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Chapter 25. Selenium in biology and human health: Controversies and perspectives

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Summary: Important unresolved questions raised by the contributors of this book and addressing roles of selenium in biology and human health are discussed. Resolving major scientific controversies in the field should further highlight a bright future for selenium in fundamental science, biotechnology and medicine.

Introduction

The chapters of this book make a compelling case for the remarkable progress in selenium research on the role of this element in biology and medicine in recent years. Still, many questions remain unanswered and contradictions unresolved. Research in these areas should provide investigators with many exciting years in the field.

In this concluding chapter, some of the areas, which were selected by the contributors of this book to be important unresolved questions, are highlighted. Answers to these questions should lead to major advances in the field. These unresolved issues are supplemented with topics, which may constitute important challenges for future research or enhance applications of selenium biology in medicine and biotechnology.

Mechanism of selenocysteine incorporation

Recent findings yielded long-sought components of the eukaryotic Sec insertion machinery, the SECIS-binding protein [Chapter 6] and the Sec-specific elongation factor [Chapter 7]. Further characterization of these and other components of the eukaryotic Sec insertion system [Chapters 2-5 and 8] should lead to advances in our understanding of the mechanism for Sec biosynthesis and insertion into polypeptide chains.

Future experiments should also reveal whether all components responsible for Sec insertion have now been identified. One question to be resolved is the role of the kinase in phosphorylating serine that is attached to selenocysteine tRNA [Chapter 3]. The presence ofphosphoserine has long been recognized, but its function remains unknown. A second uncharacterized protein that may be specific for the eukaryotic Sec insertion system is the methylase that is

involved in the formation of mcmUm at the anticodon position in Sec tRNA. Eukaryotes have two Sec tRNA isoacceptors [Chapter 3] and two selenophosphate synthetases [Chapter 4] and future studies should reveal specific roles for each of these factors.

In the last decade, many studies in the eukaryotic system were built on classic experiments by Bock and his colleagues that identified and characterized the principal components and the mechanism of Sec insertion into protein in bacteria [Chapter 2]. However, recent studies revealed unexpected complexities in composition and regulation of the eukaryotic Sec insertion system, where RNA-based mechanisms, such as nonsense mediated decay [Chapter 8], the role of the SECIS element [Chapter 5], hierarchy in selenoprotein expression [Chapters 8 and 14] and alternative splicing in selenoprotein genes, as well as multifunctional protein machinery [Chapters 6 and 7] appear to play dominant roles.

Finally, it is not clear if the mechanism for Sec insertion is common to all systems. Bacterial Sec insertion has only been characterized in *E. coli* [Chapter 2]. One limitation of this system is that *E. coli* has only three selenoproteins and these exhibit extensive sequence homology. Characterization of the Sec insertion system in other bacteria as well as in archaea should provide an answer as to whether the Sec insertion mechanism is general to all organisms [Chapter 2].

Selenoproteins and regulation of cellular processes

Only a few physiological processes in humans are known that are mediated by selenoproteins. These include activation and inactivation of thyroid hormones [Chapter 16], antioxidant defense [Chapters 14 and 15], sperm maturation [Chapter 22] and control of cellular redox processes [Chapters 14 and 15]. Prokaryotic processes involving several selenoproteins are better understood, but major unresolved questions also remain with respect to selenoprotein function and the specific role of selenium in protein [Chapter 10]. Less than a half of known eukaryotic selenoproteins have been characterized with respect to function, although ongoing studies may result in identification of functions for several additional selenoproteins [Chapters 9 and 11-14]. Identification and functional characterization of new selenoproteins will also reveal other processes in which selenoproteins are involved. Future research may extensively use functional genomics approaches, such as cDNA microarrays, to reveal a global picture of selenium regulation.

Human selenoproteome

Currently, the number of known vertebrate selenoproteins is 22 [Chapter 9]. With the completion of the sequencing of the human genome, it should be possible to identify, in the near future, the majority, if not all, human selenoproteins through a combination of bioinformatics and functional genomics approaches. This goal is complicated by the fact that no reliable tools exist that identify selenoprotein genes because currently available programs recognize Sec-encoding TGA codons as stop signals. However, recently developed bioinformatics tools that analyze SECIS elements and homologies between selenoproteins and their homologs should be very useful in identifying selenoprotein genes [Chapter 9]. In addition to the human genome, all or the majority of selenoprotein genes may soon be identified in several other eukaryotic genomes, such as rats, mice and zebrafish. These approaches will also be useful to determine how widespread is the use of selenocysteine in organisms on earth. Although selenoproteins were found in the three major domains of life (e.g., bacteria, archaea and eukaryotes), certain representatives of these organisms lack selenoproteins.

Mechanism of cancer prevention by selenium

The landmark study by Clark et al. provided strong support for the cancer chemoprevention effect of dietary selenium and is consistent with the majority of epidemiological and animal studies [Chapter 17]. Nevertheless, available data do not justify the use selenium as a cancer preventive supplement in the human population. Clearly, additional studies are necessary to support the conclusion that supplementation of the diet with selenium decreases the incidence of human cancers, and to determine which cancers are prevented by this trace element and to what extent.

Future clinical trials will be assisted tremendously if the mechanism for cancer prevention by selenium is known. The lack of information on the mechanism appears to be the major drawback for further advances in this area. A current view on how selenium prevents cancer implicates low molecular weight selenium compounds in the chemoprevention effect of selenium [Chapters 17 and 23]. The argument in favor of this hypothesis is that cancers are best prevented by selenium concentrations greatly exceeding those needed for maximal expression of glutathione peroxidases 1 and 3. These enzymes are chosen as markers because they located at the bottom of the selenoprotein hierarchy and their expression is thought to be consistent with the selenium status of an organism [Chapter 24].

However, evidence also emerges for the role of selenoproteins in cancer prevention [Chapters 13 and 17]. For example, the recently identified 15 kDa selenoprotein may be one of the proteins involved in this process. Its expression is changed in cancers relative to normal tissues, its gene is located in a chromosomal region that encodes a possible tumor suppressor gene, and the selenoprotein has polymorphisms that affect expression of the protein in an allele- and selenium-dependent manner [Chapter 13].

Questions also remain as to whether glutathione peroxidases 1 and 3 best illustrate selenium requirements under environmental and genetic stresses. It

is possible that in some individuals, who genetically predisposed to cancer, requirements for selenium differ from those in the normal human population.

Selenium and human diseases other than cancer

The role of selenium in etiology of several diseases has been established and the number of disorders, in which selenium is implicated, has steadily expanded over the past decade. As reviewed in this book, selenium is involved or implicated in Keshan and Kashin-Beck diseases [Chapter 18], viral suppression [Chapter 19], HIV infection [Chapter 20], aging, immune function [Chapter 21], male reproduction [Chapter 22] and other disorders and pathophysiological conditions [Chapter 18]. However, molecular mechanisms for these effects remain largely unknown. Further research should define the mechanisms and identify other biomedical areas in which dietary selenium is involved.

Selenium nutritional levels in a general population versus individual-specific requirements

The chemopreventive mechanistic considerations appear to be linked to a more general question of whether selenium requirements in the general human population can be adapted to satisfy specific ethnic, age and genetic needs of groups of individuals or even needs of a single individual. With the ongoing advances in cDNA microarrays, microchips and parallel genomic sequencing, information on the genetic make-up of an individual is not out of reach in the next decade or so. It is possible that the use of these new technologies will lead to determination of individual requirements for dietary selenium.

Applications of selenium in biotechnology

Recent discoveries of new selenoproteins [Chapter 9], characterization of reaction mechanisms and properties of selenoproteins [Chapter 10] and advances in the mechanism of selenocysteine incorporation [Chapters 5-7] may lead to various biotechnological applications. Selenium in the form of selenomethionine is already extensively used in x-ray crystallography in solving the phasing problem. The targeted incorporation of selenium into proteins has also been used occasionally for protein characterization, but technically was difficult to achieve. The finding that efficiency of selenocysteine incorporation is higher than previously thought and that it may be regulated by adjusting levels of components of the selenocysteine insertion machinery [Chapters 6-8] may allow expression of high levels of proteins containing selenocysteine at a specific place in the sequence. These proteins may then be characterized in vivo in cell culture or animal models or in vitro mechanistically and spectroscopically. In particular, this method should be useful to evaluate functions of specific cys-

teine residues. Cysteine and selenocysteine differ by a single chalcogen atom and exhibit similar chemical properties. Nevertheless, nucleophilicity and redox properties of selenocysteine differentiate this residue from cysteine and thus provide unique opportunities for functional characterization.