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The role of the 14-3-3 protein family in disease

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Abstract. 14-3-3 protein is a dimer protein extracted from bovine brain cells, a highly conserved protein prevalent in eukaryotes. There are seven subtypes in mammals, respectively σ, ζ, β, γ, η, ε and τ. The subtypes differ in content and function. It was found that the protein interacts with corresponding ligand protein in regulating life activities, such as: cell cycle regulation, cell development, the transmission of cell signal molecules plays an important role. At the same time, related regulators have been developed based on cell-cell interaction. In recent years, the exploration of 14-3-3 protein has been deepening gradually. Inhibition or stabilizers of the 14-3-3 protein in question have been studied or discovered, and have become a new target for treating diseases. This paper reviews the effects of 14-3-3 protein on neurological disease, cardiovascular and cerebrovascular diseases and cancer are reviewed. It is found that protein subtypes affect the occurrence of diseases.

Keywords: 14-3-3 protein, disease, neurological disease, cardiovascular disease and cerebrovascular disease, tumors.

1. Introduction

In 1967, Moore and Perez first discovered the 14-3-3 protein in cow brain monomers, at the time its designation depended on the number of DEAE-cellulose fragments and the location of migration in gel electrophoresis, and the molecular weight of the monomer is 27-31 KDa. It is ubiquitous in eukaryotic cells. It is also a kind of a highly conserved and acidic heterodimer protein. Seven protein subtypes have been found so far in mammals, respectively are σ, ζ, β, γ, η, ε and τ. The differences between different isoforms are mainly reflected in facultative grooves of protein structure, there are binding sites to different ligands in facultative grooves-it is important structure for the14-3-3protein. Studies have shown that the 14-3-3 protein can regulate the function of different proteins through cytoplasmic isolation, regulation of enzyme activity, prevention of degradation, and promotion of protein modification, so the 14-3-3 protein and the corresponding ligand protein play an important role in different areas of life, such as: regulation of metabolism, cell cycle regulation, cytoplasmic transport transcription, malignant tumor suppression and so on [1,2]. Meanwhile, in the area of protein-protein interactions (PPIs), the 14-3-3protein family was also the midpoint of the study. By combining small molecules or proteins with 14-3-3proteins, new drug nave been developed to tread various diseases. There are hundreds of small molecules that can bind to 14-3-3proteins, known inhibitors and stabilizers are 14-3-3 protein and chaperone protein PPI types, R18 is the first protein inhibitor to be discovered that binds to this protein and has inhibitory effect on tumor cells. Subsequently, lacoceramide, HSP20,

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FOBISNI101 and other small molecules were identified by scientific and technological means to bind to 14-3-3 protein. Clostridium A, CotyledoninA and semi-synthetic clostridium extracted from natural products can be used as the stabilizer of14-3-3protein [2]. In recent years, 14-3-3 protein has become one of the important proteins in the study of novel objects. This paper reviews the effects of protein families on different diseases.

2. Diseases of nervous system

14-3-3 protein is widely distributed, the most abundant is found in nerve tissue cells. It plays an important role in the expression and function of nerve cells [3]. Common neurological disorders include Parkinson's disease (PD), Alzheimer's disease (AD), Depressive disease (MDD) [3-5].

2.1. 14-3-3 protein and Parkinson's diseases

When dopaminergic neurons disappear in the cerebral cortex and substantia nigra and ubiquitin-positive protein inclusion functions appear in the remaining dopaminergic neurons (Lewy corpuscles), people will suffer from PD. The main components of the Lewy corpuscles are σ-eukaryotic protein. Some studies have found that Lewy corpuscles contain 14-3-3 ε, τ, ζ, η subtype protein. On the one hand, these subtypes can combine with σ-eukaryotic protein to form structures similar to Lewy corpuscles, so it reduces the Lewy corpuscles. On the other hand the ζ subtype protein binds to the dopamine rate-limiting enzyme Tyrosine-Hydrogenase (for short TH) to promote dopamine synthesis. Because the σ-eukaryotic protein and 14-3-3 protein sequences have a certain similarity, so it also binds to TH, which effects dopamine synthesis. In the interaction of the three on dopamine, that it plays an important role in the regulation of PD patients [3].

2.2. 14-3-3 protein of Alzheimer's disease

AD disease is associated with the formation of neurofibrillary tangles (for short NFTs) from the aggregation of Tau proteins associated with paired spirals of hyperphosphorylated microtubules. NFTs contain five different subtypes of protein. Tau proteins are stimulated by protein kinases activated by 14-3-3ζ proteins, so it destabilizes the Tau proteins and cause structural variation, leading to NFTs, and increasing the incidence of AD disease [3].

2.3. 14-3-3 protein and depression

Some studies have found that hippocampal glucocorticoids increase after stress, which is easy to produce MDD disease. Ginsenosides showed protective effect on hippocampal nerve cells after stress. 14-3-3 protein has a strong affinity with panoxadiol, the main ingredient in ginsenosides [5]. It reflects that the 14-3-3 protein may be to prevent or treat depression.

3. Cardiovascular and cerebrovascular diseases

The occurrence of cardiovascular and cerebrovascular diseases is caused by atherosclerotic blood vessels. If it occurs in the heart, it is cardiovascular disease, while if it occurs in the brain, it is cerebrovascular disease.

3.1. 14-3-3 protein and diabetic cardiomyopathy

The scientists compared mice genetically modified for DN14 3 3ηsubnovel protein with wild mice that developed diabetes. No significant difference in blood sugar was observed but the loss of heart function was significantly greater in mice that lacked14-3-3 protein. The immunofluorescence of AsK1 is obvious in the left ventricle, the myocardial cells are enlarged, and the content of other substances is different. One of the reasons why macrophages become polarized is that fatty acid metabolism is altered during DCM. Meanwhile, the anti-inflammatory M2 type is weaker than the anti-inflammatory M1. Both metabolic polarization and macrophage polarization during DCM can be mediated by14-3-3 protein. It has been found that a high-fat diet in mice lacking14-3-3 protein increase the expression of the M1-macrophage marker protein, and the expression of anti-inflammatory proteins was reduced. So people get inflammation. The lack of the 14-3-3 subtype protein may be regulated through other signaling pathways in the body. It causes stress in the endoplasmic reticulum. which promoting myocardial

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apoptosis in diabetic mice. The difference of 14-3-3 protein expression based on the study data can provide a new idea for the study of blood glucose diseases. It is also possible to further control the prevention and treatment of diabetes by regulating the AsK1signal through 14-3-3 protein, or regulating the expression of M1 and M2 -type cell marker protein in macrophages [6, 7].

3.2. 14-3-3 protein and atherosclerosis

Atherosclerosis is the swelling of the endothelium of the arteries, leading to narrowing and hardening of the blood vessels. The adhesion of platelets to other secretions is one of the causes of disease. Special granule and compact granule are two types of platelet granule, and 14-3-3ζ protein subtype is mainly distributed in dense particles, and have the function of activating platelet secretory protein to promote atherosclerosis. And research have found that the presence of protein is found in the atherosclerotic plaque of the human abdominal aorta [7, 8].

4. Cancer

The imbalance between cell death and cell proliferation is one of the important causes of cancer [9]. At present, 14-3-3protein subtype has been found to be expressed in liver cancer, rectal cancer, lung cancer and other cancer cells. Different subtypes have different effects on different cancers [8].

14-3-3η protein and prostate cancer

The factors that determine the formation, metastasis and mutation of prostate cancer cells are androgens. The androgen-dependent character of prostate cancer was discovered by Huggins and Hodges in 1941. Androgens bind to estrogen receptors (AR) and act similarly to transcription factors, so they can regulate the expression of a large number of genes. Removal of testicles is a clinical treatment for prostate cancer. But there is a possibility of relapse. Subsequent studies by Mark et al. on recurrent prostate cancer cell line CMR-R1 found that endogenous AR receptors were activated by protein 14-3-3η at low oxygen dihydrotestosterone concentrations, and at the same time, enhance the role of AR. Androgen increase the expression of 14-3-3η, and 14-3-3η played a regulating role in AR. Several months were observed in mouse castration experiments, 14-3-3η protein content changed but eventually returned to pre-castration. It is known that androgen changes or deficiencies occur in prostate cancer that the 14-3-3η protein acts as an androgen agonist [8]. This could lead to new ways of treating prostate cancer.

14-3-3Σ protein and cancer

After DNA damage, 14 3 3σ protein is the only subtype that can normally inhibit cell growth and cell cycle progression. P53 is a tumor suppressor that can be activated after oncogene damage or disorder which stops the cell cycle in its tracks and programmed cell death, and at the same time inhibit the formation of other tumor cells [2]. It is a key factor affecting tumors. P53 can induce the expression of 14-3-3σprotein in DNA damage [10]. Upon induction 14-3-3σ binds to and sequesters the cyclin G2 complex in the cytoplasm, and prevents the nuclear localization of mitosis, so that the cell cycle to stall. This allows damaged DNA to be repaired before the cell cycle progresses. The results indicate that 14-3-3σprotein inhibited tumor activity [2,10,11]. In addition, 14-3-3σ protein is down-regulated in dysplastic tissues and cells, and it can be seen that early signs of tumor development may be reduced function of 14-3-3σ protein [12].

5. Conclusion

In recent years, the research on14-3-3protein has been deepening gradually, and the mechanism of action of the protein on the disease has been discovered. 14-3-3 protein originally found in the brain of cattle, so it is most closely related to the brain. It plays an important role in the function of the nervous system, such as: nerve signal conduction, nerve cell development, nerve cell connection and so on. In addition, further research has also shown that the 14-3-3protein family has important function in different parts of the body. They interact with other proteins. The regulation of cell cycle, cell apoptosis and signaling molecules are all dependent on14-3-3protein. At the same time, 14-3-3 protein is a new target for developing drugs to treat disease. Not only can affect the nervous system, cardiovascular

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cerebrovascular, tumor cells, but also has unknown effects on other diseases. Although some of the functions of14-3-3protein have been discovered and applied, the regulation of 14-3-3protein on human function is not fully understood. For example, no key drug has been developed to treat a disease with protein as the main body, and the mechanism of action of protein subtypes on different subtypes of the same disease. The 14-3-3protein is a large family, and as technology continues to improve, its role in diseases and improve life activities will eventually be discovered.

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