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Sirtuins and Age-Related Diseases

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For the time since their discovery, the sirtuin proteins of deacetylase enzymes have been involved in the extension of the life expectancy of certain organism and individuals. The main sirtuins involved in the cytoplasm and mitochondrion involve the SirT1 and SirT3. Both of these sirtuins demonstrate capabilities to extend the life span in biology. They either slow the age related diseases or suppress them depending on the protein involved. These proteins need physiological effects in order to carry out their processes and pathways. This review will cover all of these ideas, and show how many of these diseases are either slowed or treated before-hand or after the initial disease has taken place.

Introduction

Cancer is a leading cause of death worldwide and the second cause of death in the United States after heart disease [2,80]. There are many diseases out in the world that lower the life expectancy of an individual. Researchers have gone to new limits by unveiling certain proteins that others have thought could enhance an individual's life expectancy by setting a pace on the aging. The proteins called sirtuins and have been thought to slow the aging in mammals [3, 561]. There are different types of sirtuins in the cell of an individual. The sirtuins can be similar in effects, but also some have distinct avocation. Sirtuins have been analyzed since the molecular era of aging research which began in the 1950s [3,561]. Over the years, researchers have stated that sirtuins have adapted to other factors in the physiological side of an animal [3,561]. These adaptations would be the acute dietary factors such as fasting and calorie restriction. The main types of sirtuins that have really been studied more in depth along with these adaptations would be SirT1 and SirT3. Both of these sirtuins have been said to slow the aging process due to different factors in their physiological effects [3,561]. Even though some of the affects may be the same, SirT1 and SirT3 have different rolls; in example SirT1 works more in the cytoplasm while SirT3 is more in the mitochondria.

Recent Progress

Roles and Regulation of Nuclear and Cytosolic Sirtuins

"SirT1 is the most widely characterized protein in the sirtuin family, and as such, a great deal of information has been amassed regarding its regulation over the past decade" [1,282]. The role that was found amongst this sirtuin that greatly influenced pharmacological intervention is its vital physiological pathways [1,282]. One of the roles in SirT1 research has been its caloric restriction. The caloric restriction has been known to increase the life expectancy of different organisms in different ways. This was all founded upon experimenting on sirtuin activity in worms and yeast. They developed a hypothesis that stated that a gain or loss in SirT1 homologue would increase or decrease the life span of an organism [1,282]. The effects were measured by the availability of NAD+, a sirtuin activator, which increases during caloric restriction. NAD+ is needed for the sirtuin protein to function. Later research revealed that caloric restriction also affected the abilities of sirtuin through a variety of NAD+ -linked redox pathways in yeast. In example, caloric restriction can increase nicotinamide levels which in turn are inhibitors to sirtuins affecting their tasks in redox reactions. The research demonstrated that NAD+ was involved in controlling the sirtuin function of organisms to an extent. Caloric restriction has also proven to increase the expression in proteins of different sirtuins. This increase in expression has demonstrated to enhance their deacetylase functions.

The research that demonstrated that SirT1 homologues increase the life expectancy of organisms led to the searching for a great pharmacological sirtuin activator. The activator that was found is best known as resveratrol. Resveratrol is a weak antioxidant usually found in red wine. Resveratrol betters the enzyme chemical reaction of SirT1 by improving its function to

bind and deacetylate substrates [1,282]. When resveratrol was increased in yeast, the SirT1 homologue, SirT2, was activated which in turn increased DNA stability and lengthening the life expectancy by 70% [1,282]. Further research displayed an increase in the life span of flies and worms up by 20-30% [1,282]. The experimenters treated mice and rat diabetes models with these different sirtuins and came to find that their overall metabolic function improved, while their diabetic progression was greatly reduced [1,282]. All of these experiments stumbled upon the results of and upregulation in metabolic function in the mitochondria. This would lead to other answers showing that SirT1 is part of the reason aging process was slowed by restricting or reducing diseases in the organisms tested. Large scaled organisms such as humans have not been tested upon causing a lack of answers overall.

Roles and Regulation of Mitochondrial Sirtuins

Mitochondrial sirtuins have proven similarities to cytosolic and nuclear sirtuins in ways, but mitochondrial sirtuins are more focused on cancer biology and aging due to oxidative stress caused by reactive oxygen species affecting mitochondria and cells in horrid ways. The mitochondria holds a vast amount of key molecules such as SirT3, a sirtuin that regulates cell survival, death, and metabolic pathways and help maintain homeostasis between health and disease [2,82]. The main role SirT3 holds in mitochondrial biology is contributing to cell survival by regulating oxidative stress pathways. A researcher demonstrated that by getting rid of the gene responsible for causing high blood pressure and other pathological like kidney, heart, and brain diseases, the organism tested had an improvement on life expectancy [2,82]. The reason the gene can be controlled has to do with the upregulation of the mitochondria, decrease in oxidative stress, and the increasing of SirT3 levels. SirT3 is responsible for the protection of certain cells from oxidative stress-mediated cell death. These cells are protected from apoptosis when SirT3 binds and deacetylates other proteins such as Ku-70 [2,82]. SirT3 protects the heart from cardiac hypertrophy by decreasing reactive oxygen species. Caloric restrictions still prove to affect the SirT3 levels in the mitochondria as SirT1 levels are regulated in the cytoplasm. Under caloric restrictions, SirT3 deacetylates and activates superoxide dismutase 2. Superoxide dismutase 2 protects certain cells from reactive oxidative species-mediated cell damage [2,82]. For example, cochlea cells get reactive oxidative species damage due to aging, but the SirT3, produced under caloric restriction, have stopped reactive oxidative species-mediated damage to the cochlea cells.

SirT3 has been noticed to carry out a prosurvival job in a vast variety of cancer pathways. "A tumor suppressor, p53, was recently been identified as a new target for SirT3 deacetylation in bladder cancer" [2,82]. The discovery caused researchers to report that higher transcriptional levels of SirT3 were involved with other cancers. In example, during breast cancer the SirT3 levels were lower than normal, but when the breasts were normal the levels of SirT3 were considerably higher. The levels of SirT3 in breast cancer lead to other research in other cancers, such as oral squamous cell carcinoma. They discovered that in oral squamous cell carcinoma the SirT3 levels were lower in comparison to the individual with no cancer. All the experiments they performed on the levels of SirT3 in cancer led to a discovery that SirT3 is highly involved in regulation of cancer. In comparison, different reports prove a proapoptotic role for SirT3. Researchers have investigated that SirT3 stops the growth and causes apoptosis in in different cancer cells but not in non-cancer cells. This discovery is still controversial in some cancer cells like leukemia, but research is still being done.

Experiments have continued to be performed on SirT3 and show that it is a tumor suppressor. These experiments involved the use of mice in order to verify the answers needed in the experimentation of this protein. In the experiment the mice were injected on the hind limbs with fibroblast negative in SirT3 and the other set of mice were injected with SirT3 positive protein in the same location. A couple weeks later the SirT3 negative mice began to develop tumors, while the SirT3 positive mice didn't develop any. In addition, SirT3 expression was found to be decreased in commercially obtained tissue microarray samples of the human breast and in other cancers [2,83]. These results suggested that SirT3 is a tumor suppressor. All the experiments in the humans with no breast cancer also concluded that the individual's levels of SirT3 were lower or not even in existence. In combination of all the facts, the negative amount of SirT3 in tumors caused the tumor to grow at a faster rate and grew larger in comparison to tumors with positive amounts of SirT3.

Metabolism is important in cancer development and prevention [2,83]. The mitochondria determine the energy regulation, metabolic balance, and cellular life, and in the mitochondria, the SirT3 protein regulates a vast amount of metabolic pathways. These results show that SirT3 is a main regulator of cancer processes. A number of experimentations have demonstrated the job of SirT3 in the metabolism and homeostasis. Some researchers stated that SirT3 is a tumor suppressor found that mice negative in SirT3 have lower levels of adenosine triphosphate in the kidney, liver, and heart, and a higher rate of production in reactive oxidative species [2,83]. The higher levels of reactive oxidative species promote mutagenesis and gene instability as shown amongst the negative SirT3 mice. Even though a couple of studies have really proved SirT3-mediated metabolism is linked

to cancer, the cases that were experimented on have proven that SirT3 is a critical regulator in the metabolism of the mitochondria [2,84].

Several studies in Sirt3 demonstrated that is a great target for many of the age-related diseases, such as cancer. The issue that has brought discrepancies is that researchers do not know how exactly Sirt3 is really involved with cancer and is not very clear. Having a clear understanding on that matter would really help escalate a better answer on how they really help in possible therapies.

Discussion

We finally are beginning to understand the role of sirtuins in treating age-related diseases. Many issues still are creating controversies in the research already done. Even though researchers are not too sure on how the sirtuins affect certain cancers, they know that this creates an importance on studying the topic more to get a more in depth answer on the matter. The data that was presented demonstrates that SirT1 does affect the cell because of the physiological effects on it. These effects helped lengthen the life span of certain organisms to a certain level. Studies still need to be done to better know how they can eliminate the age-related diseases through deacetylation. SirT3 studies conducted also displayed good results in the mitochondria by helping regulate and maintain the mitochondria stay balanced. This protein also demonstrated signs that it affected cancer and tumors in positive ways, but not enough research has been done to conclude on how it actually does the effect to these tumors and cancer. Further research on sirtuins needs to be done within the future in order to find better answers to conclude what we can do with these proteins in therapy and other related fields. Once every study comes to a positive conclusion on sirtuin effects, it will bring a new era to the world. This era will show new possibilities for future studies to come on aging.

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