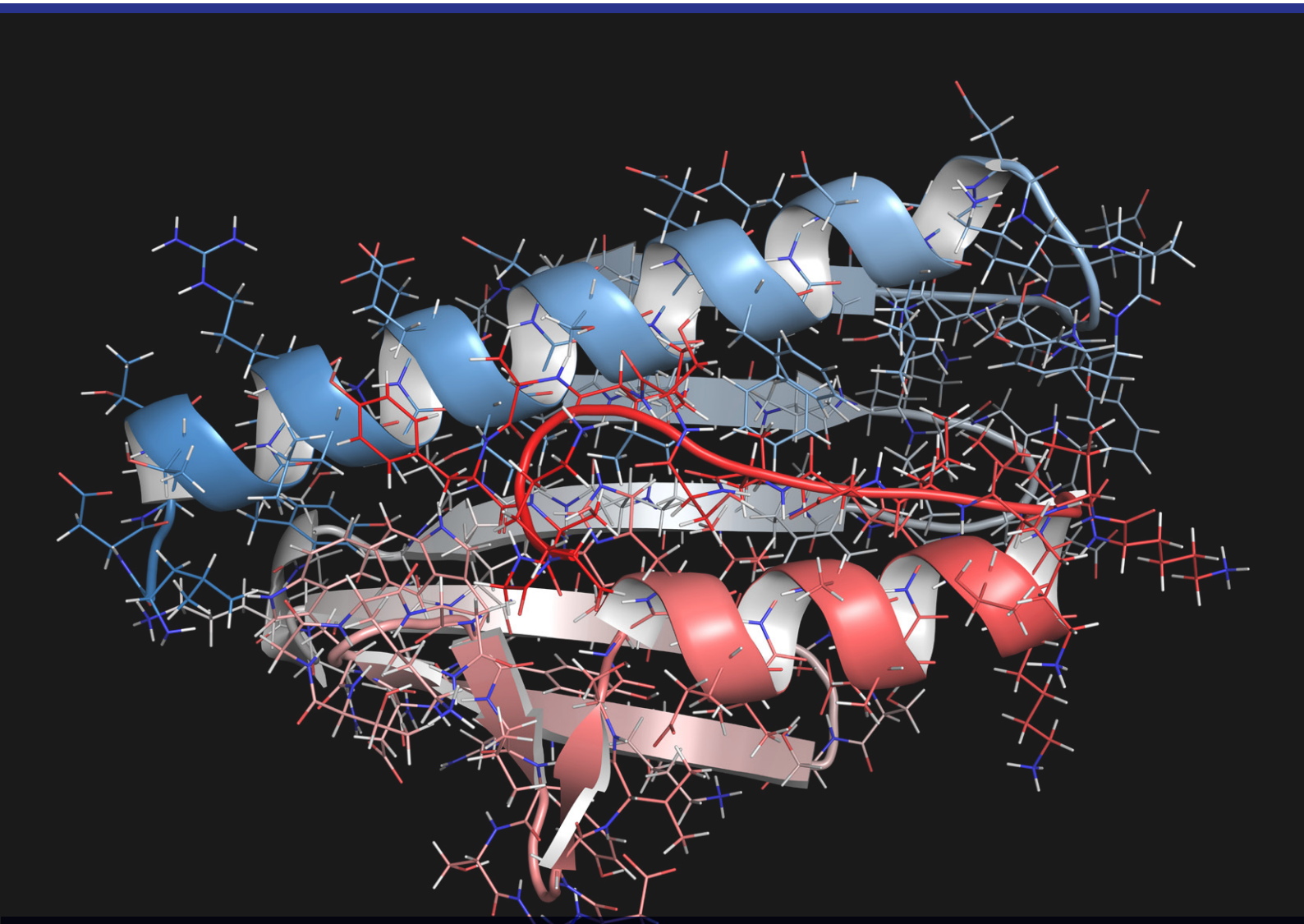

The role of iron and sulphur in a hereditary disease

Details

e: RdnyShac@aol.com
e: rshackelford@health.southalabama.edu
t: +1 318 525 6479

Address

Department of Pathology
University of South Alabama College of Medicine
2451 University Hospital Drive
Mobile AL 36617
USA

Collaborators

- Christopher G Kevil, PhD
- The A-T Children's Project

Bio

Dr Rodney Shackelford has a PhD in molecular pathology from Duke University and later attended medical school in Des Moines, Iowa. He is certified in anatomic, molecular, clinical, and renal pathology, and has researched various aspects of the ATM gene's function for 26 years.

Further reading

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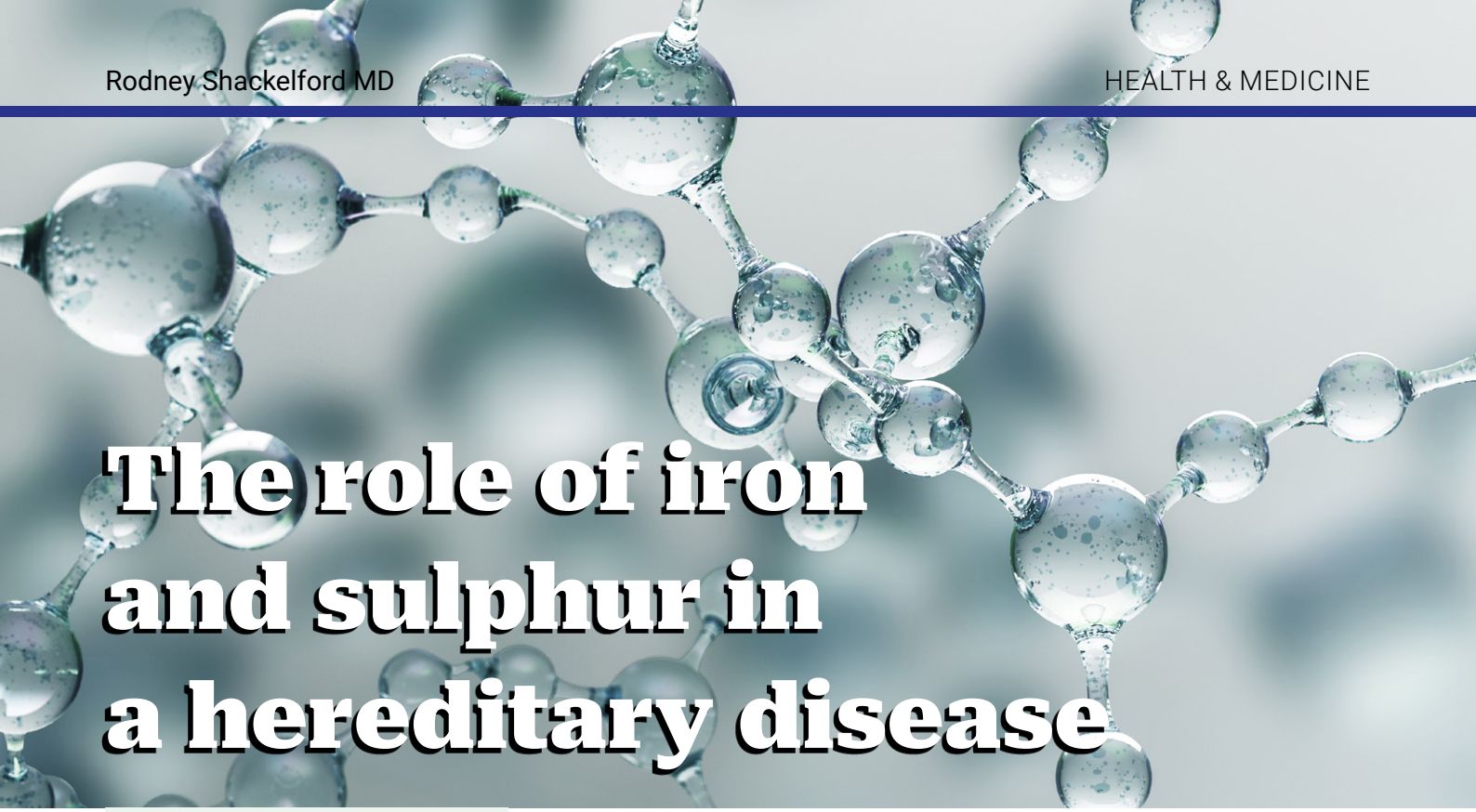


The role of iron and sulphur in a hereditary disease

- *Ataxia-telangiectasia* (A-T) or Louis-Bar syndrome is a hereditary disease that causes severe disability.
- Sufferers are born with two defective *ataxia-telangiectasia mutated* genes (ATM), which play an important role in healthy cell functions.
- Dr Rodney Shackelford at the University of South Alabama, USA, has been studying iron–sulphur clusters inside A-T cells, to better understand the effects of the defective genes – and potential therapies for A-T.

Ataxia-telangiectasia (A-T), or Louis-Bar syndrome, is a rare hereditary disease that causes severe disability. Ataxia means an inability to control body muscles, resulting in an inability to walk, talk, or even swallow. Telangiectasia is a term that describes the presence of tiny red lines on the skin and in other areas, also called spider veins. People with A-T are very prone to infections and one out of three will develop cancer at some point in their lives, most commonly blood cancer and cancers of the immune system.

ATM: a precious gene

A-T is caused by a mutated (defective) *ataxia-telangiectasia mutated* gene (ATM). A person must inherit two defective ATM genes to have the disease, one from each parent. The ATM gene plays a vital role in keeping our cells healthy by producing a protein called the ATM kinase, which helps adjust some of the cells' important functions, such as energy production, repairing damaged DNA, and protecting the cells from harmful substances and radiation. It has also been shown that A-T cells, which lack the ATM gene, are not able to grow properly when exposed to high iron levels, likely due to aberrant A-T cell iron metabolism, where 'free' or chemically unbound iron is not properly processed by the A-T cell, resulting in increased cell damage. This inspired Dr Rodney Shackelford and his team at the University of South Alabama, USA, to compare the clusters of iron and sulphur molecules, which play a role in controlling cell functions, between normal and A-T cells.

Shackelford's study brings to light new understanding of the ATM gene.

H_2S: not just another smelly gas

Hydrogen sulphide gas (H_2S) is produced in tiny amounts in our cells and prompts several vital chemical reactions. It can exist free in our cells, bound to proteins, or in iron–sulphur (Fe-S) clusters which are contained in Fe-S cluster proteins. These clusters play an important role in energy production inside the cell, copying and repairing the DNA, protein, and metabolite synthesis, and protecting the cells against viruses.

Immortal cells and Trojan horses

Cell lines are often used by scientists to study the features of specific diseases. A cell line is a population of identical cells that all come from one original cell. Because of certain mutations in their DNA, they can continue multiplying forever, creating an immortal colony. In their experiments, Dr Rodney Shackelford and his team used two

> **One out of three people with A-T will develop cancer at some point in their lives.**

cell lines from the same A-T cell, one of which they had altered so it could express the ATM gene. To make this alteration, they inserted a healthy ATM gene inside the defective A-T cells using viruses as tiny Trojan horses. The healthy ATM gene is attached to the viral DNA and when this enters the cell, it starts working as if it belongs to it, creating a line of normalised cells. The researchers next compared the levels of H_2S in all its forms including the iron–sulphur clusters, in both lines. They also measured the levels of several proteins, including NFS1 and NFU1 (two proteins

Ataxia-telangiectasia or Louis–Bar syndrome is a hereditary disease that affects patients' ability to walk, talk, or swallow.

important for stepwise iron–sulphur clusters synthesis inside cells), the enzymes that produce H_2S, and a small protein called glutathione, which is an antioxidant that protects cells from damage caused by free radicals (atoms or molecules with at least one unpaired electron).

Iron–sulphur and protein differences in A-T cells

After comparing their measurements for the two cell lines, the team was surprised to find that, although there was no significant difference between the free H_2S, protein-bound sulphur and the total sulphur levels, there were actually six times more Fe-S clusters formed in the normalised cells than in the A-T cells. By using a variety of laboratory techniques, the researchers found that the NFS1 and NFU1 proteins were increased for the normalised line, while the H_2S-producing enzyme levels were higher in the A-T cell line. They also discovered that the cells with the corrected ATM gene had higher levels of glutathione and that the normalised cells were far more protected against free-radical damage than the A-T cells.

> **There were significantly more iron–sulphur clusters formed in the normalised cells than in the A-T cells.**

These results show that the ATM gene product increases the number of Fe-S clusters and the proteins that are related to Fe-S cluster functions. The team is now investigating the possibility that A-T cells compensate for the lower Fe-S cluster levels by increasing a protein called ferritin that helps sequester iron in the cells to keep them active and healthy. With the adjustment of iron levels being a key factor for cellular health, the researchers think that treatments with medications that increase Fe-S clusters could benefit patients with A-T in the future. The fact that Fe-S cluster levels are also low in heart disease indirectly suggests that there might be a connection between the ATM gene and heart function too.

Dr Shackelford's study has brought to new light information on the little-known function of the ATM gene and will hopefully become an inspiration for further research in the field, leading to potential new treatment strategies and solutions in the treatment of A-T and cardiovascular disease.

Personal response

What inspired your research on the ATM gene and how did you come up with the idea of measuring the cell's sulphur pool and counting iron-sulphur clusters?

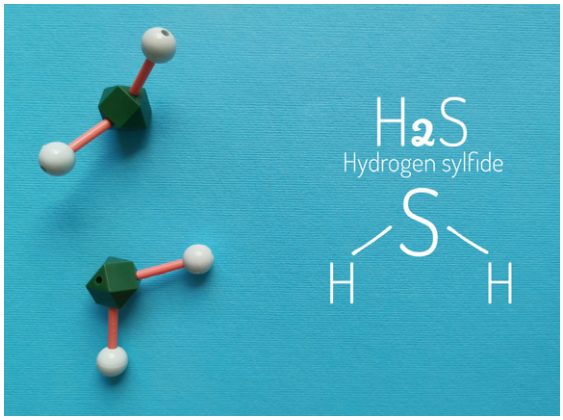
Unbound or 'free/labile iron' is toxic to cells. I found that drugs which bind up iron make A-T cells grow better, while they conversely inhibit the growth of normal cells. This data suggested that the ATM protein, which is absent in A-T cells, plays a role in binding iron and thus removes free (unbound) iron from the cell. My research revealed that this is the case, as the ATM protein is needed for Fe-S cluster synthesis, which binds up free iron.

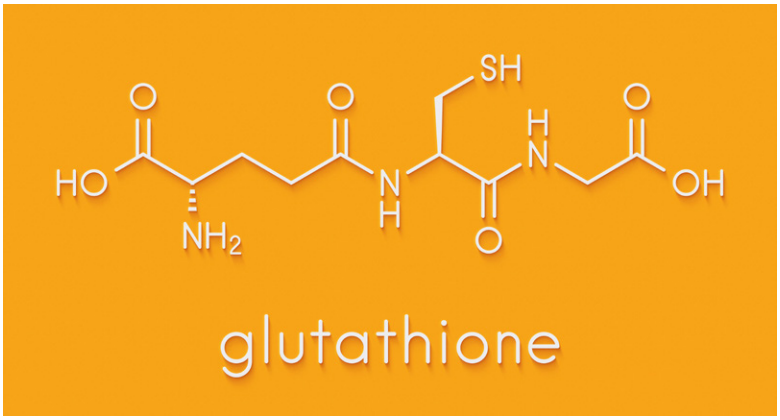
How will your findings influence the next stages of research on A-T?

The research shows a new and biologically profound function of the ATM protein. It places the ATM protein at the centre of almost all cellular biochemical functions, as Fe-S clusters regulate nearly all chemical reactions within cells. Thus, the research will make Fe-S cluster synthesis a central part of research concerning ATM protein function.

Could your research on iron–sulphur clusters be applied to the study of other diseases?

The research can be applied to the study of diabetes, cardiovascular and neurodegenerative disease, and cancer.





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