Rare, but essential – the amino acid selenocysteine

Based at the University of Bonn, Germany, **Professor Dr Ulrich Schweizer** is leading research into revealing the role of selenoproteins in mammalian physiology. By elucidating the mechanisms underlying their function, his work is yielding new insights into a wide array of human diseases affecting the brain and thyroid hormones. At the core of Prof Dr Schweizer's research is the rare selenium-containing 21st amino acid selenocysteine (Sec), the defining component of selenoproteins.

Selenocysteine (Sec) is an essential amino acid component in selenoproteins, which are involved in a variety of cellular and metabolic processes. Increasingly, their deregulation is being associated with neurodegenerative and other diseases, for which the underlying mechanisms have remained unclear. However, using novel transgenic mouse models, Prof Dr Schweizer and his team have uncovered a wealth of information regarding the mechanisms behind their function. His team's extensive research has found that reducing the expression of selenoproteins in the mammalian brain impairs brain development and healthy functioning, consequently causing a broad spectrum of disorders, including epilepsy and neurodegeneration.

Selenoproteins are proteins within which Sec is incorporated in the polypeptide chain. The importance of Sec had, until recently, been overlooked – perhaps due to its low abundance and discovery after the other 20 canonical amino acids. In Sec, an atom of the trace element selenium (Se) replaces the sulphur atom of cysteine. Selenium possesses similar but more reactive properties than sulphur, and is always housed in the active centre of selenoenzymes.

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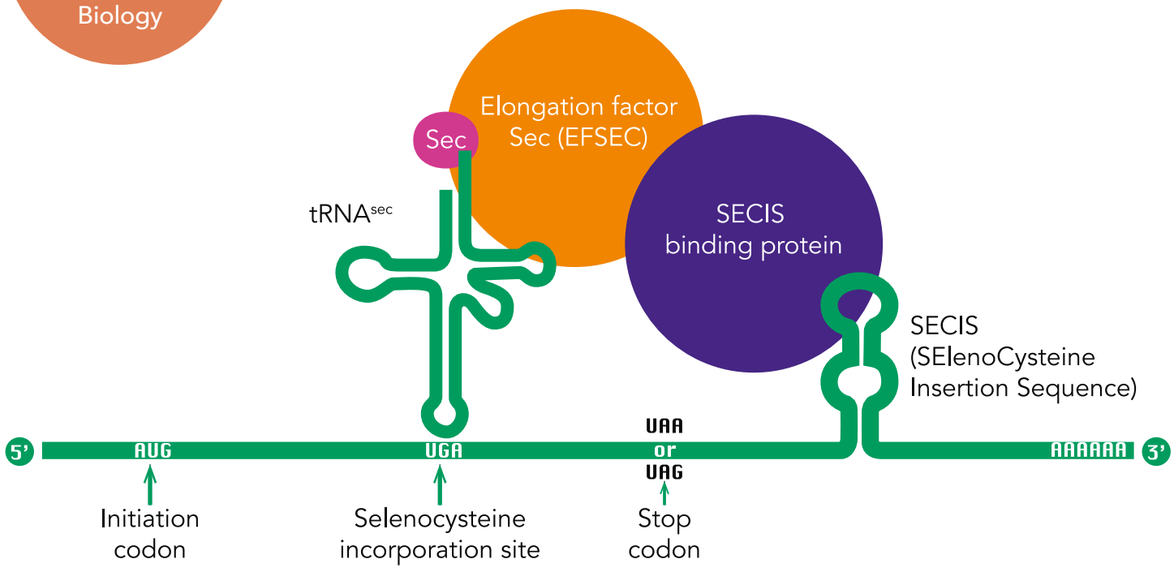
INVESTIGATING THE RAREST AMINO ACID

Sec eluded the Nobel Prize winning scientists who deciphered the genetic code, because Sec is encoded by what has been regarded exclusively as a termination codon, UGA. How can the cell distinguish between termination and Sec incorporation? There is a specific element within the mRNA sequence that directs the re-coding of UGA, called the selenocysteine insertion sequence (SECIS). The SECIS is recognised by a SECIS-binding protein, which in turn instructs the ribosome not to terminate but to incorporate Sec – see the figure overleaf.

The human genome contains 25 selenoprotein-coding genes. Mice have the same selenoprotein genes as humans, but one less. Out of the selenoproteins encoded by the human and rodent genomes, around half of their functions remain unknown. Dr Schweizer and other scientists realised that the genetic analysis of transgenic mice in which specific gene function has been disrupted or altered could shed light on the roles of individual selenoproteins. In fact, several selenoproteins are essential for mammals. With the rapid development of human genetics more and more mutations



have been identified in humans that disrupt selenoprotein function.

SELENIUM AT THE CORE OF CRUCIAL ENZYME ACTIVE SITES

Proteins that function as enzymes, in which Sec is a key component, are known as selenoenzymes. These are most established as anti-oxidative enzymes that fight 'free radicals' within cells, and are therefore implicated in ageing and metabolic disorders. In addition, selenium and the selenoenzymes it is incorporated into, are critical to the regulation of thyroid hormone activity. This became apparent when patients with mutations in the SECIS-binding protein were found to have growth delay and blunted response to thyroid hormones. Both can be explained by Sec's presence in deiodinases. Deiodinases are a group of selenoenzymes that are responsible for the activation and deactivation of thyroid hormones on the tissue level. Thyroid hormones are known to be central to development and play a key role in energy expenditure and metabolism and, as discovered more recently, play crucial roles in stem cells, regeneration, and cancer.

How deiodinases work exactly remained poorly understood, until Dr Schweizer teamed up with protein crystallographers to become the first team to solve the crystal structure of one of these enzymes. Quite remarkably, the enzyme resembles ancient peroxide-degrading enzymes and must have acquired its vertebrate-specific function after losing its original function.

SURPRISING PHENOTYPE SHIFTS FOCUS TO NEURONAL DEVELOPMENT AND DEGENERATION

While completing his PhD on another topic, Dr Schweizer discovered that one of the knockout mice he had created was epileptic, sparking his realisation that selenoproteins may be of vital importance to brain function. Since then, Dr Schweizer and his researchers have embarked on a project to investigate the role of selenoproteins in neuronal function, looking at how they are implicated in neurological disease.

Prior to this discovery, only few earlier reports had highlighted the potential link between epilepsy and low levels of selenium in the blood. During this time though, the majority of selenoprotein functions remained uncategorised, and therefore the connection to selenocysteine had not been made. Prof Dr Schweizer and his team's research has since found that selenoproteins are essential for brain development, and they have succeeded in working out some of the specific mechanisms involved. They have identified a specific class of GABAergic interneurons, in which dysfunction is fundamental to the clinical manifestation of epilepsy, finding that two selenoproteins are intrinsically linked to this process.

To do this, Prof Dr Schweizer and his team disrupted neuronal selenoprotein biosynthesis in their mice models, deleting the gene that encodes the tRNA essential for Sec biosynthesis. When specifically inactivated in the neurons, the researchers discovered a developmental defect affecting a specific subgroup of inhibitory interneurons. This found that there was not only a reduction of interneurons, but the mice also suffered from seizures and ataxia, a failure to gain postural control, and a failure to coordinate their movements. Histological analysis of the mouse brain tissue showed progressive neurodegeneration underlying these phenotypes. Work on other mutant mouse models revealed that cellular glutathione peroxidase (GPX4) and cytosolic thioredoxin reductase (TXRND1) were involved in this process. Very recently, Dr Schweizer's research has revealed that mutations in the gene for TXNRD1 are present in patients with generalised epilepsy.

Moreover, patients with congenital mutations in the selenocysteine synthase gene have been found to suffer from a complex neurodevelopmental and degenerative disorder that involves a wide spectrum of features, including microcephaly, delayed intellectual and motor development, spasticity and epileptic seizures. Recently, patients have been identified carrying very mild mutations in the gene explaining why they are only afflicted with lower IQ, but do not suffer any neurodegeneration.

INBORN ERRORS IN SELENOPROTEINS LINKED TO WIDE ARRAY OF DISORDERS

Other disorders, in addition to epilepsy and neurodegeneration, have also been linked to mutations in selenoprotein genes. For example, mutations in selenoprotein N (SEPN1) result in a spectrum of muscular disorders, which are known collectively as SEPN1-related myopathy.

It is likely that, as the function of selenoproteins becomes better understood, many more rare diseases caused by selenoprotein deficiency will soon be uncovered. Prof Dr Schweizer and his team are hopeful that their research will open up new avenues for the diagnosis and treatment of neurodegenerative diseases.

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Q&A

Among all trace elements, what is so special about selenium in particular?
Selenium is unique in that selenoproteins have selenium attached by stable chemical bonds – making analysis much easier than for example zinc, which is less tightly bound. Also, selenoproteins can be detected based on genome sequences. So identification of a selenoprotein in rattle snakes or polar bears does not require wet chemistry. Another advantage is the limited number of selenoproteins. Roughly two dozen selenoprotein genes foster my hope to finally understand all their functions within my lifetime.

Did you ever regret leaving the area of neurological disorders after your chance discovery of epilepsy in the selenoprotein knockout mouse?
To many people's surprise, no. Colleagues often assume that research in the selenium field is hard to get funded. This is not correct, at least in my case, probably because we are not doing nutritional science, but hard-core molecular biology and biochemistry. But it is true, if you say you work on Alzheimer's, stem cells or cancer, one catch word is often enough to explain yourself...

Why do you think selenocysteine is essential to mammals but is absent from many other organisms?
One reason might be that a selenoenzyme may be 1000-fold faster than the same enzyme with cysteine. For complex cells, like ours, the selenoenzyme thus saves a lot of space that can be occupied by other enzymes doing other things. Ask yourself: Would you rather invite five smart people home for dinner or instead five thousand boring guests?

Have you had any thoughts on how the knowledge you have gained regarding the function of specific selenoproteins in epilepsy could be used to develop targeted therapeutic treatments?
This is too early at this moment, but I firmly believe that biochemistry helps to i) diagnose disorders, ii) understand their pathomechanisms, and with this knowledge iii) guides rational treatment strategies. There are many very good examples in the medical field for this opinion, among them all the inherited disorders that are included in the perinatal screening programmes which help many kids get the right treatment in time and thus prevent the development of severe mental disability.

What are your plans for the future of your research?
Clearly, I would like to further delineate the functions of selenoproteins in the brain and find out what exactly each selenoprotein does in each brain cell type and how. In addition, I have recently started to investigate the biochemistry of selenoprotein biosynthesis, i.e., how exactly the ribosome is instructed to incorporate Sec – instead of terminating protein biosynthesis. Along these lines, we are studying the function of the tRNA carrying Sec, which has recently been found to be mutated in a patient with abnormal response to thyroid hormone.

Detail

RESEARCH OBJECTIVES

Prof Dr Schweizer's research focuses on the biochemistry and molecular biology of selenoproteins. His previous research has found that reducing selenoprotein expression in the brain leads to developmental defects and neurodegeneration in mouse models.

FUNDING

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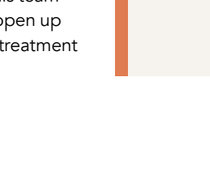
COLLABORATORS

Dr Schweizer collaborates with many scientists in his field, but he would like to highlight the mentorship of Dr Dolph L. Hatfield, NIH, Bethesda, and Prof Dr Josef Köhrle, Charité Berlin



BIO

Dr Schweizer received his degree in biochemistry at University of Bayreuth and his PhD in Neurobiology at University of Würzburg. He then moved to Charité-Universitätsmedizin Berlin to become a junior group leader at the Neuroscience Research Centre. He is currently Professor of Biochemistry at Rheinische Friedrich-Wilhelms-Universität Bonn.

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