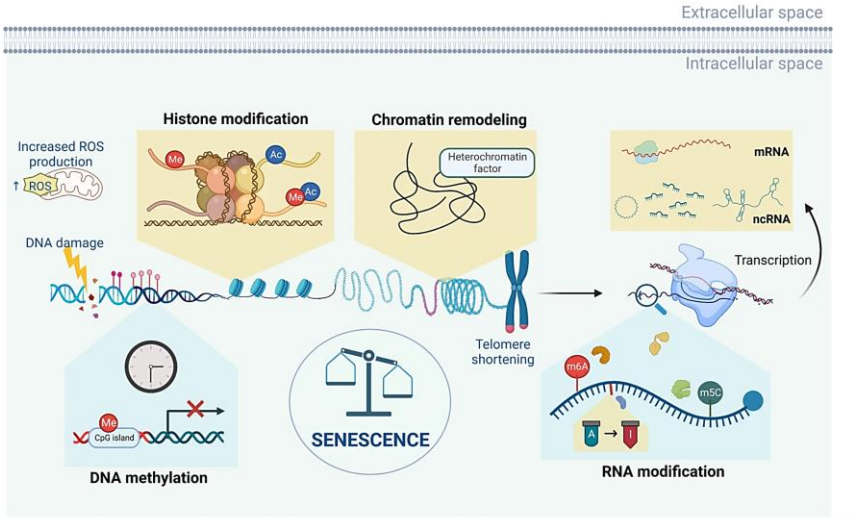

Figure 1 An overview of the aging epigenome. During aging and the emergence of cellular senescence, a series of epigenetic changes occur in cells, including alterations in DNA methylation, chromatin remodeling, histone modification, RNA modification, and ncRNA regulation.[4]

exacerbates biological aging whereas exercise and an anti-oxidant rich diet helps preserve youthful epigenetics.[5-7]

Lasers and energy based devices like radiofrequency and ultrasound therapies mainly work by thermal injury. Latest research shows that medical lasers also act as molecular reset devices. In aesthetic practice lasers and energy based devices are used for skin rejuvenation and treatment of hirsutism, scars and pigmentation. Lasers including fractional CO2 and Er:YAG activate natural repair processes which are regulated by epigenetic pathways. Fractional lasers decrease the hypermethylation of DNA activating the genes for the production of collagen and elastin. Activation of histone acetyltransferases enzymes by the laser-induced stress relaxes the chromatin leading to expression of pro-regenerative genes. Laser therapy also causes miRNA modulation in which specific miRNAs like miRNA-21 are upregulated promoting angiogenesis and miRNA-29 which inhibit collagen synthesis are downregulated. All these processes align the cellular behaviour with a more youthful profile.[2,3,8]

There are many clinical uses of lasers in clinical practice which are beyond the rejuvenation role. Their role has also been established in cancer prevention, pigmentation and vascular diseases as well as a synergistic role with topical medication to enhance molecular efficiency. A randomized trial showed that fractional laser resurfacing re-establishes IGF-1 signaling in older skin, restoring UVB radiation response and in turn reducing the risk of actinic keratosis and non-melanoma skin cancers for at least two years. DNA methylation by lasers halts the melanin producing genes controlling melasma and by Vascular Endothelial Growth Factor (VEGF) modulation by which conditions like rosacea can be managed. Combination of lasers with topical medications like retinoids and dihydromyricetin by inhibiting DNMT1 can reduce the biological age of cells by approximately two years.[9-12]

The future treatment plans will use Artificial intelligence (AI) programs to analyze the complex epigenetic datasets to precisely identify the points for intervention and patient-specific response to treatment will be predicted. Ethical considerations should also be kept in mind to enhance patient well being and protect the patient's data and psychological impact of revealing the patient's biological age.[2]

Conclusion

The role of medical lasers as catalysts for cutaneous longevity by addressing the epigenetics and molecular resets to promote rejuvenation and disease prevention is evolving. The future is focused on holistic care in which lasers, microbiome-targeted therapies and lifestyle modification to maintain cutaneous longevity.

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