An Essential Overview of Skin Aging and its Genetic Mechanism

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Abstract

Skin ageing occurs through multiple intrinsic and extrinsic factors such as inherited genetic makeup and UV radiation exposure. It is seen in past research that the cells that have entered senescence play a role in ageing which is indicated by its relation to oxidative stress leading to the production of ROS (reactive oxygen species) and telomere shortening. Furthermore, the misregulation and deregulation of genes are involved in the process of ageing. This review aims to answer how epigenetics causes ageing through skin wrinkling. Various papers related to skin ageing will be thoroughly reviewed and discussed within this paper. The results of this paper will lead to a better understanding of how ageing occurs under natural conditions and how it can lead to anti-ageing therapeutics for cosmetic industries.

Keywords: Skin ageing, intrinsic, extrinsic, ROS, and telomere shortening

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1. Introduction

Aging has always been thought to be an unstoppable process that one cannot think to reverse. However through multiple experiments and discoveries, research has shown that there is potential for humans to reverse ageing starting with the skin. Ageing can be defined as the loss in cell identity over time that leads to its dysfunction in a tissue which affects the function of an organ in the organism (Kaeberlein, 2007). Ageing has been a dilemma to mankind for a long time since our appearance and bodily functions change as we age. It is well known that ageing causes many organs to lose their quality in function and can cause various diseases as well as visual changes to the individual. For instance, the heart's ability to effectively pump blood around the body at high frequencies during vigorous exercise may be decreased as we age leading to increased change of heart failure as we age (Masoli et al., 2022); the brain's ability to remember new information or its ability to process information decreases in efficiency (Stephan et al., 2018); and lastly, the skin's ability to retain its smooth, bouncy, and even skin tone, will eventually deteriorate through age (Russell-Goldman & Murphy, 2020).

This paper's main focus is going to be on the epigenetics aspect of skin ageing. Epigenetics on ageing is a big discussion amongst scientists as there is evidence that ageing is caused by epigenetic factors such as histone methylation (Wang & Dreesen, 2018). The skin is the human's biggest organ and is essential for understanding various skin diseases such as dermatoses arising from ageing of the skin (Csekes & Račková, 2021). Furthermore, information regarding skin ageing is crucial to the cosmetic industry due to high demand for effective skincare products that can potentially undo the ageing process.

Skin ageing is a natural occurrence that causes many social and psychological concerns in humans especially females ((Porcino, 1985). Ageing is visibly noticeable to the naked eye as organs or tissue lose their quality over time;

the phenotypes of skin ageing include wrinkles, abnormal pigmentation, sagging, and thinning of the epidermis (Ng & Chew, 2022). These signs of skin ageing can be impacted by intrinsic genetic factors as well as extrinsic environmental stimuli which can speed up the process of ageing (Wang & Dreesen, 2018).

There are various epigenetic changes that occur with ageing such as global hypomethylation of DNA, altered histone marks, and changes in ncRNA abundance. There are many positive and negative epigenetic implications that occur in relation to ageing. Some of the most common changes that occur during ageing are related to epigenetics. Recent studies have shown that reprogramming of these age-related epigenetic changes in cells can reverse age-related phenotypes of organisms (Lu et al., 2020).

2. Epigenetics recap

Epigenetics is referred to as reversible changes in the DNA that indirectly affects the base sequence (Duan, 2022). As such, gene expression is governed by epigenetics which leads us to understanding various genetic diseases as well as the ageing process. Skin ageing occurs through a myriad of intrinsic and extrinsic factors including inherited genes for intrinsic and pollution for extrinsic. It is seen in past research that the presence of senescence plays a role in ageing which is indicated by its relation to oxidative stress leading to the production of reactive oxygen species (ROS) and telomere shortening (Wang & Dreesen, 2018). Furthermore, many genes are involved in the process of ageing including sirtuin (Kane & Sinclair, 2019), MMPs, AMPK, and mTOR.

This paper will discuss various papers found on pubmed on reversing the process of ageing as well as the normal development of skin ageing with reference to intrinsic epigenetic factors such as histone modifications. In addition, areas where future research should look into for reverse ageing will also be discussed. The results of this paper may lead to a better understanding of how ageing occurs under natural conditions and how it can lead to anti-ageing therapeutics for cosmetic industries.

3. Skin anatomy and ageing

The skin is the largest organ of the human body with its main function being to protect pathogens from entering and infecting the body. The skin consists of 3 main layers including: epidermis, dermis, and the hypodermis (Yousef et al., 2023). The main layers involved in the phenotype of ageing such as wrinkling and tightness of the skin are the epidermis and the dermis. The interaction between the two layers allows for the thickening of skin to maintain its elastic like properties. The layers of cells in the dermis called the dermal papillae allows this interaction to occur. The digging of the dermis into the epidermis, also known as the dermis-epidermis junction (DEJ), allows for a stronger and bouncier skin tone as known for in young skin; however, as one ages, the number of dermal papillae decreases which consequently decreases the thickness of the skin (Russell-Goldman & Murphy, 2020).

There are a total of 56 skin ageing phenotypes which can be grouped into 4 key categories by their morphology: [A] skin wrinkling and sagging, [B] skin colour related (pigmentation), [C] skin cancer related, and [D] skin global impression phenotypes (Ng & Chew, 2022). The main results of ageing that will be discussed in this paper include the following phenotypes on the skin; skin wrinkling, pigmentations, skin cancer, thinning of skin, and skin sagging.

In young normal skin, the maintenance of strong skin is mostly regulated by collagens in the extracellular matrix (ECM). The presence of fibroblasts in the ECM helps maintain a sturdy, smooth, and evenly toned skin by producing collagen (Fisher et al., 2008).

However, as one ages, the outer appearance of their skin would begin to wrinkle, sag, and thin. These phenotypes of ageing are one of the easiest to identify but are most unwanted and avoided by society – especially those of the female as indicated by their considerable spending on cosmetics (S. Zhang & Duan, 2018).

The epidermis, also known as the stratum corneum, is the outermost layer of the skin responsible for protecting the body from invading pathogens. Although the epidermis is the layer of skin being seen with all the wrinkles, the main cause comes from the change in the dermis layer. The dermis is an important skin layer as it contains the fibroblast which contributes to the production of collagen such as COL1A1. Collagen is a protein that works alongside elastin in the ECM of the dermis to help maintain a strong and thick skin. High concentrations of collagen and elastin, the skin will look young and maintain its wanted qualities. However with a decrease in concentration of these proteins as we age, wrinkles would occur more often and deeper (Reilly & Lozano, 2021). The decrease in fibroblasts is most likely due to the accumulation of photoageing and DNA damage that causes the cell to lose its identity.

Furthermore, skin repairing is an important process for organismal survival; an important cell involved in epidermal regeneration is transient amplifying cells (TA-cells) that are located in the basal layer of the epidermis. Since the process that maintains the integrity of the epidermal structure involves the clonal conversion from stem cells (SC) to TA-cells (Barrandon et al., 2012), cellular damage that causes a minor change in progenitor cell identity has a large impact on skin ageing. The decrease in TA-cells would lead to weaker and thinner skins. The decrease in SC that are programmed to differentiate into fibroblasts also decreases as we age. With the addition of this, the concentration of collagen would decrease, causing the ECM in skin cells to be weaker; thus leading to the ageing phenotypes of skin sagging, wrinkling, and thinning.

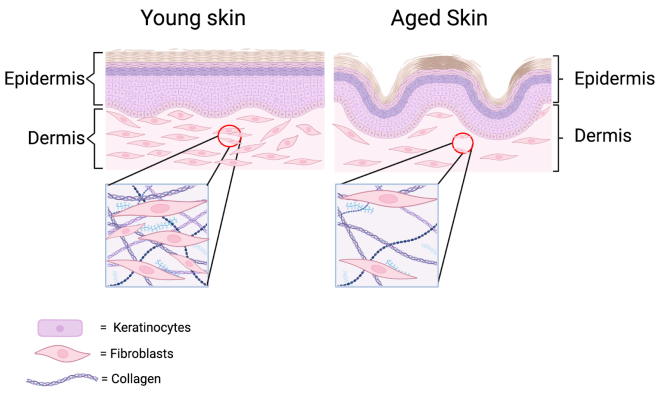

Figure 1. *Anatomy of young skin compared with aged skin. The epidermis layer is demonstrated as the thick purple and the brown colours. The dermis layer is demonstrated as the cream coloured portion of the skin. The zoomed-in mini-figure on the left hand side demonstrates the normal amount of elastin, fibroblasts, and collagens in the ECM; whereas the one on the right hand side demonstrates the decrease in elastin, fibroblasts, and collagens as well as an increase in damaged cells.* [Created with BioRender.com]

As seen in figure 1 above, the concentration of fibroblasts decreases as we age and therefore also impacts the concentration of collagens in the ECM of the skin . Furthemore, the increase in keratinocyte stem cell dysfunctions leads to the thinning of the epidermis (Orioli & Dellambra, 2018). The decrease in healthy stem cells that can differentiate into efficiently functional fibroblasts causes a decrease in concentration of collagen and is thus associated with the decrease in wound healing capacity (Orioli & Dellambra, 2018) and increase in skin sagging.

4. Main causes of cellular ageing

The process of ageing is driven by intrinsic and extrinsic factors. Intrinsic factors to ageing refers to the changes in DNA under epigenetic or genetic processes; these include histone modifications, gene upregulation and downregulation, telomere shortening, and DNA damage from reactive oxygen species (ROS). Extrinsic factors to ageing refers to the impact from external environmental factors such as UV exposure, pollution, and hydration.

Both intrinsic and extrinsic factors induce DNA breaks and lead to loss in cell identity which is the main mechanism for ageing. Once cells lose their identity and ability to properly function, maintenance of the functions they carry and repair of these cells become increasingly challenging. Damage to DNA would lead to misregulation, upregulation, or downregulation of certain genes that may cause adverse effects to its proper cell functions.

The main focus of this paper would dive deeper into the intrinsic factors of ageing including histone modification, genes involved in ageing, telomere shortening, and DNA damaged by ROS.

4.1 Histone modifications

Histone modification is an epigenetic process as it is an addition of molecules on top of the genome and impacts gene expression. Histones are proteins that help condense the DNA and are involved with gene expression. When the gene is not being read, the DNA will wrap neatly and tightly around the histones – vice versa.

Genes are located in specific regions of the DNA and the accessibility of the histones and DNA allow the genes to be expressed as it is easier for transcription proteins such as ribosomes to access the region and read the code for further processing. The histone can be modified in many ways such as methylation – the addition of a methyl group – acetylation – the addition of actyl groups – and lastly, phosphorylation – the addition of a phosphate group to the histone protein. The main modifications that will be discussed in the lens of ageing, however, are acetylation and methylation.

These histone modifications occur as a result of ageing. However, whether or not it increases or decreases the process of ageing depends on the location on the genome in which it is affecting (Kane & Sinclair, 2019). This is because histone modifications can either upregulate or downregulate the expression of either genes that strengthen or decrease DNA stability. Strengthening the DNA stability would ultimately lead to a longer lifespan as less of the DNA is damaged. Likewise, weakening of the DNA would lead to a shorter lifespan. A gene marker found to be involved in ageing is the H3K36me3 histone mark. Trimethylation of Lys36 on H3 or histone mark at H3K36me3 is associated with splicing and transcriptional elongation in a myriad of organisms (Kane & Sinclair, 2019). Greater aberrant gene expression is linked to decreased levels of this mark as we age which implies that the presence of H3K36me3 mark may contribute to ageing (Pu et al., 2015).

Although histone modifications such as methylation is seen accompanied by ageing, it may be a necessary process for the survival of an organism since it can promote the silencing or expression of a gene.

4.1.1 Skin Aging Biological Clock In Relation To Methylation

With the knowledge of methylation in ageing, biological clocks have been made to determine and predict one's health and life expectancy (Hillary et al., 2021; Horvath, 2013). The first biological clock was discovered by Steven Horvath and thus coined the term Horvath clock or epigenetic clock.

The biological clocks of the first generation such as the Horvath clock utilised DNA methylation (DNAm) as an indicator of biological age (Poganik et al., 2023). Counterintuitively, methylation is said to be an essential process in life and has many positive impacts on many biological processes (Menezo et al., 2020). Thus, a definite conclusion on the impacts of methylation may not be made yet.

Nonetheless, it was also known that each organ in the body ages at different rates, causing new and more accurate biological clocks to be made for different organs. In such a short timespan, many organ specific biological clocks have been created including the skin's biological clock

However, in 2016, a study reported that aged skin demonstrated a reduction in DNA methylation (Bormann et al., 2016). Later in 2023, Yang et. al, claims that the loss of epigenetic information is the cause of ageing. The interpretation of this finding supports previous research that loss of epigenetics is one of the causes for ageing. Since epigenetics helps regulate gene expression, the loss of this epigenetic information could lead to the deregulation or misregulation of gene expression.

4.2 Histone Acetylation

As the name suggests, this process is the addition of acetyl groups to the histone proteins specifically on lysine residues (positively charged basic amino acids) located on histone tails (Duan, 2022). This addition seems to correlate with the process of ageing as seen in the increase in skeletal and muscle acetylation in mice as they age (Yeo et al., 2020). Nevertheless, the human body contains a myriad of histone deacetylases (HDAC) to reverse the process of acetylation. One of the known HDACs involved in ageing are the Sirtuin family genes that produce sirtuin proteins. This family will be further discussed later throughout the paper.

4.3 Telomere shortening, Senescent cells, and Reactive oxygen species (ROS)

On the tip of the chromosomes contain what is called telomeres. These telomeres act as protection from the major parts of the DNA that contain genes. It is known that there is a limit to how much a cell can divide and that limit is called the hayflick limit which is governed by the length of the telomere; the longer the telomeres in the cell of an organism, the more divisions it can make until it must undergo the process of cell death called apoptosis (Csekes & Račková, 2021). Under normal conditions, cells would undergo apoptosis, however, in some cases where DNA damage is highly prevalent, cells lose the ability to perform apoptosis. In such cases, with the excess cell division and DNA damage, the cell becomes senescent. A senescent cell is a cell that stays in the tissue of an organism and does not divide – thus often referred to as a "zombie cell".

Senescent cells secrete many chemicals known as SASP (senescence-associated secretory phenotype). Many families of soluble and insoluble factors constitute SASP and can affect surrounding cells by activating various cell-surface receptors. This corresponding signal transduction pathway

may lead to multiple pathologies such as cancer (Coppé et al., 2010). More specifically, the acquisition of a Senescence-Associated Secretory Phenotype (SASP) turns senescent fibroblasts into proinflammatory cells that have the ability to promote tumour progression (Coppé et al., 2010).

The accumulation of senescent cells as we age occur through many factors – one of which is the by-product of ROS. The train of effects of this process leads to the damaging of the DNA as the ROS reacts and alters the DNA. In addition, ROS also occurs as the by-product of wound healing which involves re-epithelizing the injured area using stem cell progenitors (Russell-Goldman & Murphy, 2020); the ROS can induce breaks in the DNA and can lead to tumorigenesis. Free radical oxygen molecules with unpaired electrons are highly reactive as they have the ability to take electrons from other components; this induces damage to cell structures including cell membranes and DNA which can result in cell death, mutations, and cellular ageing (Zargaran et al., 2022). It is said that excessive amounts of ROS can significantly decrease lifespan (Blagosklonny, 2019).

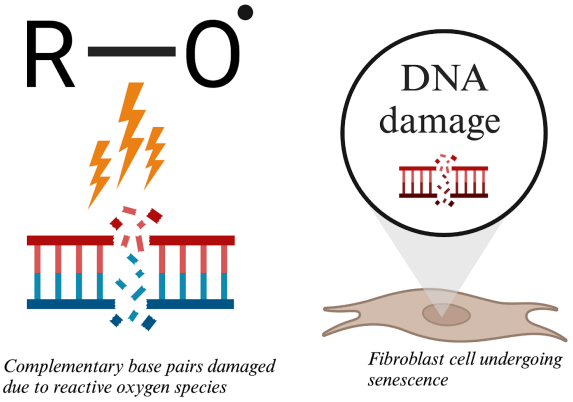

Figure 2. *The R-Oº represents the reactive oxygen species as the R-Oº complex demonstrates a reactive oxygen species; the R is any functional group or molecule attached to the Oº which is the oxygen radical. The lightning bolts are just a visual representation of the exchange in electrons that occur between the nitrogenous bases of the DNA and the ROS which induces the DNA breaks.* [Created with BioRender.com]

Please note that this is not an accurate depiction of how ROS interacts with DNA since its purpose is to help readers better understand the interactions between different molecules.

However, recent studies have shown that the accumulation of senescent cells can be prevented to slow or reverse ageing. Exercise performed at a regular basis can help increase DNA and telomere resilience to prevent augmented DNA repair when damage occurs which ultimately prevents the accumulation of senescent cells (Demaria et al., 2023; X. Zhang et al., 2022). A study conducted on mice with senolytics – drugs that clear senescent cells – demonstrated that the reduction of senescent cells in the skin reverses skin ageing (Xu et al., 2018). Thus, with the supported evidence, it can be concluded that the causes of skin wrinkling and other phenotypes of ageing is the accumulation of these senescent cells (McHugh & Gil, 2018).

This leads to the next point behind the genetic mechanism of ageing which is a common process amongst most organisms including humans. The molecular process of ageing is practically identical in every organ of the human body and involves many mechanisms which all lead to the loss of cell identity – DNA damage. Surprisingly, there are a few genes that are actively involved in ageing whether it is slowing, preventing, or accelerating ageing; these include sirtuins, mTOR, MMPs and AMPK.

5. Genes involved in ageing

5.1 Sirtuins (Silencing Information Regulator 2 – SIR2)

Sirtuins are a family of 7 genes named from SIRT1 to SIRT7. These names also correspond to the proteins that they code for which have the same names as the gene. The SIR stands for Silent Information Regulator and the T is for 'two' since it is the second SIR discovered in yeast. The sirtuin family comprises a class of Nicotinamide adenine dinucleotide (NAD) dependent enzymes that have known deacetylase activity; this means that they function with the presence of NAD, and are mostly known to function as HDACs (Yeo et al., 2020). However, apart from histones, sirtuins, such as SIRT1, have been observed to deacetylate other proteins such as p53. Tumour protein 53 plays an essential role in preventing cancer and a mutation of it, such as acetylation, can cause it to become an oncogene. Therefore, by deacetylating p53, SIRT1 plays an important role in preventing tumorigenesis (Amano & Sahin, 2019). Since sirtuins downregulates and decreases in expression as we age (Morris, 2021, p. 4), the chance of developing cancer in the later stage of life increases.

The pathway of sirtuins and p53 are also intertwined with the functioning of telomerase which is responsible for maintaining the length of telomeres on chromosomes to slow ageing (Amano & Sahin, 2019). According to Amano &

Sahin's 2019 paper the telomere-p53-sirtuin link could lead to a progressive deterioration of cellular function and a cycle through feedback mechanisms. First, SIRT1 and SIRT7 have been shown to inactivate p53; however, their inactivation by p53 in the setting of telomere dysfunction could further enhance p53 activity. Second, the low levels of SIRT1 and SIRT6 could further destabilise telomeres and activate the DNA damage response and p53. Thus, these sirtuin–telomere and sirtuin-p53 feedback mechanisms could prolong and accelerate ageing of already damaged cells, particularly in post-mitotic cells whose primary response to telomere dysfunction would not lead to apoptosis, growth arrest and senescence (Amano & Sahin, 2019). Although sirtuins may be called the longevity genes, perhaps under some circumstances it will increase the rate of ageing; this may cause wrinkling to be more prominent at an earlier age in some individuals compared to others and may be the reason why some young adults contain a more saggy skin compared to older adults. Nevertheless, many genetic factors could determine the rate of wrinkling as the genetic pathways of sirtuin is not the only one.

Sirtuin 6 is a vital protein with anti-ageing effects on the body's cells, tissues, and organs. SIRT 6 inhibits ageing from four main pathways of reaction: maintenance of the normal telomere structure of chromosomes, regulation of glucose, NAD+ metabolic balance, regulation of SASP, and promotion of DNA damage repair (Li et al., 2022). All of these pathways positively impact the prevention of ageing and therefore increase in expression of SIRT6 could lead to increased lifespan and possibly reversal of skin ageing. Evidence on monkeys suggests that loss of sirt6 causes severe metabolic defects and rapid ageing (W. Zhang et al., 2018). With the loss of sirt6 as we age, we lose the ability to repair damaged DNA and therefore develop malfunctional fibroblasts. One can hypothesise that the malfunctioning of fibroblasts is the main cause of the decrease in collagen concentration in the ECM, not just because of the decrease in number of fibroblasts themselves.

The 3 sirtuins mentioned previously – Sirt 1, Sirt 6, and Sirt 7 – are all located in the nucleus but are not the only sirtuins involved in ageing (Chang & Guarente, 2014). SIRT 2 has been shown to promote cell death in order to clear damaged cells in conditions of high oxidative stress (Sola-Sevilla et al., 2021). This demonstrates that SIRT 2 could be linked with oxidative stress resistance which plays a crucial role in controlling the process of ageing.

The expression of SIRT 3 is associated with preventing age-related cellular dysfunction as it exerts control over a wide range of mitochondrial functions including energy metabolism and defence against oxidative stress (Zhou et al., 2022). Global SIRT7 depletion contributes to premature ageing, especially in the backbone, the heart, and white adipose tissues (Zhao et al., 2020). As sirtuins are NAD dependent, thus activated by the components that make up NAD such as Nicotinamide mononucleotide (NMN) and Nicotinamide riboside (NR). These two molecules are currently being clinically trialled to test for beneficial and adverse effects on ageing (Fukamizu et al., 2022).

5.2 mTOR (mammalian Target Of Rapamycin) and AMPK (AMP activated protein Kinase)

mTOR or mammalian/mechanistic Target Of Rapamycin is a protein that interacts with AMPK, AMP-activated protein kinase, in response to glucose and amino acids in order to stimulate protein synthesis. mTOR is a master controller of protein synthesis and its level of expression are impacted by many factors including the food we eat and the genes it interacts with such as sirtuins. When expression levels of mTOR are high, it stimulates growth and may even trigger tumorigenesis; when expression levels are low, it stimulates repair and maintenance such as autophagy and the recycling of proteins. Low levels of expression of mTOR is involved in ageing as promotion of apoptosis leads to the recycling of materials in the body. This reduces the accumulation of senescent cells and therefore is an important gene for the reversal of ageing.

The master regulator mTOR exists as two complexes: mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2). The mTORC1 consists of mTOR, Raptor, mLST1, Deptor, and PRAS 40 (Zou et al., 2020). mTORC1 is activated by amino acids (especially leucine), and growth factors but inhibited with the presence of AMPK as well as rapamycin (Zou et al., 2020). The signalling cascade of AMPK acts as a cellular energy sensor and is activated by the drop in cellular ATP:AMP ratio. This may be due to the metabolic stressors that block the generation of ATP or enhance the consumption of ATP to maintain the body at a low energy status (Shinde et al., 2022). Thus, the reduction of ATP during vigorous exercise activates AMPK which in turn inhibits mTOR expression (Richter & Ruderman, 2009). However, controversially, it is also reported that mTORC1 is activated by strength exercise (Watson & Baar, 2014). Nevertheless, as activation of mTORC1 prompts protein

synthesis and growth, its expression is an essential for the development of the human body; the activation of mTOR also leads to inhibition of autophagy (Cayo et al., 2021).

On the other hand, mTORC2 consists of mTOR, Rictor, mLST1, Protor1, Protor2, and mSin1 (Zou et al., 2020). It is activated by growth factors and is known to regulate cytoskeletal organisation and cell-survival pathways (Hu et al., 2020; Saba et al., 2021).

Overall, the reduced food availability inhibits mTOR through the AMPK pathway which results in translational inhibition and autophagy activation through effectors such as S6K phosphorylation (Shinde et al., 2022).

By inhibiting mTOR through reduction in food consumption to trigger autophagy, the body can start to recycle materials and cause senescent cells to undergo apoptosis (Cayo et al., 2021); this reduction in senescent cells can halt the production of SASP and therefore reduce excessive ROS production that damages the DNA. Therefore with the involvement of mTOR, reduction in food consumption can lead to less damaged DNA in skin cells which could bring back healthy fibroblasts to produce more collagen and make the skin thicker and less wrinkled: younger looking skin.

6. Discussion/Summary

Ageing is defined as the loss in cell identity over time that leads to its dysfunction in a tissue which affects the function of an organ in the organism (Kaeberlein, 2007).

The skin is the largest organ of the body with 2 main layers involved with the phenotype of ageing: epidermis and dermis. With the most observable ageing phenotypes, the skin ages due to the malleable structure of the ECM. The decrease in strength of ECM caused by reduction in fibroblast and thus reduction in collagen decrease the skin to sag and wrinkle. The weaker the ECM, the deeper the wrinkles. Furthemore, the DEJ decreases with age and thus the skin layer thins with age.

The ageing of the skin is similar to how ageing occurs in other organs of the body as it is essentially the loss in cell identity that leads to its dysfunction and age. The cell loses its identity through DNA damage which is induced by various intrinsic and extrinsic factors. The intrinsic factors mentioned in this paper include histone modification, senescent accumulation, ROS, and telomere shortening.

The process of ageing is essentially cyclic as the DNA damage from minor changes in DNA epigenetics leads to the shortening of telomeres which can lead to the production of senescent cells where the SASP and ROS induces even more DNA breaks. Further accumulation of senescent cells ultimately lead to DNA damage; ROS induces DNA breaks and causes the DNA to destabilise and thus cycling back to DNA damage again. This cycle repeats itself over the course of ageing and increases the loss of cell identity therefore causing the organism to malfunction and can die of age.

Although histone modifications such as methylation is seen accompanied by ageing, it may be a necessary process for the survival of an organism since it can promote the silencing or expression of a gene. There are biological clocks that measure the amount of methylation and other histone modifications to determine the biological age of an organism. Specific biological clocks for different organs exist such as the skin and thus improvement or deterioration of skin can be measured quantitatively. The discovery of skin biological clocks can help determine which skin treatment is more useful and whether or not the genes suspected to be involved in ageing are truly doing so.

Furthermore, there are families of genes that are programmed to be involved in ageing such as: sirtuins, MMPs, mTOR, and AMPK. Sirtuins are NAD dependent and therefore act upon the presence of DNA. As NAD levels in the body decrease as we age, the expression of sirtuins also decreases. Thus sirtuin activators such as NMN and NR are being clinically trialled to see if there is benefit as well as adverse effects.

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