

To What Extent Does the Role of Mitochondria Affect the Life and Death of Human Skin Cells?

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ABSTRACT: *Mitochondria are thought to be one of the most vital organelles in cellular metabolism. One key function of mitochondria is to generate the energy currency of the cell, however, there are several other ways in which mitochondria are critical to cellular survival. The objective of this article is to investigate to what extent the role of mitochondria affects the life and death of human skin cells. In terms of the methodology, the study will be carried out using qualitative research to exhibit the substantial role of mitochondria through release of free radicals, mitochondrial DNA, apoptosis and use of anti-ageing reagents. Further research could be conducted to examine the impacts of exercise, diet and environment on mitochondrial function.*

KEYWORDS: mitochondria, mitochondrial DNA, apoptosis, free radicals, anti-ageing

INTRODUCTION

Known as the ‘power stations’ of all eukaryotic cells, mitochondria are able to release 95% of the energy needed by our cells (J G, McCormack, 1996). Their unique ability to change shape and movement enables them to meet cells of high energy requirements. Besides their crucial ability to regulate cellular metabolism, research has shown that mitochondria play a prevalent role in regulating the life and death of cells, specifically ageing (S B Ong, 2021). The definition of ageing is a process affecting all cells, tissues, organs, limiting homeostasis and weakening organisms. Ageing is affected by both extrinsic and intrinsic factors. Hence, this article will examine the extent to which mitochondria can be modulated and adapted to fulfil this role. The main purpose of the research will be to gain an understanding of the processes behind ageing, living skin cells and cell death. However, this prospective article cannot cover a thorough review of both factors using experimental results; therefore, it will only focus on the effects of intrinsic factors on human skin cells in correspondence to ageing and death.

FINDINGS

In order to scrutinise the fundamental role of mitochondria in bridging the gap between the life and death of skin cells, various books and articles have been analysed. The key aspects

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Mitochondria have faults that have detrimental effects on cells and the body as a whole. One example of fault is when electron electricity leaks out of the mitochondria, resulting in the generation of toxic free radicals (G Brown, 1999). Toxic free radicals are molecules that have an unpaired electron. Once a free radical collides with another free-radical, a chain reaction is initiated. Generally, free radicals cause damage to the contents of a cell, including DNA, proteins, and the cell plasma membrane, through oxidation. Hence free-radical damage is phrased as oxidative damage. As a result, these cellular components lose stability to function or even death (S Lou, 2011), hence affecting the appearance of human skin cells.

Next, we move onto the role of mitochondrial DNA. Since mitochondria produce energy, through oxidising glucose, there is a continuous production of reactive oxygen species. The first proposal for the mitochondrial theory of ageing was made by Denham Harman, pioneer of free radicals in biology, in 1972 (N Lane, 2005). Harman elucidated that mitochondria are the main source of oxygen free-radicals in the body. These reactive oxygen intermediates contribute to oxidative stress, causing further mutation of the mitochondrial DNA. Damaged mitochondrial DNA reduces energy production (S Shanbhag, 2019). In turn, this affects the energy supply to cells leading to cellular dysfunction. Subsequently this triggers the key reasons for ageing, including degeneration, rupture and leakage of free-radicals.

As these mutations and dysfunctions occur internally, the external surface of the skin begins to illustrate the two major signs of ageing; wrinkling and sagging. These physical appearances are resulted by the accumulation of altered elastic fibres and the degradation of collagen bundles in the dermis. In addition to this, research has shown a correlation between oxidative stress and age-related loss of elasticity of the skin, highlighting excessive reactive oxygen intermediates as the main cause of oxidative stress. Nevertheless, levels of reactive oxygen species can be adapted by various catalases or exposure to UV rays, in particular UVA rays, for instance. Not only do reactive oxygen species play a role in ageing, they also act as a 'toxic agent' in developing cancer, cardiovascular disease, inflammation and other age-related diseases (S Shanbhag, 2019).

Mitochondria are central to how cells control apoptosis (A Gilmore, 2019). Recent research suggests that mitochondria play a more active role in killing cells. Cells die in two different ways, controlled suicide or chaotic explosion. These ways can otherwise be classified as apoptosis. Apoptosis is the process by which damaged cells undergo programmed suicide (A Gilmore, 2019). This process is an important part of tissue homeostasis (where tissues constantly remove old or damaged cells by replacing them with new cells). It ensures that cells die quickly and that dead cells are safely and efficiently removed.

The sequence of events taking place in apoptosis are illustrated in figure 1. Firstly the cell shrinks as its DNA is hydrolysed by enzymes into smaller fragments. These fragments of the membranes of dead cells exhibit signals from the surface. This allows them to identify

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neighbouring cells in order to ingest them. When cells undergo apoptosis, caspases, which are proteases, are activated. Caspases bind different proteins in a cell to form a particular characteristic change seen when cells die. They can be presented as inactive precursors which live in healthy cells. For caspases to be activated, cytochrome c is essential for the conversion of inactive precursor caspases. Cytochrome C is a heme protein found between the inner and outer mitochondrial membrane that initiates the respiratory chain (J A Dykes, 2007). Cytochrome c is released into the cytosol to react with the protein product of the APAF1 gene. The APAF1 gene activates the caspases (A Gilmore, 2018). Therefore this shows the importance of the mitochondria in terms of the release of proteins essential for apoptosis.

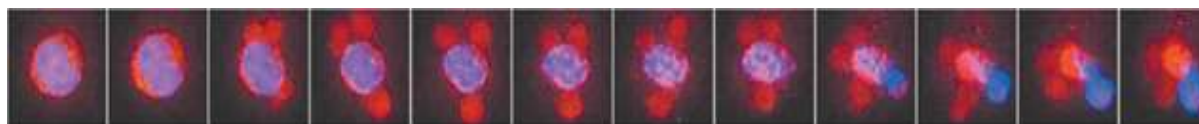


Figure 1 illustrates the sequence of events in apoptosis

The following section will explore the senescence of the external surface. For instance, the skin epidermis thickens, wrinkles deepen, hair discolours and the skin becomes rougher and duller. Additionally, sagging and wrinkling, caused by the further loss of skin elasticity, increases, contributing to slower wound healing, primarily in the elderly. Despite these deteriorations, the physical appearance of ageing has triggered strategies to combat ageing, mainly the use of moisturising, botulinum toxin, antioxidants and anti-wrinkling treatment (S Shanbhag, 2019). These strategies are purely chemical based, however some natural strategies include simply drinking more water, reducing stress, intaking a healthy diet and exercising regularly. This article will scrutinise anti-wrinkling products. Two commonly used anti-ageing agents are hyaluronic acid and botulinum toxin:

Hyaluronic acid(HA), which is made by bacteria by the process of biofermentation (K Liu, 2020), provides preservation of hydration and elasticity of the skin. As a humectan (B Goh, 2020) , in other words a common moisturizing agent found in hair and skin products (K Cherney, 2019), HA can also retain moisture whilst preserving all other properties of the product. While HA has a significant impact on reactive oxygen species produced by mitochondria, botulinum toxin(BTX) prolongs the visible ageing process through injections.

Discussion

Free Radicals

One of the most significant findings was that oxidative damage caused by free radical mechanisms affects the functioning of human cells. Scrutinising on free-radical mechanisms, free radicals are generated by anti-oxidative mechanisms, specifically in intrinsic aging. This mechanism functions by the constant generation and removal of free radicals, which maintains an equilibrium in the body(S Shanbhag, 2019). A decrease in this oxidative mechanism leads to the leakage of free radicals in our body. Furthermore, excessive free radicals are formed because of an imbalance in the process; this is toxic to the body, hence contributing to cellular

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ageing. There is evidence that the process of ageing itself may be due to the build-up of free radical damage to the body. For instance, the wrinkling of skin and the decline in eyesight with age appear to be due to this damage (G Brown, 1999). Therefore, this finding potentially shows that mitochondria, in terms of the release of free radicals, are primarily responsible for the ageing of cells.

Mitochondrial DNA

Another important finding was the response of manipulating mitochondrial DNA to leaking free radicals and cellular dysfunction. Harman further explained that there was a biological relationship between metabolic rate and mammalian life span. Explicitly he labelled the mitochondria as a 'biological clock' (N Lane, 2005). Moreover, mitochondrial mutations were found to accumulate with age (N Lane, 2005). If the mutations affect the respiratory chain in mitochondria, then the rate of free-radical leakages rises, spinning the vicious cycle faster. As a result, the cell loses control over its function. When this overcomes a sizable proportion of the cells in a tissue, the organs fail and place the remaining functional organs under great strain. The inevitable outcome is ageing and death. Fewer cell mutations are detectable before the age of 30 or 40 but after these ages' mutations rise exponentially (G Brown, 1999); there would be a significant proportion of mutations in mitochondrial DNA. Hence, this may significantly damage the ability to generate energy, which suggests that these cells with little use will eventually die.

Apoptosis

An obvious finding was the contribution of apoptosis to the life and death of human skin cells. As Guy Brown states, excessive programmed cell death can cause degenerative diseases such as Alzheimer's, Parkinsons and stroke (G Brown, 1999). When apoptosis is overactivated, mutations allow cancerous cells to thrive. Moreover, damage to cell DNA can cause cells to malfunction and harm the body. In turn this can have severe consequences on a disease. For instance, when a cardiac arrest or stroke occurs, cells cannot obtain a sufficient supply of oxygen due to the blockage of blood vessels supplying the heart and brain. During this stage, the outer mitochondrial membrane opens its pores to increase permeability. Once the pores are open, pro-death proteins including cytochrome c are released. Consequently, this results in apoptotic cell death (S B Ong, 2012). Therefore, it seems that mitochondria have a substantial part in apoptosis.

Anti-ageing reagents

One anticipated finding was the use of anti-ageing agents, HA and BTX, in reversing the process of ageing and bringing life to cells. It can be highlighted that HA can be presented in different molecular sizes (K Liu, 2020). Large HA molecules tend to bind more easily than smaller molecules. Despite this, large molecules can only sit on the epidermis of the skin when applied to the skin. Although small molecules of HA bind weakly to water, they can penetrate deeper through the epidermis. Both molecule types offer hydration despite the differences. The benefits of using HA is that it does not irritate sensitive skin nor does it induce allergic reactions (K Liu, 2020). A drawback to using HA is that it cannot be solely applied topically to very dry skin. In this case, HA should be applied alongside a moisturiser to prevent moisture uptake

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from deeper layers of the skin. This procedure helps to seal the layers in dry skin (B Goh, 2020). In relation to the topic of research, an experiment was carried out on chondrocytes to see the impact of HA on mitochondrial activity. (Chondrocytes are metabolically active cells, derived from mesenchymal stem cells(MSC) in cartilage (H Akkiraju, 2015). When cultures of primary human chondrocytes were exposed to reactive oxygen species, there was a rise in mitochondrial dysfunction, mitochondrial DNA damage and mitochondria- apoptosis. However, when these chondrocytes were pretreated with hyaluronic acid, the results saw a decrease in mitochondrial DNA damage and improvement in apoptosis. Additionally, the ATP levels were further preserved (V Grishko et al, 2009). Based on the above properties and the results of the experiment, we can justify that HA is an effective anti-ageing agent in prolonging the effects of ageing. In contrast, BTX can be classed as the most effective cosmetic procedure as it diminishes wrinkles and facial lines, caused by facial muscular contractions. Moreover BTX does not cross the blood brain barrier nor does it penetrate through the skin (S Shanbhag, 2019).

If the process of ageing is sequenced by the generation of oxidative species, the process could potentially be reversed through the incorporation of antioxidants to anti-ageing products. An example of this is Alpha Lipoic Acid (ALA). This not only provides protection to the cell membrane, but also neutralises free-radicals (M S Shamka, 2011). Furthermore, antioxidants have been proven to inhibit inflammation leading to collagen depletion and shields against oxidising components of UV radiations (S Shanbhag, 2019). They work by reacting with superoxides and suppressing the skin diseases caused by reactive oxygen species. From this, we can therefore see that anti-ageing creams decrease the effects of ageing, by the removal of dead skin cells, allowing for brighter and smoother skin cells to come to the surface.

CONCLUSION

In conclusion, the purpose of this research was to examine the extent to which mitochondria play a role in the life and death of human skin cells. The findings reveal that mitochondria are dynamic organelles that are able to adapt to cell changes through secreting proteins, leaking electrons and contributing to apoptosis; therefore, these findings provide indicators for curing diseases and dysfunction. The extent of this research was limited to factors affecting mitochondria on an intrinsic level. Despite this limitation, this research forms a qualitative foundation for identifying influences of mitochondrial behaviour towards sustaining life of skin cells, and hence using mitochondria as prospective drug targets for the future. Overall, the research has found several fundamental implications for future research of ageing and anti-ageing products.

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