NARRATIVE REVIEW

Acupuncture and cellular mechanisms: the role of foxo transcription factors in autophagy and senescence

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Abstract

The current narrative review was planned to elucidate the interplay between acupuncture, a cornerstone of Traditional Chinese Medicine, and the modulation of cellular mechanisms via Forkhead box O transcription factors, focussing on autophagy and cellular senescence. Autophagy, essential for cellular health, and cellular senescence, associated with aging and age-related diseases, are both significantly influenced by Forkhead box O transcription factors among other regulatory factors and pathways. These factors, known to diminish with age, play a pivotal role in promoting longevity. The current review analysed experimental models demonstrating acupuncture's capacity to activate Forkhead box O transcription factors, thereby inducing autophagy and reducing cellular senescence. Evidence from studies on human fibroblasts, ageing animal models, obesity-induced insulin resistance, and osteoporosis corroborates the beneficial effects of acupuncture. Despite these promising findings, the complexities of Forkhead box O transcription factors' activation by acupuncture and their precise impact on cellular processes warrant further investigation with a particular focus on the distinct roles of Forkhead box O isoforms.

Key Words: Acupuncture therapy, Autophagy, Forkhead transcription factor O, Transcription factors, Cellular senescence, Aging, Traditional Chinese medicine.

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Introduction

Acupuncture is a type of Traditional Chinese Medicine (TCM) that has been practised in China for more than 2,500 years.[1] Acupuncture stimulates the body's natural healing processes and restores balance by inserting thin needles into specific body points, modulating the nervous system and releasing endogenous opioids.[2,3] TCM postulates that the human body is composed of a network of energy routes called meridians, which are the conduits for the circulation of qi (pronounced 'chee'), also known as the life force. These postulates are based on the observation that the human body is a dynamic system that is always changing. It is possible for sickness and disease to develop if this flow of energy is interrupted or hindered. It is claimed that acupuncture may assist in restoring the body's natural balance of qi and improve the body's inherent ability to heal itself.[4]

The Forkhead box O (FoxO) transcription factors are a family of proteins that play a significant role in the regulation of autophagy and cellular ageing process.[5,6] There are four members of the human family that have been identified as belonging to the FoxO gene family; FoxO1, FoxO3, FoxO4 and FoxO6. These proteins are transcription factors, which means that they control the expression of genes by binding to deoxyribonucleic acid (DNA) and regulating the production of certain proteins. FoxO proteins are engaged in a wide range of physiological processes, including metabolism, the regulation of the cell cycle, apoptosis, and the response to stress. These proteins also play a role in the ageing process.[7]

FoxO proteins are highly important factors in the regulation of autophagy and cellular senescence.[7] The expression of genes that play a role in cellular senescence may be controlled by these proteins. Furthermore, depending on the condition of the cell, these proteins can either encourage or inhibit the process of autophagy. Therefore, FoxO proteins contribute to the prevention of age-related disorders. Due to these reasons, the role of FoxO proteins in autophagy and cellular senescence has been the subject of a substantial amount of research for years.[8]

Autophagy is the process by which cells degrade and recycle malfunctioning or damaged cellular components, such as proteins and organelles.[9,10] It can be triggered by multiple factors, including food scarcity, cellular stress

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and pathogen infection.[11] By eliminating potentially hazardous compounds and supplying energy and building blocks for other cellular activities, this mechanism contributes to the preservation of cellular homeostasis.[9,10] On the other hand, cellular senescence is a condition in which cells cease to proliferate, and undergo alterations that may contribute to the ageing process and the development of illness.[12] The process of cellular senescence may be induced by a wide number of signals, such as the shortening of telomeres, the damaging of DNA, or oxidative stress. Senescent cells are characterised by changes in gene expression, metabolism and shape. In addition, senescent cells often release inflammatory chemicals that may harm tissue, and contribute to the development of chronic illnesses.[13]

While autophagy and cellular senescence are two separate processes, they are intimately intertwined with one another. Senescent cells are capable of interfering with autophagy and contributing to the accumulation of hazardous chemicals in the body. On the other hand, autophagy may assist in the elimination of senescent cells and prevent the accumulation of damaged cellular components.[14] As a result, the investigation of the mechanisms controlling autophagy and cellular senescence remains a highly active research area. These phenomena hold the promise of elucidating the pathogenesis of age-related disorders.

The current narrative review was planned to explore the signalling pathways influenced by acupuncture that regulate FoxO activity. Gaining a deeper understanding of these pathways and how FoxO proteins govern autophagy and cellular senescence would provide new perspectives on age-related disorders, and lead to novel therapeutic approaches, including acupuncture.

Acupuncture and autophagy

FoxO proteins have the ability to regulate the expression of autophagy-related genes in their target cells. These proteins may either stimulate or suppress autophagy inside the cell, depending on the state of the cellular environment.[15] A number of studies have been conducted to assess the involvement of FoxO proteins in the regulation of autophagy. FoxO proteins regulate autophagy partly by activating autophagy-related genes, like microtubule-associated protein light chain 3 (LC3) and Beclin-1. Similarly, the expression of lysosomal genes, which are necessary for the breakdown of autophagosomes, may also be upregulated by FoxO proteins. FoxO proteins can also inhibit autophagy under specific circumstances, in addition to activating it. For instance, in the presence of growth factor signalling or sufficient nutrients, FoxO proteins may activate the mammalian/mechanistic target of rapamycin (mTOR) pathway, thereby suppressing autophagy. Furthermore, FoxO proteins can inhibit autophagy by controlling the production of autophagy-inhibitory molecules, like B-cell leukaemia/lymphoma 2 (Bcl-2) and ubiquitin-binding protein p62.[16]

The regulation of autophagy by FoxO proteins is a complex process. Thus, more research is needed to fully elucidate the mechanisms by which these proteins manage autophagy. Regarding the relationship between acupuncture, FoxO transcription factors, and the autophagy process, studies have been conducted.[17]

Studies have been conducted to explore the mechanisms via which acupuncture influences autophagy, and these investigations have uncovered a number of signalling pathways.[15,18] The stimulation of adenosine monophosphate-activated protein kinase (AMPK), which is a cellular energy sensor that controls autophagy, is one of the ways that acupuncture has been proven to induce autophagy.[19] A study evaluated the effect of acupuncture on autophagy and FoxO expression in a rat model of traumatic brain injury, and found that acupuncture not only increased the expression of autophagy-related genes, including LC3 and Beclin-1, but also increased the expression of FoxO1 and FoxO3 proteins.[20] Similarly, in another study, researchers investigated the effects of acupuncture on a mouse model of cardiac ischaemia-reperfusion injury. Acupuncture was shown to stimulate autophagy by activating a FoxO signalling pathway, and lead to an increase in the expression of autophagy-related proteins, such as LC3 and Beclin-1. It also lead to an upregulation in the expression of FoxO3 and sirtuin 1 (SIRT1), which is a protein that is involved in the control of autophagy. This provides support for the hypothesis that acupuncture may trigger autophagy.[21]

Due to the ability of acupuncture to initiate cellular autophagy, it has the potential to complement conventional medical treatments for a variety of diseases. However, more research is needed to thoroughly understand the mechanisms behind acupuncture and to evaluate its effectiveness in treating conditions involving autophagy and FoxO pathways.

Acupuncture and cellular senescence

In response to various challenges, such as DNA damage and oxidative stress, cells can enter a state of cellular senescence, which is an irreversible halt in their growth.[22] Once this pause occurs, the cell's development cannot resume. This state is marked by changes in gene expression and the production of pro-inflammatory cytokines, both of which contribute to tissue dysfunction

and age-related diseases.[23] Senescent cells are identifiable by these characteristics and are commonly found in tissues at the end of their lifespan.

Similar to autophagy, FoxO transcription factors play a crucial role in regulating cellular senescence. Numerous studies have indicated that FoxO factors are key in managing this process. For example, FoxO1 and FoxO3a have been shown to promote cell survival and delay senescence in response to various stressors, including oxidative stress and DNA damage. These FoxO factors achieve this by inducing the expression of genes involved in DNA repair, antioxidant defence, and other protective pathways. Additionally, FoxO factors may limit the production of pro-inflammatory cytokines, a trait associated with cellular senescence. By managing the production of certain cytokines, FoxO factors can influence the inflammatory response during cellular senescence.[24, 25]

The potential of acupuncture to delay the process of cellular senescence and aging offers promising hope for its use in treating age-related disorders. In one study, researchers found that acupuncture increased the production of transcription factors FoxO1 and FoxO3a, which, in turn, extended cellular lifespan and reduced the number of senescent cells. This suggests that acupuncture may be able to prevent or postpone the start of cellular senescence via activating the FoxO signalling pathway.[26] This evidence supports the hypothesis that acupuncture could influence cellular senescence through the modulation of FoxO factors. Acupuncture might prevent the formation of senescent cells by triggering senescence in response to severe stress, while also promoting cell survival and delaying senescence in reaction to various stressors. This mechanism could help avoid the accumulation of senescent cells by regulating FoxO factor expression, thereby enhancing the survival of cellular components.

FoxO transcription factors play a crucial role in regulating cellular senescence. They achieve this by enhancing cellular survival, inducing senescence under certain conditions, and controlling the inflammatory response during the senescence process. Acupuncture may influence cellular senescence by activating the FoxO signalling pathway[26] Given that age-related diseases are characterised by the accumulation of senescent cells, acupuncture shows potential as a treatment for these conditions.[27] However, further research is needed to fully understand how acupuncture modulates FoxO factors and cellular senescence.

Implications for future research

Acupuncture has the potential to prevent or slow the progression of many age-related disorders by promoting autophagy and reducing cellular senescence[27]. Researchers are currently investigating the use of acupuncture as a treatment for neurodegenerative conditions, such as Parkinson's disease and Alzheimer's disease.[28] These diseases are characterised by protein aggregation and disrupted autophagy.

Acupuncture has also been shown to be effective in the treatment and prevention of age-related metabolic diseases, such as type 2 diabetes and obesity.[28] It has been proven that cellular senescence plays a role in the development of metabolic disorders. It has also been demonstrated that decreasing the amount of cellular senescence may improve metabolic performance. In animal models of these illnesses, acupuncture has been shown to reduce cellular senescence and boost metabolic function, suggesting that it may have potential as a therapy for these disorders.[29,30]

Osteoporosis is marked by a loss of bone density and an increase in senescent cells in the bone marrow. Acupuncture may hold promise as a treatment for osteoporosis due to these characteristics. In animal models, acupuncture has been shown to reduce cellular senescence and increase bone density, indicating its potential as a treatment for this condition.[31]

Overall, there is optimism regarding the potential therapeutic applications of acupuncture in regulating autophagy and cellular senescence. However, further research is necessary to fully understand how acupuncture influences these processes and to determine the most effective treatment protocols for various illnesses. Additionally, acupuncture should be integrated with other therapies as part of a comprehensive approach to treating age-related disorders.[29-31] Similarly, despite promising research suggesting a link among acupuncture, FoxO transcription factors, autophagy, and cellular senescence, more studies are needed to elucidate the underlying mechanisms and to establish the best treatment protocols for different patient populations.

The current narrative review has several limitations. Primarily, most pre-clinical acupuncture research is conducted on animal and cell models, necessitating further clinical studies to confirm the impact of acupuncture on autophagy and cellular senescence in humans. There is also considerable uncertainty regarding the precise molecular pathways through which acupuncture affects autophagy and cellular senescence. In addition, while most existing studies focus on the

immediate effects of acupuncture, there is a significant gap in research concerning its long-term impact on aging and age-related disorders. Therefore, longitudinal studies are required to thoroughly assess these long-term effects. Finally, further investigation is needed to explore acupuncture's potential as a preventive or supplementary treatment for complex, multifactorial illnesses.

Conclusion

Acupuncture, an ancient TCM practice, is recognised for its therapeutic effects on various conditions. Recently, its potential to counteract ageing and age-related diseases has garnered attention due to its ability to modulate cellular processes. Central to this potential are FoxO transcription factors that play a crucial role in managing autophagy and cellular senescence; two key processes associated with ageing. These factors, known to diminish in activity with age, play a significant role in promoting longevity, alongside other regulatory elements and pathways. Notably, acupuncture has been shown to influence the activation of FoxO, particularly FoxO3a, which may enhance autophagy and delay senescence. However, the exact mechanisms through which acupuncture affects FoxO proteins, and consequently autophagy and senescence, remain unclear. Therefore, further research is imperative to explore these pathways in-depth, evaluate acupuncture's efficacy and safety through rigorous clinical trials, and compare its outcomes with other therapeutic interventions.

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LZ: Visualisation, reviewing and editing.
XL: Concept, validation, writing and final approval.
JA: Drafting, writing and formal analysis.
ND: Data curation, writing, aims and objectives.