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Reversing Skin Aging Through Partial Epigenetic Reprogramming

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Abstract. Skin aging is a complicated biological process that is associated with structural and functional progressive degradation; one of its core driving mechanisms is the disruption of epigenetic regulation. Among potential anti-aging intervention strategies, partial reprogramming has attracted widespread attention recently. It aims to reverse the epigenetic state of senescent cells towards a younger direction while not eliminating each specialized identity of cells. This paper systematically illustrates the research progress of epigenetic partial reprogramming in rejuvenating skin aging. Starting from the mechanism connection between epigenetic erosion and cellular identity loss, it analyses the experimental evidence in animal models, in human fibroblasts, and in vitro skin tissues, while emphasizing the crucial obstacles when translating this technology to clinical use. Current findings indicate that partial reprogramming is capable of reversing aging-related epigenetic markers while, to some extent, recovering some cellular functions, such as collagen synthesis, migration ability, and extracellular matrix remodeling, etc. However, all this evidence stems from preclinical investigation, yet has not been fully verified in terms of the safety, persistence, and functional significance of reprogramming effects in intact human skin. This review concludes that partial reprogramming has potential as an experimental strategy, but whether it could be developed into a real clinically feasible intervention depends on whether future investigation could gain substantive breakthroughs in terms of precisely controlling the intensity of reprogramming, maintaining cell identity, ensuring long-term safety, and achieving tissue-specific delivery..

Keywords: Skin aging, partial epigenetic reprogramming, cell identity, epigenetics, clinical translation

1. Introduction

The process of skin aging is a multifactorial and irreversible phenomenon of biological nature which involves the progressive change of both structure and function. Such alterations stem from the interaction between intrinsic aging and extrinsic environmental influences and are associated with reduced barrier performance, poor regenerative potential, disorganization of the extracellular matrix, and loss of tissue homeostasis—functional failures that reduce the protective and regenerative properties of the skin, which not only affect its appearance but also impact its general health and tissue integrity.

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More and more evidence indicates that epigenetic dysregulation is a key molecular cause of skin aging. Critical epigenetic changes, such as changes in DNA methylation, histone modifications, chromatin structure changes and dysregulation of non-coding RNAs, may be able to change the expression of genes related to aging and collagen synthesis without altering the genome sequence. It turns out that epigenetic changes are main drivers of the aging process rather than merely passive effects of that process. In contrast to irreversible DNA mutations, epigenetic changes are potentially reversible, providing a theoretical basis for interventions aimed at slowing down or even reversing skin aging at the cellular level.

Recently, research has shown rejuvenation-related outcomes of partial epigenetic reprogramming on a variety of preclinical systems. In contrast with the complete reprogramming that eliminates cellular identity, partial reprogramming modifies age-associated epigenetic signatures but maintains the original cellular identity and physiological properties [1, 2]. Studies of animals have revealed that cyclic reprogramming may reduce the epigenetic age and enhance wound healing in aged mice [3]. Human cell experiments also show that transient reprogramming rejuvenates the dermal fibroblast transcriptome and epigenome, which is associated with increased collagen production and cell migration [4]. Other newer tissue-level models also indicate the regenerative capabilities of reprogrammed fibroblasts [5]. All these findings imply that partial reprogramming has the potential to reverse the aging-related alterations at the molecular as well as the cellular and tissue levels. However, current studies are mostly preclinical: the interactions among epigenetic rejuvenation, cell identity preservation, long-term functional stability, and biosafety are yet unknown, and translational research in human skin remains limited [2, 6].

Considering these research gaps, this review will discuss existing evidence on the partial epigenetic reprogramming for skin rejuvenation in three interconnected areas: epigenetic processes involved in skin rejuvenation, physiological responses recorded using experimental models, and translational challenges which limit clinical practice. Through comparison between the evidence obtained through animal models, human fibroblasts and tissue-engineered skin, this review will determine the strengths and weaknesses of the current evidence. Finally, this review will provide a framework for assessing whether reprogramming is clinically applicable or an experimental strategy that remains promising but unproven at present.

2. Mechanistic basis linking epigenetic erosion and partial reprogramming

Skin aging is also associated with progressive disruption of epigenetic mechanisms, which tend to ensure stable gene expression and cellular identity. Age-associated DNA methylation, histone modification, and chromatin structure modifications may alter the gene regulation of cellular senescence, extracellular matrix stability, and tissue regeneration. Such changes are particularly important because they are the modifiable parts of aging, not the irreversible changes in the DNA sequences. This dysregulation might be most apparent at the functional level in the progressive loss of cell type identity. One of the best examples of this loss is mesenchymal drift, a common phenomenon in which various cell types within human tissues progressively up-regulate the expression of mesenchymal genes as they grow older. Critically, this drift is linked to aging and age-related diseases and may be reversible prior to the complete cell dedifferentiation—a result that indicates rejuvenation not only limited to individual molecular marker reset but also is about restoration of a steady epigenetic state that preserves cell identity.

Complete cellular reprogramming will revert the epigenetic status of the differentiated cells to the pluripotent state, which would also erase the specific identities necessary to perform their regular tasks in tissues. In contrast, partial epigenetic reprogramming seeks to accomplish rejuvenation

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without dedifferentiation by limiting the length and intensity of the reprogramming process so that the age-related molecular characteristics can be altered before the cells undergo dedifferentiation [2, 6]. To demonstrate how this distinction really works at the epigenetic level, Camacho et al. studied DNA methylation patterns in the skin of partially reprogrammed old mice and discovered that the epigenetic changes related to aging and rejuvenation are very similar to the ones seen in genomic region targeted by Polycomb repressive complex 2 (PRC2) [7]. Since Polycomb-mediated regulation plays a role in keeping gene expression patterns and cell identities stable, this indicates that partial reprogramming might affect those regulatory regions that may be particularly susceptible to aging, instead of the entire epigenome being reset. This interpretation was also corroborated by human cell studies: Gill et al. showed that brief reprogramming caused a significant decrease in the age indicators at the transcriptome and the epigenetic levels in human dermal fibroblasts while allowing the cells to recover their fibroblast identity [4]. Altogether, in addition to the fact that mesenchymal drift can be halted prior to the full dedifferentiation, these results confirm one of the main principles behind partial epigenetic reprogramming: successful rejuvenation requires making cells younger at the molecular level without completely altering the identity that is necessary to perform their specialized functions [8].

This balance in the skin is particularly crucial, since the main role of dermal fibroblasts is to maintain the extracellular matrix and support tissue repair. Given that age-related impairment of fibroblast function leads to a reduction in collagen production, alteration in extracellular matrix structure, and declining regeneration capacity, the biological value of restoring fibroblasts to their younger molecular state will be very limited if fibroblasts simultaneously lose the required cellular properties to perform these functions. Gill et al.'s research results are relevant to this, as the reprogrammed fibroblasts not only restored their cellular identity, but also exhibited increased collagen production and enhanced migration ability [4]. Thus, the effect of partial reprogramming on the skin may unfold simultaneously at multiple interrelated levels: epigenetic regulation shifts towards a youthful state, specialized cell functions are restored, and ultimately may promote the improvement of tissue maintenance and repair capabilities. However, the rationale at the mechanism level cannot replace the verification of treatment effectiveness, especially when clinical evidence has not yet accumulated. Therefore, whether these changes at the molecular and cellular levels can be stably transformed into practical skin rejuvenation effects still requires systematic and comprehensive evaluations in animal models, human cell systems, and tissue-engineered skin models, rather than making judgments based solely on experimental data from a single level.

3. Preclinical evidence across animal, human cell and reconstructed tissue platforms

Whether partial epigenetic reprogramming can confer therapeutic benefits depends on the extent to which the molecular changes related to rejuvenation can be translated into measurable improvements in cellular and tissue functions. Browder et al. conducted a long-term partial reprogramming study in a mouse model of physiological aging, which had the ability to preserve the systemic and intertissue interactions that were absent in cultured cells. Multiple tissues were found to exhibit changes associated with rejuvenation, especially the skin. The cyclic expression of the four factors OSKM (Oct4, Sox2, Klf4, c-Myc) reserved epigenetic age measurements and decreased the levels of inflammatory and senescence-related markers. It is worth noting that the skin of the treated group showed a greater ability to heal wounds, linking the molecular changes with functional recovery in the intact organism [3]. Such a functional improvement shows that partial reprogramming-induced molecular changes may also influence the repair of tissues. But wound healing is the combined outcome of several different cell types and biological processes, while this

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research does not clearly elucidate which cellular processes played a role in this change. Indeed, these findings do provide evidence of association with functional improvement, yet they cannot confirm that individual epigenetic changes are causally responsible for improved tissue repair.

As Browder et al. reported, the level of rejuvenation depended on the duration of treatment and different tissues reacted differently to the treatment [3]. The same inconsistency is observed in other similar studies: species, cell type, treatment schedule, recovery period impact the outcomes [9]. Hence, even though animal experiments have shown that partial reprogramming can cause a rejuvenating phenomenon in vivo or living environments, this finding cannot be used to establish that the same effect can be induced in human skin.

Gill et al. applied maturation-phase transient reprogramming to human dermal fibroblasts and reported substantial reductions in both transcriptomic and DNA methylation measures of cellular age [4]. Moreover, the cells were able to recover the original characteristics of fibroblasts, which means that their cellular identity was preserved and brought back once the treatment was completed. Simultaneously, the levels of type I and type IV collagen were also enhanced and approached youthful levels [4]. In addition to that, the migration ability of the cells showed some degree of improvement, yet their responses varied across different samples [4]. Taken together, these results indicate that the rejuvenation induced by partial reprogramming did not just enhance the molecular age parameters but also the cellular functions, including the maintenance of the extracellular matrix and repair of the tissues—during the rejuvenation process, cells were able to maintain their original specialized functions without losing their original cellular identity.

Rejuvenation was assessed using multiple molecular and functional indicators, strengthening the interpretation of the study by avoiding using only a single aging marker. The isolated cells lack the cellular diversity, immune interactions, extracellular environment, and mechanical conditions present in living skin—factors that can influence fibroblast behavior in vivo. Comparative analyses further indicate that partial reprogramming effects are context-dependent and may vary across experimental systems [9]. Human fibroblast studies provide evidence for molecular and cellular rejuvenation, yet whether equivalent changes would improve the organization, structure, or function of intact human skin remains unclear.

Roy et al. used mechanical reprogramming rather than the OSK- or OSKM-based approaches that form the primary focus of this review [5]. As mechanically reprogrammed aged human dermal fibroblasts were transplanted into an in vitro aged model of human skin, extracellular matrix proteins such as collagen I, elastin, and fibronectin production increased [5]. The treated fibroblasts promoted extracellular matrix synthesis and organization at wound sites, and transcriptomic analysis showed increased activity in pathways related to tissue regeneration and wound healing [5]. Overall, these findings demonstrate that reprogrammed fibroblasts can, beyond isolated cellular changes, influence their surrounding tissue environment as well.

Mechanical and transcription-factor-mediated reprogramming may operate through different mechanisms, though the two cannot be assumed to produce equivalent outcomes. The findings therefore reveal a broader principle that partial cellular rejuvenation may produce beneficial effects within an aged skin-like tissue environment, but there is no direct evidence supporting the idea that OSK- or OSKM-based reprogramming would have the same effect in human skin. Systemic circulation, immune regulation, and long-term tissue renewal—factors that could affect how reprogrammed cells behave in vivo—are also absent from in vitro skin models. Therefore, evidence will be needed from transcription factor-based approaches in more physiologically representative human skin systems to address these gaps.

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Rather than being interchangeable, the experimental systems examined above provide complementary evidence: cultured human fibroblasts offer species relevance but lack tissue-level context, while reconstructed skin models provide greater tissue-level complexity by incorporating cell-matrix interactions but lack the systemic physiological environment present in vivo. Each level therefore contributes information that the others cannot provide, while retaining its own experimental limitations. What emerges is a coherent picture of biological potential, yet the direct applicability of current findings to intact human skin remains uncertain. The evidence supports molecular and functional rejuvenation without yet demonstrating safe, durable, or clinically meaningful effects in humans. Whether partial reprogramming moves beyond experimental models toward therapeutic application will be determined by these unresolved issues: treatment control, long-term safety and translation.

4. Key barriers for therapeutic translation

The core of partial reprogramming lies in maintaining a balance between rejuvenation and cell identity: inducing a youthful state of cells while avoiding complete dedifferentiation. If the degree of reprogramming is insufficient, the resulting rejuvenation effect may be limited. Conversely, if the expression time of reprogramming factors is too long or the expression level is too high, it may affect the maintenance of the original identity of somatic cells. Therefore, maintaining cell identity is an important prerequisite for effective rejuvenation through partial reprogramming, because the treated cells still need to retain or restore the specific functions of their original cell type [10]. This is especially important for skin tissue: taking dermal fibroblasts as an example, these cells still need to have normal extracellular matrix production and tissue repair capabilities after receiving reprogramming treatment. In addition, the effect of partial reprogramming is not consistent in all cases. Cell type, experimental model, and specific treatment regimen can all influence the outcomes. The differences observed in existing studies indicate that it is difficult to achieve completely consistent rejuvenation effects in different cell populations through a uniform treatment schedule or experimental regimen [9].

Targeted expression strategies may offer a more refined way of regulating this balance, and recent discussion of precision reprogramming has highlighted cell-state-specific targeting as a potential approach for restoring aged cellular function while preserving cellular identity [2]. Sahu and colleagues adopted an age-associated, cell-specific OSK expression system and documented improvements in aging-related phenotypes in naturally aged mice without an accompanying increase in tumor incidence [11]. Collectively, all these findings suggest that restricting partial reprogramming to the selected cell state may reduce the risks brought about by unnecessary exposure of non-target cells. However, all this related evidence was preclinical, yet it is uncertain whether the balance between "rejuvenation and identity maintenance" observed under specific experimental conditions can be reliably reproduced in a more complex human skin environment.

Safety, for its part, remains a distinct and significant challenge. The factors in orchestrating reprogramming especially play a regulatory role in the key pathways involved in pluripotency, proliferation, and the maintenance of somatic cell identity. Excessive or uncontrolled expression may therefore result in serious unintended consequences [10]. These concerns are also supported by recent in vivo comparative analyses [12]. Continuous, unremitting OSKM expression has been confirmed to be associated with the complete loss of cellular identity, a sharp drop in weight, and, in the most severe cases, premature death—whereas it must be conceded that the adoption of shorter, more tightly regulated expression regimes can reduce some of these adverse effects [12]. Accordingly, the key to therapy is not simply about the attainment of a quantifiable reduction in

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biological age but accomplishing this feat without inadvertently engendering aberrant cellular states or compromising the functional integrity of normal tissue in the process.

Durability is another important problem that partial reprogramming confronts. Unlike permanently integrated genetic modifications, epigenetic states induced by transient reprogramming are potentially reversible. After treatment withdrawal, cells are still influenced by aging-associated biological processes; therefore, the epigenetic characteristics that have been altered may gradually regress. According to some experimental data, some transcriptional features related to rejuvenation still persist for a period after ceasing expression of reprogramming factors, yet the actual duration and long-term stability of such beneficial changes are currently poorly characterized [10]. Temporarily reducing molecular age and restoring skin function chronically and stably have different significance. Future investigations, therefore, need not only to clarify whether epigenetic and functional improvements are sustained, but also to determine whether delayed adverse effects might emerge during subsequent cycles of tissue turnover and homeostatic maintenance.

Any strategy that could possibly be applied clinically needs to take into account the imperative of spatial control—the capability of controlling where reprogramming will occur accurately. Systemic delivery will lead to many cells that are not yet aged or are not therapeutic targets being exposed to reprogramming factors, while these factors could perturb fundamental pathways governing proliferation and cellular identity; thus, such non-specific exposure might bring additional risks [10]. In contrast, the use of tissue- or cell-specific delivery methods can more effectively limit the scope of reprogramming. Sahu and his colleagues employed AAV-mediated expression, placing it under the control of the age-associated Cdkn2a promoter, and were able to demonstrate that the intradermal delivery of targeted OSK constructs could indeed bring about improved wound healing in aged mice [11]. This finding provides valuable proof of concept for cell-specific targeting and local delivery, yet it is insufficient to establish definitive scalable delivery workflows suitable for human skin application.

Effective delivery represents only one set of technical obstacles; its clinical translation is also restricted by the high structural and functional complexity of human skin. Fibroblasts, keratinocytes, immune cells, vascular networks, and extracellular matrix components also maintain dynamic interactions in skin, while being affected by constantly changing mechanical conditions and biochemical conditions. None of the experimental models discussed previously could simulate this complex, intricate physiological environment. Accordingly, contemporary reviews have increasingly emphasized that understanding the specific responses of different skin tissues and cells to reprogramming and developing more selective rejuvenation strategies are necessary steps before considering extensive therapeutic application [2, 10]. Future investigations should clearly consider the most suitable skin cell types for reprogramming, the required duration and intensity of reprogramming, how long the treatment effect can last, and which molecular and functional indicators can serve as practical criteria for evaluating rejuvenation.

In the field of skin rejuvenation, the goal of investigations in the next stage is to go beyond merely demonstrating the reversibility of aging-related molecular markers. More importantly, the question is whether this reversibility could be controlled and maintained in a long-term manner and safely restore normal tissue function while preserving cellular identity and long-term safety. Currently, all these requirements constitute the vital thresholds that partial reprogramming must overcome to transition from a promising experimental phenomenon into a viable human intervention. Addressing these problems will require the development of more precise reprogramming strategies and a deeper understanding of which specific skin cell types and their functions are most suitable as targets for rejuvenation interventions.

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5. Conclusion

As a conceptually transformative anti-skin aging strategy, the unique benefit of partial epigenetic reprogramming is its capability to reverse age-associated molecular markers, while maintaining or even recovering the specialized functional identity of cells in most cases—and this identity is crucial for maintaining tissue stability. All that this article has reviewed, including a large amount of preclinical evidence, mouse models, primary human fibroblasts, and reconstructed skin equivalents, has collectively demonstrated that brief or periodic expression of reprogramming factors could weaken multiple key drivers of skin aging, including epigenetic drift, age-related changes in cellular state, extracellular matrix degeneration, and impaired wound healing ability. All these findings, undoubtedly, generated considerable optimism regarding the potential application of this kind of treatment.

However, after a careful assessment of the existing evidence, the fact that the current investigative foundation is still entrenched in the preclinical stage should not be overlooked. Before partial reprogramming can, in reality, be transformed into clinical dermatological intervention methods, several severe obstacles are still waiting to be overcome. Firstly, the expression intensity and duration of the reprogramming factor have not yet been precisely controlled—it will be difficult to trigger an effective rejuvenation response if the expression is too weak or the duration is too short; it would otherwise induce dedifferentiation, genomic instability, and even tumor transformation. This treatment window that straddles between "ineffective" and "unsafe" therefore has not yet been systematically defined in the human skin system. Secondly, the persistence of epigenetic and functional improvements induced by partial reprogramming still currently lacks adequate characterization. If its effect is short-lived or delayed adverse events occur after the treatment has ended, the clinical value brought by the transient molecular rejuvenation is extremely limited. Lastly, developing safe, scalable delivery systems that can achieve cell type-specific targeting in the highly structurally and functionally heterogeneous human skin environment is a very challenging engineering task that has not been solved to this day.

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