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Review

Human selenoproteins at a glance

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Abstract. The public perception of selenium has changed significantly over the last decades. Originally mainly known for its high toxicity, it was later recognized as an essential trace element and is now (despite its narrow therapeutic window) almost being marketed as a lifestyle drug. Indeed, some clinical and preclinical studies suggest that selenium supplementation may be beneficial in a large number of clinical conditions. However, its mode of action is unresolved in most of these cases. Selenocysteine – identified as the 21st amino acid used in ribosome-mediated protein synthesis – is incorporated in at least 25 specific, genetically determined human selenoproteins, many of which have only recently been discovered. Restoration of normal selenoprotein levels may be – apart from direct supranutritional effects – one possible explanation for the effects of selenium supplements. In this review we provide a brief but up-to-date overview of what is currently known about these 25 acknowledged human selenoproteins and their synthesis.

Key words. Selenoprotein; selenium; selenoprotein biosynthesis; redox metabolism; antioxidant.

Historical landmarks

The essential trace element selenium was discovered in 1817 by the Swedish physician and chemist Jöns Jakob Berzelius when he was seeking the etiology of a mysterious disease amongst workers at a sulfuric acid plant in Gripsholm (Sweden).
With reference to the Greek moon goddess Selene, Berzelius named it selenium (Se), as it is closely related to the element tellurium (Te; tellus (Lat.) = earth) discovered afore. Most selenium derivatives are rather toxic, some even more than intravenously applied cyanide [1]. Moreover, selenium and most of its compounds exhibit a characteristic, very penetrative and acrid, garlicky smell, which is often already detectable at extremely low concentrations and persists on contaminated surfaces and skin. These features make selenium and selenocompounds a rather unattractive research problem. It is thus not surprising that biomedical studies remained scarce for over a century after selenium's discovery. Those published [2, 3] – such as the study by Gassmann [2] on selenium content of bones and teeth in healthy individuals (In this publication, Gassmann also speculated on the biological importance of selenium.) – were largely neglected, or – as pointed out by Behne and Kyriakopoulos [4] – rejected by the scientific authorities of the time.
Selenium's reputation went from bad to worse when field research showed that selenium poisoning was the leading cause of alkali and blind staggers disease [5], threatening livestock in large farming communities such as the Great Plains in the US and elsewhere. In addition, laboratory studies declared selenium a potential carcinogen [6, 7].
Today's favourable view of selenium, even referred to as selenophilia [8], is inseparably associated with the name of Klaus Schwarz. His publication (Schwarz and Foltz,

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1957), which provides strong evidence for a beneficial and essential role for selenium, is a milestone in biochemical and biomedical research [9] and changed the perception of the moon element. Schwarz, a German biochemist, had started his work on vitamins and selenium in Richard Kuhn's laboratory at the Kaiser-Wilhelm Institute for Medical Research (now Max-Planck Institute) in Heidelberg (Germany) in 1939. He emigrated to the US where he finished his studies on the protective effect of the selenium-containing (still not well defined) factor 3 against liver necrosis at the Bethesda National Institute of Health (NIH) [10,11]. During the same era, Patterson and coworkers independently published a study in 1957 showing that selenium supplements prevented exudative diathesis in poultry [12]. Selenium's essential role for certain physiological processes was confirmed later [13, 14].

In 1973, the same year Turner and Stadtman [15] established bacterial glycine reductase (EC 1.21.4.2) as a selenoprotein, glutathione peroxidase (GPx, EC 1.11.9.1) was the first specific (that is genetically coded) mammalian selenoprotein discovered. Following initial work in Hoekstra's group [16, 17], Leopold Flohé (granted the Klaus Schwarz Commemorative Medal in 1997 [8]) succeeded in showing that selenium is an integral part – covalently bound in stoichiometric quantities – of glutathione peroxidase [18]. Selenium was shown to be incorporated as selenocysteine (Sec; U in one-letter code) first in bacterial glycine reductase in 1976 [19] and in GPx in 1978 [20] where Sec is located and required in the enzyme's active site [21–23]. Still being in the pregenomic era, it took another 6 years until the amino acid sequence of glutathione peroxidase was solved by Günzler et al. [24]. This subsequently led to the establishment of selenocysteine as the 21st proteinogenic amino acid ('Proteinogenic' describes an amino acid used in ribosome-mediated protein synthesis.) [25]. In the next two decades following the discovery of selenium in GPx, only a handful of other proteins were detected in pro- and eukaryotic cells and shown to be specific selenoproteins [15, 26–28]. This difficulty in detecting selenoproteins is attributed to the fact that the codon used for selenocysteine incorporation is not as unambiguous as for the other proteinogenic amino acids. Indeed, the codon-defining selenocysteine, TGA, is normally interpreted as a stop signal by the cell's protein biosynthesis machinery (UGA also codes for tryptophan in mitochondria and some bacterial organisms [29].), (Recently, an additional amino acid, pyrrolysine, was identified as the 22nd proteinogenic amino acid. It is inserted in response to a UAG codon – serving normally also as a stop-codon – in some methanogenic archaea [30]. However, the incorporation mechanism of pyrrolysine seems to differ from the mechanism used for selenocysteine [31].). The dual use of the stop codon, another key observation in understanding selenoprotein biosynthesis, was first made by Chambers and co-workers for murine GPx [32] and later confirmed for all other (specific) selenoproteins [28, 33]. Therefore, selenocysteine insertion requires additional signals, allowing the reinterpretation of the stop signal as a selenocysteine incorporation command. This signaling is achieved via the interaction of several proteins with a special messenger RNA (mRNA) secondary structure, known as the SECIS element (*se*leno*c*ysteine *i*nsertion *s*equence). Our current understanding of this process is primarily built upon the work of August Böck and Thressa Stadtman [34–36]. The details of the steps involved apparently differ between species – particularly between pro- and eukaryotes [23, 37, 38]. Furthermore, no simple mRNA sequence exists that allows an easy and definite prediction of additional selenoproteins in a genome, even though radiolabeling studies can indicate their existence [39, 40].

With the rapid advancements of genome sequencing and its concomitant success in bioinformatics over the last decade, the number of newly identified selenoproteins has almost doubled within a short period of time [38, 41–43]. In fact, the number of identified prokaryotic selenoprotein genes has increased by more than 100 to a total now of approximately 310 in a recent publication by Zhang et al. using a computational approach [44]. Functional analysis of recently discovered selenoproteins has not kept pace with the rapid identification of new selenoproteins. Yet, their vital importance – at least for mammals – is underlined by selenocysteine transfer-specific RNA (tRNA)-knockout experiments, which are lethal in utero [45].

In addition to basic biochemical research, various studies, particularly in livestock farming [46], population-based surveys [47] and many clinical trials [48, 49] indicate the biological importance of selenium. One of the most influential, that is most cited, publications on clinical selenium research is the study by Clark et al. [48], indicating a tumor-preventive effect of selenium. However, as discussed later, in a subsequent follow-up reanalysis the protective effects were not reproducible for all carcinomas as initially reported [50, 51]. Furthermore, a closer look at the data reveals that patients with a very low baseline selenium status profited most from selenium supplementation, whereas those participants with higher levels might actually be at increased risk of cancer.

At present, most clinical and many animal studies are phenomenological in nature: the study participants or laboratory animals essentially serve as black boxes studied in the presence or absence of selenium (supplements). Since many of these studies do not consider a precise mode of action, the recorded parameters are difficult to interpret and often inadequate to reach valid conclusions. With uncontrolled confounding variables, the general applicability of the results is limited.