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Selenium

Its Molecular Biology and Role in Human Health

Third Edition

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Dedication

This book is dedicated to Drs. August Böck and Thressa Stadtman. These outstanding scientists have had a major impact on the selenium field and are responsible for key discoveries in the biochemistry and molecular biology of this fascinating element.

Dr. Böck's research provided the foundation of how selenium makes its way into selenoproteins as selenocysteine, the 21st amino acid in the genetic code, in eubacteria. In his first work in the field, he identified unique requirements for selenocysteine incorporation into protein [1]. His second publication in this area was a highly significant collaboration with Dr. Stadtman showing that the in-frame TGA codon in the formate dehydrogenase gene corresponded to selenocysteine in the protein [2]. Dr. Böck then turned his attention to solving the question how selenium was incorporated into protein, discovering genes required for the pathway, characterizing their function, and ultimately establishing the mechanism for selenocysteine biosynthesis and insertion in bacteria (see reviews and Dr. Böck's and his group's many landmark discoveries in [3–5]). All subsequent research, including that in eukaryotes and archaea, benefited from these pioneering efforts. Dr. Böck followed these major discoveries with many elegant, highly important findings that provided the groundwork for conducting selenium research in subsequent years. These latter studies are summarized elsewhere [6, 7].

Among Dr. Stadtman's many accomplishments in the selenium field, there are those that provided the foundations for selenoprotein research, selenocysteine as the selenium-containing amino acid in protein, and the mechanism of how selenium is activated for synthesizing selenocysteine. In the first of these landmark studies, she identified glycine reductase as a selenoprotein in eubacteria in 1973 [8]. Then, in 1976, she and her research group identified the form of selenium in proteins as the amino acid, selenocysteine [9]. Later, Dr. Stadtman and her group identified selenophosphate as the selenium donor in the biosynthesis of selenocysteine [10]. In addition, her group demonstrated that the UGA codon in thioredoxin reductase codes for selenocysteine rather than being a terminator [11]. The many seminal accomplishments of Dr. Stadtman highly impacted the selenium field, opened up many new doors of research and changed how we view the field.

Drs. Böck and Stadtman collaborated on several innovative studies that also had a huge impact on the selenium field. The initial of these collaborations showed, as noted above, that the TGA codon in the formate dehydrogenase gene corresponded to selenocysteine in the selenoprotein product [2]. This study suggested that UGA dictated insertion of selenocysteine into protein, and this important point was later proven in another collaborative study of Drs. Böck's and Stadtman's showing that selenocysteine was biosynthesized on its tRNA in eubacteria [12]. At the same time, Dr. Stadtman and one of us, DLH, collaborated in showing that selenocysteine was biosynthesized on its tRNA in mammalian cells [13]. These two studies demonstrated that it is selenocysteine itself that was the 21st amino acid (rather than an intermediate that was incorporated into protein and then converted to selenocysteine posttranslationally). Another very important finding that Drs. Böck and Stadtman collaborated on was the demonstration of catalytic superiority of selenocysteine over cysteine [14]. Drs. Böck and Stadtman also worked together on several studies that influenced our understanding of the role of selenium in proteins (see refs. [15–17]).

It is a great honor and privilege to dedicate this book to Drs. August Böck and Thressa Stadtman. Without their pioneering studies, the selenium field would not be as we know it today, and certainly not with the firm foundation that provides the basis on which so much of the current work relies. We are deeply indebted to them for their many major discoveries, made both independently and in collaboration.

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Foreword

Selenium (Se), a metalloid mineral micronutrient, is an essential component for the adequate and healthy life of humans, animals, archaea, and some other microorganisms. Research into Se essentially commenced with its discovery as protective factor 3 against liver necrosis in rats by Schwarz and Foltz [1] and its role in formate dehydrogenase in *Escherichia coli* by Pinsent [2]. Biochemists, nutritional scientists, molecular biologists, bioinformaticians, biologists, and physicians have since worked out basic Se metabolism and some roles of selenoenzymes. This exciting Se history is compiled in the first book chapter. Six decades later we likely know most of the biochemical players, i.e., selenoproteins, products of 25 genes in humans [3], but we are still at the very beginning of understanding their physiological roles for maintenance of human health. Classical features of Se deficiency already described in life science textbooks years ago are not yet explained at the molecular level, e.g., liver necrosis, white muscle disease, cardiac, and skeletal muscle degeneration in Keshan disease or inappropriate chondrocyte differentiation in Kashin-Beck disease.

This third edition of the book, *Selenium: Its Molecular Biology and Role in Human Health*, edited by three leading scientists in selenoprotein research, Dolph Hatfield, Marla Berry, and Vadim Gladyshev, compiles in 45 chapters, organized under four sections, representing the state of the art in this rapidly expanding area of biomedical research. Research on the essential trace element Se has made unique progress with the identification of the opal UGA stop codon and its 21st proteinogenic amino acid, selenocysteine, which expanded the universal genetic code. It is an astonishing fact that selenocysteine, the key amino acid exerting most of Se's action, is the only amino acid that cannot simply be recycled for de novo selenoprotein biosynthesis, but has to be completely degraded in an enzymatic process catalyzed by selenocysteine lyase to a reduced form of Se. This can then reenter the complex cotranslational insertion process of selenocysteine into the nascent protein chain, provided that many of structural conditions are met by its respective mRNA and a series of *cis*- and *trans*-acting translation-assisting factors are in place. This major focus of the recent efforts in Se research is covered in Part I of the book, *Selenocysteine Biosynthesis and Incorporation into Protein*. Leading experts contribute seven

chapters elaborating on components and mechanisms involved in biosynthesis of selenocysteine and selenoproteins. Details of the SECIS elements of the corresponding mRNAs and SECIS binding proteins which regulate the expression of the selenoproteome in various phyla are presented in this section. Evolutionary aspects and the degradation of selenocysteine by a dedicated lyase complete this first part.

Thirteen chapters in Part II of the book, contributed by competent selenoprotein researchers, are devoted to the biochemistry and functional aspects of selenoprotein physiology. Successful approaches combining current molecular biology and recent developments in bioinformatics revealed identity, evolution, and function of selenoproteins and their genes are reviewed in the first chapter of this section. Descriptions of selenoprotein structures and the peculiar hierarchy of Se availability for individual selenoproteins follow. The central role of selenoproteins in redox-regulation involving the thioredoxin/thioredoxin reductase system and individual members of the glutathione peroxidase family is covered in the subsequent chapters which address clinically relevant Se functions in the cardiovascular redox system, diabetes, muscular and nervous system development and their degenerative diseases, as well as in various forms of cancer. Further chapters of this section also review the tremendous recent progress in understanding the role of selenoproteins M, N, and P. Sel N is essential for muscle development and function as indicated by identification of several mutations leading to rigid spine muscular dystrophy and multiminicore disease. Sel P has been identified as the main hepatically secreted selenium distribution and transport protein in serum. Several selenoproteins are involved in quality control of protein synthesis in the endoplasmic reticulum.

The 19 chapters of Part III of this impressive book focus even more on the relationship between Se and selenoproteins in human health. The first five chapters cover the area of Se's still controversial role in cancer promotion and prevention as recently featured by the unexpected premature termination of the SELECT trial that examined the role of selenium in prostate cancer prevention. Se and selenoproteins are also involved in pathogenesis and progress of diseases such as schizophrenia, thyroid dysfunction including autoimmune diseases, impaired reproduction function in males and females including pregnancy, infections such as HIV/AIDS, and parasite-related diseases such as malaria. These topics are covered in subsequent chapters, also addressing mechanistic aspects of impaired selenoprotein synthesis and function and disturbances leading to enhanced oxidative stress. Se's role in inflammation, antioxidative defense, redox signaling, methionine sulfoxide reduction, Alzheimer's disease, and even methylmercury exposure risks are also presented. Not surprisingly, there are also clinically relevant variations in Se metabolism in males and females and important progress has been made in understanding Se metabolism in prokaryotes impacting on infectious diseases and their treatment. The last two chapters cover functional aspects of the genomics of selenoprotein and Se-related genes and review dietary sources and human Se requirements.

The final part with three chapters represents a highlight of current biomedical translational research taking advantage of novel mouse models for elucidating the role of Se and selenoproteins in health and disease. Several mouse models for

glutathione peroxidase 4's function and deficiency have provided major insight into the role of Se for mammalian development and diseases of the adult brain, the cardiovascular system, and male reproduction. The last two chapters complement molecular and functional insight into selenoproteins by discussing mouse models targeting removal or overexpression of the selenocysteine $tRNA^{[Ser]Sec}$ gene and interpret lessons learned from *Trsp* deletion in murine bone and cartilage progenitor cells and their impact on skeletal development and diseases.

This book impressively illustrates significant conceptual, methodological, and scientific changes of paradigm which occurred with novel input from bioinformatics, genome, transcriptome and proteome research, and the stringent application of mouse genetics. These powerful novel tools and the clever design and application of knockout, knockdown, knock-in and overexpression approaches of specific "selenogenes," their mutants or variants in cellular, and transgenic mouse models clearly identified molecular mechanisms related to Se action. The first molecular identifications of human phenotypes of deficient selenoprotein expression and function supported cause-effect relationships beyond previous assumptions which were based on mere correlations or observational and epidemiological studies on Se and human health and disease.

Pioneers from the first hours of Se research are still active in the field and contributed to this book together with a new generation of highly motivated and skilled researchers, who have rejuvenated the field introducing new methods, contributing novel ideas, altered paradigms, and innovative concepts such as molecular biology, genomics, bioinformatics, and developed novel drugs and agents.

Se research thus has matured and has now a firm mechanistic basis. The classical theory of selenoprotein action as antioxidative devices degrading peroxides and preventing generation of reactive oxygen and nitrogen species proved too limited. Many new questions are emerging: Are the many Se effects related to efficient differential expression of selenoprotein isoforms from a single gene? Are selenoproteins located at strategic positions controlling entire metabolic or functional pathways? Is this mediated by redox-regulation of proteins, by modulation of small molecule messengers, or both? Why do we, animals, archaea, and some microorganisms need the peculiar chemical properties of selenocysteine while other organisms, including plants and fungi, get along with cysteine alone? How are issues of deficiency, adequacy, excess, and toxicity related to specific Se forms and species? Does the genetic makeup of an individual interfere with Se uptake, metabolism, selenoproteome expression, and is this relevant for pathogenesis or treatment of major diseases?

We will convene to discuss further progress achieved at the next International Selenium Meeting in Berlin in a couple of years. Hopefully we also will soon need another edition of this illuminative book documenting these discussions and novel developments in the exciting field of biomedical Se research.

Berlin, Germany Josef Köhrle

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Preface

The selenium field is expanding at a rapid pace and has grown dramatically in the last 10 years since the first edition of *Selenium: Its Molecular Biology and Role in Human Health* was published in 2001. All aspects of selenium biology have advanced with many new approaches and insights into the biochemical, molecular, genetic, and health areas of this intriguing element. In the first edition of this book, there were 25 chapters with 46 contributors that increased to 35 chapters with 71 contributors in the second edition. In the present edition, there are 45 chapters with 96 contributors. At this pace of expansion, and provided the fourth edition of *Selenium: Its Molecular Biology and Role in Human Health* is undertaken for publication in 2016, we can envision two volumes containing 29–30 chapters per volume with more than 125 contributors.

This book addresses many of the new and exciting discoveries that have occurred since the last edition was published in 2006. The numerous selenoproteins and proteins involved in the incorporation of selenium into protein that were described in the first two editions have been further characterized, new observations made, and mutant forms of some selenoproteins have been shown to be linked to human diseases. New factors have been detected that are involved specifically in the incorporation of selenium into protein. Mouse models targeting the removal of a specific selenoprotein, or removal of all selenoproteins, have further defined the role of selenoproteins in health and development. One of these has provided a potential model for Kashin-Beck disease.

Various aspects to glutathione peroxidase 4 (GPx4) are discussed in several chapters and its targeted removal suggested that it plays significant roles in proper function of numerous tissues and organs. GPx4 is now regarded as one of the more important selenoproteins in development. A role of selenium in cancer prevention has been purported for many years but we have learned in only the last few years that there are at least three selenoproteins that appear to have roles in preventing as well as promoting cancer. A role of selenium in male reproduction has also been purported for many years and the roles of specific selenoproteins in this process are now known and their functions elucidated.

Investigators in the selenium field are now looking at selenium differences in males and females and the role of selenium in pregnancy. In addition, the biosynthetic

pathway of selenocysteine in eukaryotes and archaea has been elucidated since the last edition – selenocysteine is not only the 21st amino acid in the genetic code but it was also the last known protein amino acid whose biosynthesis had not been resolved in eukaryotes and is the only known amino acid whose biosynthesis occurs on its tRNA in eukaryotes. Very recently, sulfur was found to replace selenium in the biosynthesis of selenocysteine in eukaryotes providing a novel pathway for cysteine biosynthesis that results in the replacement of selenocysteine with cysteine in selenoproteins.

The purpose of the present edition of the book is to bring readers up-to-date with the many new discoveries in the selenium field and to inform them of our present knowledge of the molecular biology of selenium, its incorporation into proteins as selenocysteine, and the role that this element and selenium-containing proteins (selenoproteins) play in health and development. In addition to being regarded as a chemopreventive agent, several other health benefits have been attributed to selenium. It has been touted as an inhibitor of viral expression and may prevent heart disease and other cardiovascular and muscle disorders, slow the aging process, delay the progression of AIDS in HIV positive patients, and have roles in development and immune function. Thanks to the many elegant techniques developed in recent years for examining selenium metabolism and selenoproteins in greater detail, investigators are now demonstrating how this element functions at the molecular level to bring about these many health benefits.

The present book is divided into four sections. Part I is entitled *Selenocysteine Biosynthesis and Its Incorporation into Protein* and it describes in detail our current understanding of the means by which selenium makes its way into protein as the 21st amino acid in the genetic code. Also discussed in this section are some of the reasons that selenocysteine may have evolved in protein and is used in place of cysteine in selenium-containing proteins. In addition, selenocysteine lyase, an important enzyme involved in selenium metabolism, is discussed. In Part II, entitled *Selenoproteins and Selenoproteins in Health*, many of the better characterized selenoproteins are examined including those that have been shown to play roles in health as defined by studies with rodents. Other chapters in this section examine such phenomena as selenoprotein hierarchy and the evolution of selenoproteins and their functions. The focus in Part III, entitled *Selenium and Selenoproteins in Human Health*, is on the role that selenium and selenoproteins play primarily in human health, while Part IV, *Mouse Models for Elucidating the Role of Selenium and Selenoproteins in Health* emphasizes the significance that mouse models have played in assessing selenoprotein roles in development and health.

The current edition of *Selenium: Its Molecular Biology and Role in Human Health* provides a most up-to-date examination of the on-going research in the selenium field. It is an important resource for investigators in the selenium field, other scientists, students and physicians, as well as those who wish to learn more about this fascinating micronutrient.

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Chapter 1
History of Selenium Research

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Abstract Selenium research must be said to have began in 1817, when Berzelius discovered this element. The first genuine publication describing this research was published by Berzelius in 1818, in a paper where he also named the element as *Selenium*. Here, in this chapter on the history of selenium research, an attempt is made to take a "bird's-eye" view at the development of this research field since 1817 until today. The tool chosen is an analysis of the scientific literature on selenium research, thereby attempting to give an unbiased assessment of this research field. Finally, as in all assessments of historic trends, we should also ask where the future of selenium research might take us. By necessity, the answer to that question is uncertain. However, we can conclude that never before has selenium research been as vigorous and expanding as it is today, which also holds major promise for the future.

1.1 Previously Published Recollections of the History of Selenium Research

Many reviews have described the development of selenium research and the findings that have shaped current day's knowledge in the field, including personal recollections by some of the pioneers of selenium research. Just to name a few, this includes some groundwork reviews on selenocysteine by Böck [1] or Stadtman [2], reflections by Dolph Hatfield and Vadim Gladyshev on how the selenocysteine recoding of the UGA codon became the first expansion of the genetic code since its original discovery [3], and the recent narrative of "*The Labour Pains of Biochemical Selenology: The History of Selenoprotein Biosynthesis*" by Flohé [4]. In his review,

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Dr. Flohé also gave an informative chronology of a number of landmarks related to research on selenium in biology (see Table 1.1 in [4]). It would be of little use in this chapter to simply repeat information given in previous reviews on the selenium research field. The reader is therefore referred to other papers on the history of selenium research for discussions on specific details or topics of that research. Information on several aspects of selenium research is also found in other chapters of this book, which together give comprehensive up-to-date insights into most aspects of current research on selenium biochemistry and molecular biology. Here, we shall instead take a "bird's-eye" view on the history and development of selenium research, using a bibliometric analysis of the trends in selenium research literature. With this as our focus, let us begin with the very first publication on selenium as published by Berzelius.

1.2 Berzelius and the Discovery of Selenium

Jöns Jacob Berzelius (1779–1848), or "Jacob Berzelius" as he was called by his peers, was one of the most important chemists of his time. He invented the term "catalysis," he constructed the major rules of chemical notation still used, and he discovered several basic elements, among them selenium. His work has been described in several publications, among which a biography written by Dr. Söderbaum should be the most comprehensive (H. G. Söderbaum, *Jac. Berzelius, Levnadsteckning*, 3 vols., Uppsala, 1929–1931). Therein, one may read how Berzelius in 1817, studying the bottom sludge remaining from a sulfuric acid preparation, realized that there was a new element in the preparation, and how he completed his initial analyses in only 4 months. This must be viewed as a major accomplishment considering the exactness and correctness by which he described selenium in spite of his, by today's standards, rather rudimentary technology. When publishing his findings in 1818, the paper was written in Swedish and, interestingly, published in a periodical that Berzelius himself was editing together with a number of colleagues (Fig. 1.1a). It was in this article that he officially named the element *Selenium* (Fig. 1.1b) and in that very publication, he also reported on several of the typical chemical characteristics of selenium that still today underpin all work on this element. Already in his first studies, Berzelius noted the close similarities between selenium and sulfur, which obviously govern the similar properties of selenocysteine-containing proteins and those of cysteine-containing orthologues, which today is a debated and active research subject as recently discussed elsewhere in more detail (see [5] and references therein).

1.3 Bibliometric Analysis of Selenium Research Since 1945

Bibliometry is today fashionable among universities, funding agencies, and policy makers for the evaluation of research output. Many aspects of this usage of bibliometry is often flawed, as a consequence of inadequate bibliometry units, year- and

a

Afhandlingar

i

Fysik, Kemi

och

Mineralogi.

Utgifne

af

J. Afzelius, N. W. Almroth, A. Arfvedson,
J. Berzelius, H. P. Eggertz, J. af Forselles,
J. G. Gahn, W. Hisinger, P. Lagerhjelm,
M. af Pontin, E. Rothoff, N. G. Sefström,
P. Ström, E. T. Svedenstierna,
P. Walmstedt.

Sjette Delen.

STOCKHOLM,
Tryckte hos Direct. H. A. Nordström,
1818.

b Det bruna ämnet, ſom vid ammoniak-ſalternas ſönderdelning afſkiljt ſig, blef nu ett föremål för underſökningen, och befanns, genom de förſök, ſom i det följande ſkola beſkrifvas, vara en egen, hittills okänd, brännbar mineralkropp, hvilken jag, för att utmärka deſs ſlägtſkap i egenſkaper med tellurium, kallat Selenium, af Σελήνη, måna.

Fig. 1.1 The first publication on selenium. The figure shows the (**a**) front page and (**b**) an excerpt of the text on p. 49 from the original reference where Berzelius first described his discovery of selenium and named the element [8]; a scanned copy of this book is at present freely available on internet through a search in Google Books. An English translation of the text given in (**b**) reads as follows: "The brown substance, which the decomposition of the ammonium salts yielded, now became an object of investigation, and was found, through the experiments, which in the following will be described, to be a separate, hitherto unknown, combustible mineral, which I, to mark its akin properties with tellurium, have named Selenium, from Σεληνη, moon (goddess)"