SESSION 1
OPENING AND PLENARY LECTURES

COMPARATIVE AND FUNCTIONAL GENOMICS OF MAMMALIAN SELENOPROTEOMES

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For selenium, both beneficial and toxic effects in human health have been described. It is now clear that the importance of having adequate amounts of this micronutrient in the diet is primarily due to the fact that selenium is used in selenoproteins in the form of selenocysteine. In this presentation, discussion will be focused on evolution and function of selenium utilization in mammals. Comparative and functional genomics methods allow assessing the use of selenium at the levels of proteins, cells, organs and entire organisms. The most challenging is the functional analysis of about a half of mammalian selenoproteins, for which no function is currently known. Several examples of ongoing research will be given to discuss progress in functional analysis of selenoproteins. Evolutionary trends in the use of selenoproteins in lower eukaryotes will also be discussed, with focus on organisms with largest selenoproteomes. Selenoproteins with known functions are oxidoreductases, and the tight link between selenium and redox biology offers an opportunity to better understand selenoproteins and use this information to examine questions central to the redox control of cellular processes. Funded by NIH.

SELENOCYSTEINE tRNA$^{[Ser]Sec}$: FROM NONSENSE SUPPRESSOR tRNA TO THE CENTRAL COMPONENT OF SELENOPROTEIN BIOSYNTHESIS

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Selenocysteine (Sec) tRNA$^{[Ser]Sec}$ was initially discovered as a minor serine tRNA in bovine and chicken livers that specifically decoded the nonsense codon, UGA. It was proposed to be a nonsense suppressor tRNA, since such tRNAs occurred in bacteria. A minor seryl-tRNA from rooster liver was found to form phosphoseryl-tRNA at about the same time as the UGA-decoding serine tRNA. Serine $tRNA_{UGA}$ was sequenced, found to be highly undermodified compared to other tRNAs and, at 90 nucleotides, the longest tRNA sequenced at that time. Two isoforms of serine $tRNA_{UGA}$ were detected that differed by a single 2'-*O*-hydroxymethyl group (Um34) and phosphoseryl-tRNA and seryl-$tRNA_{UGA}$ were shown to be the same tRNA. Its gene, designated *Trsp*, was sequenced from numerous eukaryotic organisms, was 87 nucleotides long and had a unique set of transcriptional regulatory regions. Harrison's and Bock's labs reported that Sec in mouse glutathione peroxidase 1 and bacterial formate dehydrogenase corresponded to UGA in the respective mRNAs suggesting that phosphoserine $tRNA_{UGA}$ was Sec tRNA. Bock's and my labs subsequently found that Sec was indeed the 21st amino acid in the genetic code. The two Sec tRNA isoforms, designated Sec $tRNA_{mcmU}$ and $tRNA_{mcmUm}$, were found to specifically translate housekeeping selenoproteins ($tRNA_{mcmU}$) or stress-related selenoproteins ($tRNA_{mcmUm}$), respectively. Since the knockout of *Trsp* is embryonic lethal, a number of mouse models were generated encoding various combinations of conditional knockout, standard knockout, and mutant and wild type *Trsp* transgenic mice, to elucidate the roles of housekeeping and stress-related selenoproteins in health and development. The biosynthesis of Sec, the 21st protein amino acid, the only known amino acid in eukaryotes whose biosynthesis occurs on its tRNA and the last known protein amino acid in eukaryotes whose biosynthesis had not been ascertained, was determined. Funded by the Intramural Research Program of the NIH, NCI, CCR.