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Roles for selenium and selenoprotein P in the development, progression, and prevention of intestinal disease

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Abstract

Selenium (Se) is a micronutrient essential to human health, the function of which is mediated in part by incorporation into a class of proteins known as selenoproteins (SePs). As many SePs serve antioxidant functions, Se has long been postulated to protect against inflammation and cancer development in the gut by attenuating oxidative stress. Indeed, numerous studies over the years have correlated Se levels with incidence and severity of intestinal diseases such as inflammatory bowel disease (IBD) and colorectal cancer (CRC). Similar results have been obtained with the Se transport protein, selenoprotein P (SELENOP), which is decreased in the plasma of both IBD and CRC patients. While animal models further suggest that decreases in Se or SELENOP augment colitis and intestinal tumorigenesis, large-scale clinical trials have yet to show a protective effect in patient populations. In this review, we discuss the function of Se and SELENOP in intestinal diseases and how research into these mechanisms may impact patient treatment.

Keywords

Selenium; selenoproteins; selenoprotein P; colitis; colitis-associated carcinoma; colorectal cancer

Introduction

The mammalian gastrointestinal (GI) tract is a highly complex tissue and key interaction site for the epithelium, immune cells, luminal contents, and microbiota. Maintenance of proper function and balance between intestinal cell populations is a tightly controlled process which relies heavily on proper redox homeostasis. Indeed, oxidative signaling has been shown to affect intestinal cell proliferation, differentiation, barrier function, and mucosal defenses [1,

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2]. Thus, disruptions to oxidative balance are believed to contribute to various types of intestinal injury and disease. Chronic inflammation, in particular, remains a risk factor for non-hereditary or “sporadic” colorectal cancer (CRC), which accounts for 65–85% of CRC cases [3, 4]. Here, longstanding inflammatory insult induces a microenvironment favorable to tumor initiation and progression by increasing reactive oxygen species (ROS) production, DNA damage, immune cell recruitment, and epithelial cell proliferation. Furthermore, alterations to oxidative signaling are highly associated with chronic inflammatory disorders of the intestine such as Crohn’s disease (CD) and ulcerative colitis (UC), which are often referred to together under the umbrella term inflammatory bowel disease (IBD) [5]. These patients are also predisposed to a subset of CRC known as colitis-associated carcinoma (CAC), which accounts for one to three percent of CRC cases [6, 7]. Thus, redox mechanisms to protect against oxidative stress are of great interest for both prevention and treatment of intestinal diseases and cancers.

Selenium levels in intestinal diseases

The element selenium (Se) was discovered in 1817 by the noted Swedish chemist Jöns Jacob Berzelius, who is widely considered to be the “father of modern chemistry” [8]. In the 1930s, it was recognized as a toxin when chronic ingestion of Se-rich plants was associated with both “alkali disease” and “blind staggers” in livestock [9]. In spite of these toxic effects, research by Klaus Schwarz in the 1950s determined that basal Se levels are essential for life and Se was added to the recommended daily values for human nutritional intake [10]. In the decades since, much research has investigated the effects of Se deficiency in human populations. We now know that Se nutritional inadequacy leads to detrimental outcomes, as it is a causative factor in the cardiomyopathy, Keshan disease, and also believed to contribute to the osteochondropathy, Kashin-Beck disease [11, 12]. While direct contributions have yet to be established, low serum Se levels have also been associated with a wide range of human diseases, including epilepsy and age-associated neurological disorders, and they are also associated with decreased survival following HIV infection [13–15]. Indeed, data accumulated over the years indicate that the nutrient has broad roles in human health.

Interestingly, dietary factors are of particular interest in the management of certain diseases, including IBD. These cases, especially in the setting of intestinal resection, can often result in nutrient deficiencies which complicate patient care. In fact, up to 85% of IBD patients exhibit macro- and micronutrient deficiencies due to decreased dietary intake, direct nutrient loss, and/or impaired nutrient absorption [16, 17]. For example, as compared to healthy control subjects, CD patients exhibit lower mean daily dietary intakes of phosphorous and fiber and lower serum concentrations of β -carotene, magnesium, vitamins C, D, and E, and zinc, while UC patients display lower mean daily intakes of calcium, phosphorous, protein, and riboflavin and lower serum concentrations of β -carotene, magnesium, and zinc [16, 18, 19]. Nutrient deficiencies such as these occur more often with active disease and are associated with increased mortality, heightened risk of peri-operative complications, and prolonged hospitalization [17, 20, 21].

Se has also been directly investigated in the setting of IBD. Since the 1980s, studies have routinely demonstrated significant reductions in serum Se levels in both child and adult UC and CD patients [16–19, 22–27]. Decreased Se levels are found even in quiescent disease, and serum Se levels have consistently been noted to inversely correlate with UC severity, IBD duration, and CD activity index to the point that Se has been proposed as a noninvasive biomarker for IBD activity and severity [23, 26]. Intriguingly, population-based studies have determined that New Zealand, which has one of the highest incidence rates of CD in the world, also has one of the lowest average serum Se levels [27].

However, whether the decreased Se observed in IBD patient plasma predisposes patients to intestinal disease or instead represents a byproduct of disease activity remains unclear. Decreased plasma Se levels and GPx activity were observed in mouse models of colitis driven by treatment with dextran sulfate sodium (DSS), a heparin-like polysaccharide which results in epithelial damage in a manner which mimics some features of IBD [28, 29]. As these mice had no overt change in diet as compared to control animals, these results suggest that Se levels are decreased due to altered dietary intake or nutrient absorption during colitis, although additional mechanisms could also contribute to this reduction. Se deficiency has also been observed to increase colitis and activation of protumorigenic signaling pathways, such as the epidermal growth factor (EGF) and transforming growth factor β (TGF- β) pathways, in DSS-treated mice [28, 30]. Thus, while Se deficiency is induced by disease, lower Se levels can functionally contribute to IBD pathology. Furthermore, Se supplementation may attenuate inflammation and colitis severity in both DSS and 2,4,6-trinitrobenzene sulfonic acid (TNBS) colitis models and, more recently, work from the Huang group demonstrated protection in acute DSS colitis utilizing Se nanoparticles [30–33]. However, this protection was not always observed, as Hiller and colleagues reported that long-term Se supplementation did not affect colitis in an acute DSS model [34]. Furthermore, these authors observed surprising increases in colitis severity and expression of inflammatory cytokines due to short-term selenite supplementation. Thus, whether Se supplementation constitutes a feasible treatment modality for IBD, particularly short-term supplementation in response to disease exacerbation, remains a matter of continued debate and requires further study [35].

Selenium levels in colorectal cancer

Diet and nutrient intake have also been associated with CRC development, and much research has focused on identifying nutritional factors which may protect against malignancy. In fact, in 1981 researchers postulated that practicable diet modification may prevent up to 90% of stomach and large bowel cancer deaths in the U.S. [36]. While today we realize that such an effect of dietary constituents on CRC cancer death is overstated, numerous studies still indicate that dietary components likely modulate CRC development and progression. For example, Vitamin D is inversely associated with tumor incidence and mortality in the colon, and in mechanistic experiments it has been shown to suppress the protumorigenic WNT pathway estimated to drive ~85% of CRC cases [37–40]. On the other hand, dietary factors such as red and processed meats have been widely associated with increased CRC risks, and although many potential mechanisms have been presented (*e.g.*,

microbiome alterations, *N*-nitroso compounds, polycyclic aromatic hydrocarbons), the true extent of the association and the biological mechanism(s) remain unclear [41–43].

Numerous studies have analyzed serum and tissue Se levels in relation to cancer development and severity. In the late 1960s, Shamberger and Frost utilized population-based metrics to suggest a protective effect of dietary Se, and inversely correlated Se levels in both food crops and human blood samples with cancer death rates from the same locations [44]. Later, it was shown that per-capita dietary Se intakes were likewise inversely correlated with death rates from certain cancer types, including CRC [45]. More recently, researchers have transitioned away from population-based approaches and instead measured patient plasma Se levels in order to associate these numbers with individual disease presence or severity. In the majority of studies, the inverse correlation observed by earlier researchers have been maintained. For example, patients with lower fasting plasma Se concentrations (<128 µg/L) display significantly greater likelihood and number of adenomatous intestinal polyps [46]. Likewise, low (<65 µg/L) and high (>153 µg/L) serum Se levels are correlated with greater and lesser risk of colorectal adenomas, respectively [47, 48]. There also exists an inverse correlation between serum Se concentration and advanced tumor stage, particularly among recent smokers [49, 50]. Additionally, patients with low serum Se status (<70 µg/L) display significant decreases in mean survival and cumulative cancer-related survival rate [50]. Together, these studies consistently suggest protective roles for Se dietary intake in CRC development and progression.

Se has been known to possess antitumorigenic properties since at least the 1940s, and these results have been recapitulated in numerous experimental cancer models to date. In 1949, Clayton and Baumann first demonstrated that five parts per million (ppm) dietary selenite decreased hepatic tumor incidence after exposure to a carcinogenic dye [51]. Shortly thereafter, it was reported that a Se-supplemented diet of one ppm similarly decreased skin papillomas resulting from the carcinogen 7,12-dimethylbenzanthracene (DMBA) [52]. In 1977, the protective effect of Se supplementation was extended to CRC by Jacobs and colleagues, who demonstrated that sodium selenite supplementation decreases tumor number in rats treated with colon-specific mutagens [53]. In the years since, supranutritional dietary Se has been further demonstrated to confer protection in modern CRC tumor models. For example, Se decreases colon tumors induced by the mutagen azoxymethane (AOM) both alone and in combination with DSS, as well in the genetic *Apc^{Min}* model [28, 33, 54–56]. Excess Se has also been observed to inhibit growth of human CRC cells maintained in *in vitro* culture as well as those grown as *in vivo* xenografts [57, 58].

Unfortunately, while both human epidemiological studies and animal disease models support robust anti-tumor effects of Se, results from large-scale human clinical trials have been mixed and have yet to demonstrate a clear link between Se supplementation and CRC prevention. While some studies indicate that Se supplementation reduces CRC risk, this correlation was not universally observed [59–61]. For example, the Selenium and Celecoxib (Sel/Cel) Trial displayed a modest, but significant, 18% reduction in adenoma recurrence among Se-supplemented patients with advanced adenomas at baseline, yet no reduction was observed in patients without advanced adenomas [62]. Perhaps the most notable study over the past decade is the Selenium and Vitamin E Cancer Prevention Trial (SELECT), a

randomized, placebo-controlled phase II study seeking to investigate the effect of Se and/or Vitamin E supplementation in prostate cancer prevention [63]. This study failed to demonstrate a protective role for Se (in the form of selenomethionine) in prostate cancer development, and further ancillary analysis likewise found no protection against colorectal adenoma formation [64]. Instead, Se supplementation was associated with increased incidence of type 2 diabetes (T2D) in both the Sel/Cel Trial and SELECT, and unfortunately these studies were not the first to link heightened serum Se to T2D incidence in Se-sufficient populations [62, 65–67]. Thus, widespread use of Se supplementation is cautioned against as it may lead to detrimental effects.

However, it is also important to note that many of these studies contain caveats which may limit the impact of Se supplementation. For example, both the Sel/Cel Trial and SELECT enrolled patients from Se-replete populations, who may not benefit from Se supplementation as would patients with Se deficiencies such as those observed in IBD. Furthermore, the various dietary formulations of Se utilized in these different clinical trials can greatly affect its bioavailability. For example, Se as selenomethionine exhibits nearly twice the bioavailability as Se as selenite, as measured by plasma Se levels [33, 68]. Thus, the relationship between Se supplementation and CRC development may be nuanced, and as such necessitates additional clinical trials before any definitive recommendations can be made.

Selenium-containing proteins

Se was first postulated to function as an antioxidant in 1957 because it displayed a similar protective effect as Vitamin E, which was already known to be a free-radical scavenger [10]. These results were recapitulated in the early tumor studies with Se supplementation, and today the bulk of Se's effect on intestinal disease and CRC remains mostly attributed to its antioxidant capability [52]. However, it wasn't until 1973 that the biological mechanism for Se's antioxidant capabilities was first elucidated when Rotruck and colleagues demonstrated incorporation of Se into the enzyme glutathione peroxidase (now referred to as glutathione peroxidase 1, GPx1) [69]. In the following years more Se-containing proteins were identified: selenoprotein P (SELENOP, formerly known as SEPP1) was first identified as a Se-labelled protein within the plasma in 1977 followed by identification of phospholipid hydroperoxide glutathione peroxidase (now referred to as GPx4) in 1982 [70, 71]. Today, these are collectively referred to as the selenoprotein (SeP) family, and Se is known to be incorporated into the protein structure by a Se-modified serine residue known as selenocysteine (Sec; one letter abbreviation: U). To-date, 25 SePs have been identified in the human genome, including members in the glutathione peroxidase (GPx), iodothyronine deiodinase (DIO), and thioredoxin reductase (TrxR) protein families [72]. Like the prototypic GPx1, many of these SePs contain a single Sec within the enzymatic active site by which they catalyze oxidation-reduction reactions [73].

SeP expression is a tightly controlled process dependent on specialized translational machinery. While sites of Sec incorporation are identified by the opal codon (UGA), Sec insertion also requires the presence of a conserved 3' stem-loop selenocysteine insertion sequence (SECIS) which recruits factors dedicated to Sec incorporation (Figure 1) [74–77].

It is important to note that expression of these dedicated translation factors, specifically the Sec-charged tRNA, is highly dependent on the presence of Se and only produced upon Se availability [78]. In the context of Se deficiency, the UGA codon is often read as a premature stop codon due to limited amounts of Sec tRNA, resulting in nonsense-mediated decay and mRNA turnover, although this phenomenon does not affect all SeP transcripts equally [79, 80]. Interestingly, studies which globally interfere with SeP biosynthesis via modification of the Sec tRNA indicate that Se's protective phenotypes in IBD and CRC are most likely mediated by SePs. For example, transgenic mice in which SeP translation is inhibited by expression of a dominant-negative Sec tRNA [$(t^{\text{Sec}}A^-)$ $tRNA^{\text{Ser/Sec}}$] were observed to have increased numbers of aberrant crypt foci (ACF), a type of preneoplastic colon lesion, in the AOM injection model of sporadic CRC [81, 82]. Furthermore, myeloid-specific knockout of the Sec tRNA gene (*Trsp*) utilizing a *LysM-Cre* driver led to increased ROS and oxidative stress, decreased macrophage invasion through extracellular matrix, and increased severity in the DSS experimental colitis model [30, 83, 84]. Taken together, these studies not only suggest more direct roles for Se and SePs in mediating intestinal disease development, but also indicate that Se and SeP expression can differentially regulate function in specific cell types.

Selenium transport through selenoprotein P

While a Se-containing protein itself, SELENOP is also a vital component of Se metabolism and downstream SeP synthesis. While most SePs contain a single Sec residue, SELENOP incorporates Se in up to 10 Sec residues within its primary structure, nine of which are harbored within a Se-rich C-terminal domain [85]. SELENOP is largely produced in the liver, the site of Se metabolism, then secreted into the plasma in order to transport Se to distant tissues throughout the body [85]. In fact, the majority of plasma Se (60%) is estimated to be contained within SELENOP's 10 Sec residues, thus SELENOP levels are often used in conjunction with GPx activity and plasma selenium to more accurately determine whole body Se status [86, 87]. Studies using *Selenop* floxed mice to delete *Selenop* specifically in the liver report a reduction in mouse serum Se levels by 90% and great decreases in Se levels in distant tissues such as the kidney [88]. Furthermore, as Se levels increase so do levels of SELENOP, and Se supplementation via Brazil nuts, Se-enriched milk protein, or Se-rich yeast increases rectal *SELENOP* mRNA levels in proportion to plasma Se concentration [89, 90].

SELENOP's role in Se transport makes it a necessary component for generation of other SePs, such as GPxs. After reaching target tissues such as the brain and testes via the plasma, full length SELENOP is primarily bound and internalized by the apoER2 receptor (LRP8), a member of the LDL receptor-related protein (LRP) family [91]. Binding to the apoER2 receptor is followed by endocytosis and lysosomal-mediated degradation, which then frees Sec for metabolism allowing for synthesis of other SePs (Figure 1) [92–95]. This is again highlighted in the liver-specific *Selenop* knockout (KO) model, in which plasma GPx activity is decreased by ~85%, indicating that loss of SELENOP mitigates production of the GPx1 selenoenzyme. In addition to apoER2, SELENOP can also bind the megalin receptor (LRP2) in tissues such as the kidney, although binding via megalin has not been demonstrated to contribute to SELENOP degradation and generation of additional SePs [96].

While functions of full length SELENOP (*i.e.*, containing all Sec residues) have been more widely studied, it is worth noting that several SELENOP isoforms have been identified in the plasma of both humans and rats. In humans, three isoforms have been identified of ~45, 50, and 60 kDa size, while four isoforms have been found in rat plasma [97–102]. These isoforms are most likely C-terminal truncations, due to termination at various UGA codons. Functionally, the majority of truncated isoforms (those having six Sec or fewer) are unable to bind the apoER2 receptor, which recognizes the C-terminal portion of SELENOP and thus these isoforms are less likely to contribute to Se transport [96, 103]. However, like the majority of SePs, SELENOP can still function in an antioxidant capability and catalyze peroxide oxidation through the single N-terminal, UXXC Sec, which is maintained in the all truncations [104, 105]. As the N-terminal domain also mediates SELENOP's binding interaction with megalin, these forms also retain this binding ability. Interestingly, truncated SELENOP isoforms may be the primary forms synthesized by intestinal tissues, as it has been hypothesized that only the liver, with high levels of available Se, is able to synthesize full-length SELENOP [86]. However, tissue-specific expression of SELENOP isoforms and their contribution to intestinal biology remains unknown.

Selenoprotein P in intestinal diseases and cancer

As SELENOP levels have been used to infer patient Se status, many studies have measured SELENOP in IBD and CRC patients with most reporting similar reductions to those observed in Se levels. For example, recent studies have found that CD patients exhibit significantly lower serum SELENOP levels as compared to healthy control subjects [106], and serum SELENOP concentrations have been inversely correlated with CRC risk, particularly in women [107]. However, this decrease is not restricted to plasma-derived SELENOP, which can also be produced by cells in the local intestinal microenvironment. Indeed, RNA and protein analysis of tumor tissues has additionally demonstrated reduced SELENOP expression in primary colorectal adenoma samples as compared with adjacent normal tissue [108–110]. Decreases in SELENOP expression also appear to be inversely correlated with tumor state, as stage III and IV primary colorectal carcinomas exhibit significantly lower SELENOP expression than stage II tumors [108]. However, it is worth noting that SELENOP is not universally decreased across all cancers and tumor types, and reports indicate SELENOP is increased in metastatic melanoma as compared to normal tissue and in poorly-differentiated prostate tumors as compared to those with higher-differentiation status [111, 112].

Over the past two decades, “personalized” approaches to cancer therapy have increased prevalence of whole genome sequencing and expanded our ability to discover rarer cancer-associated genomic alterations [113]. Recent studies utilizing exome sequencing have also identified a number of single nucleotide polymorphisms (SNPs) in the *SELENOP* gene which may influence cancer risk [114]. Of the six SNPs identified to-date, two of these SNPs, the G/A polymorphisms rs3877899 (Ala234Thr) in the SELENOP coding sequence and rs7579 in the SELENOP 3'-untranslated region (UTR), can significantly alter expression ratios of SELENOP isoforms and thus functionally contribute to SELENOP expression [100]. Specifically, CRC patients with the GG genotype of rs3877899 and the GA genotype of rs7579 demonstrate decreased expression of the full length 60-kDa

SELENOP isoform. Moreover, the GA genotype of rs7579 is significantly associated with increased risk of CRC [115]. Four additional SNPs in SELENOP are significantly correlated with advanced colorectal adenoma: one variant in the 5'-UTR (C/G at -4166) and three variants in the 3'-UTR (A/G 31174 bp 3' of STP, G/A 43881 bp 3' of STP, and C/T 44321 bp 3' of STP) [116]. Despite their associations with CRC, the relevance of these six SNPs to SELENOP structure and/or function awaits further elucidation.

Unlike Se, whose antitumoral effects have been investigated for almost 70 years, SELENOP's direct contribution to development and progression of intestinal diseases has only recently begun to be addressed. *Selenop* mouse models were first described in 2003, when two groups published complementary KO (*Selenop*^{-/-}) mouse lines [117, 118]. In both instances, *Selenop* KO mice demonstrate altered Se distribution and severe baseline phenotypes primarily attributed to decreased Se transport to the brain, such as decreased growth and neurological defects. These mouse models have also been used to determine the effects of SELENOP loss in colitis and CAC, the results of which have been reviewed in detail elsewhere [119, 120]. Briefly, these studies determined that in the AOM/DSS model of CAC, heterozygous *Selenop* loss was associated with increased colitis severity, tumor number, tumor size, intratumoral proliferation, and number of oxidative DNA lesions as compared to wild-type mice [121]. However, contrary to the hypothesis that SELENOP loss would augment colitis and CAC, *Selenop* KO mice were observed to be relatively protected from tumorigenesis and displayed smaller tumors with high genomic instability and increased apoptosis. Thus, reducing, but not eliminating, SELENOP is pro-tumorigenic. The protection conferred by complete *Selenop* loss is postulated to be due to the dual nature of oxidative stress, which can promote malignancy in moderate amounts yet lead to clearance of initiated cells at critically high levels [122]. This interpretation is supported by the observation that reducing the amount of injury in this system by singular treatment with either AOM or DSS increased tumor development in *Selenop* KO mice above both *Selenop* wild-type and heterozygous cohorts [121]. Furthermore, SELENOP appears to drive severity of colitis and tumorigenesis via a broad two-prong effect on antioxidant function, as mutant mouse models expressing a truncated form of SELENOP lacking the either the Se-rich C-terminal domain (which eliminates SELENOP's Se transport function) or an N-terminal serine mutant (which abolishes SELENOP's enzymatic activity) both display similar increases in disease severity as compared to *Selenop* heterozygous mice [94, 105]

Additional mechanisms for Se and SELENOP function in the gut

Although the antitumorigenic roles of Se and SePs such as SELENOP are most commonly attributed to their ability to mitigate oxidative stress and DNA damage, researchers have recently begun to analyze the role of SePs in other cellular signaling pathways which may influence inflammation and tumorigenesis (Figure 2). For example, both Se deficiency and SELENOP loss activate the WNT pathway in the colon, which is absolutely required for maintaining epithelial stem cell populations in the intestine and whose aberrant activation is widely considered the most common mechanism for CRC initiation [121, 123–125]. Interestingly, the SELENOP receptors, megalin and apoER2, belong to the same protein family as the key WNT3a co-receptors LRP5 and LRP6 [126]. As, the SELENOP binding region is conserved among all LRP family members, one potential mechanism for

SELENOP's effect on WNT pathway activation could involve competitive binding with WNT3a [103]. Alternatively, neither megalin nor apoER2 are specific to SELENOP, and each has additional functions that may modify tumor growth. Megalin, for instance, also mediates uptake of Vitamin D which has been widely shown to repress the WNT pathway and is associated with reduced cancer risk [39, 127, 128]. Megalin can additionally serve as a receptor for both Sonic hedgehog (Shh) and bone morphogenic protein 4 (BMP4), which are key developmental morphogens that often antagonize WNT3a, particularly in the intestine [129–132]. Thus, it is possible that Se and SELENOP's effects on WNT-dependent phenotypes may center on binding to LRP family receptors. However, it is also possible that the WNT activation observed may ultimately be attributed to roles in redox homeostasis, as recent works have illustrated a role for oxidative stress in maintenance of intestinal stem cell populations [2].

While WNT signaling is broadly responsible for maintenance of the intestinal epithelium, Se and SELENOP have also been found to modulate immune cell function and the microenvironment. Years of research have determined that dietary Se is critical for optimal function of both the innate and adaptive immune systems, and Se deficiency has been demonstrated to attenuate immune responses to microbes, viruses, allergens, and tumor cells [133, 134]. In part, this effect could depend on modification of cytokine production, and several studies have revealed that these levels can be modulated by dietary Se. For example, chickens on a Se-deficient diet demonstrated increased expression of pro-inflammatory cytokines, including cyclooxygenase-2 (COX-2), prostaglandin E synthase (PTGE), and tumor necrosis factor alpha (TNF- α) in gastrointestinal tissues, as well as nuclear transfer factor κ B (NF- κ B) [135, 136]. In the setting of colitis, Se-deficiency upregulated numerous inflammatory chemokines and cytokines (*e.g.*, COX-2, TNF- α , TGF- β , EGF), although in general supranutritional Se did not decrease cytokine levels as compared to observed in Se-sufficient diets [28, 30, 34]. In patient populations, the results of Se status have likewise been mixed. In women with gestational diabetes, 6 weeks of Se supplementation decreased expression of TNF- α and TGF- β , while in patients with liver cirrhosis, serum Se status was associated with lower levels of interleukin-6 (IL-6) [137, 138]. Conversely, no change in chemokine and cytokine production was observed following Se supplementation in patients undergoing hematopoietic stem cell transplant or those with autoimmune thyroiditis, overall suggesting that altered expression of inflammatory cytokines via Se supplementation may be limited to specific disease states [139, 140].

Similarly, modulation of SELENOP levels has been observed to modify production of cytokines such as of TNF- α , hepatocyte growth factor (HGF), vascular endothelial growth factor (VEGF), and IL-6 in tissue culture cell lines [141, 142]. While exact mechanisms of transcriptional regulation are still unclear, SELENOP expression appears to be modulated by a number of inflammatory cytokines, namely IL-10, TGF- β , IL-1 β , TNF- α , and interferon- γ (IFN- γ) [143–145]. SELENOP is also highly upregulated in alternatively activated (M2) macrophages as compared to those activated by classical stimuli (M1), and its loss has been shown to skew macrophage polarization both *ex vivo* and *in vivo* in the setting of AOM/DSS-mediated inflammatory tumorigenesis [121, 146]. SELENOP and SePs have also been shown to affect macrophage migration, potentially through modification of increased expression of matrix associated genes, and Se supplementation attenuated neutrophil

infiltration in the TNBS colitis model [31, 121, 147]. However, the exact role of SELENOP in immune cell populations is still fairly ambiguous, and much work is required to thoroughly elucidate Se and SELENOP-dependent effects in the microenvironment and how they contribute to intestinal disease.

It is also important to note that despite common reports of protective effects, SELENOP and other SePs may have protumorigenic effects in the intestine that offset protection derived from Se. As discussed above, complete loss of SELENOP decreased tumor number and size, suggesting that a certain level of antioxidant ability aids tumor cell survival [121]. Furthermore, while GPx2 has been reported to confer a net protective effect in inflammatory tumorigenesis, high expression of GPx2 was associated with early CRC tumor recurrence and its knockdown decreases growth of CRC cancer cells in xenograft and 3D models [148–150]. Loss of selenoprotein F (SELENOF) likewise decreases proliferation, growth in soft agar, and tumorigenicity of CRC tumor cells [151–153]. Finally, both tumor-suppressive and tumor-promoting roles have been described for thioredoxin reductase 1 (TrxR1), and its inhibition has been explored therapeutically [154]. Taken together, these results caution that broadly augmenting SeP activity and/or expression in the intestine may have unintended consequences that aid tumor cell growth, although more detailed mechanistic research should help to elucidate these contexts.

Se and SELENOP interactions with host microbial communities

The myriad microorganisms that colonize the GI tract, collectively termed the gut microbiota, are crucial for both proper nutrient uptake and effective host defense against invasive microbes. Moreover, dietary habits and gut mucosal immune responses alter gut microbiota composition in manners believed to contribute to disease pathology [35]. Interestingly, several recent studies have consistently shown reductions in overall gut microbiota diversity in IBD patients [155–160]. Additionally, longitudinal analysis of patients with active UC revealed differences in mucosal bacteria that correlate with disease severity, duration, and age, as compared to patients without IBD [161]. Moreover, Rajili - Stojanovi *et al.* found that UC patients in remission displayed significant similarities in fecal microbiota composition, regardless of age, location, or sex [160].

Recent animal studies have begun to investigate interactions among Se intake, SeP expression, and the gut microbiota. For example, germ-free (GF) mice on a Se-deficient diet demonstrated increases in plasma, liver, and cecum Se levels as well as higher expression and/or activity of SePs such as GPx1, GPx2, and TrxR in the colon and small intestine as compared to conventional (CV) mice on the same Se-deficient diet [162]. Thus, under Se-limiting conditions, it appears that the gut microflora compete with the host for Se, even though Se is believed to be primarily absorbed in the small intestine [163, 164]. Moreover, both conventionalized GF and CV mice on a Se-deficient diet exhibited decreases in gut microbiota diversity [165]. Interestingly, this same study found that CV mice on a Se-sufficient diet displayed a unique trend towards increased SELENOP protein expression [165]. Taken together, these results indicate that dietary Se impacts both establishment and composition of the gut microflora and raise the intriguing possibility that dietary Se may promote gut microbiota diversity in Se-deficient IBD patients, normalize SeP expression,

and decrease disease severity. Although the interaction mechanisms among Se, SePs such as SELENOP, and the gut microbiota are yet to be elucidated, the potential therapeutic effects of Se supplementation in this context warrant future investigation.

Conclusions and future directions

For over 70 years, research has indicated that Se and Se-containing antioxidant proteins should protect against inflammation and malignancy in the gut. Low Se levels have been inversely correlated with a number of cancers, including CRC, and studies in animal models most often associate lower Se status with greater disease severity, inflammation, and tumor formation. More recently, with the generation of KO mouse models, these results have been extended to specific SePs such as SELENOP.

While protective effects of Se and SELENOP are often associated with their antioxidant abilities, recent studies suggest that the exact mechanisms behind them may be multifactorial and quite complex. Indeed, Se and SELENOP have been observed to modify behavior of multiple cell types which contribute to intestinal disease, including immune cells, intestinal epithelial cells, and the gut microbiota. Dietary Se and SePs have also been observed to modulate specific pathways associated with disease, as loss of SELENOP and decreased Se intake both activate the WNT pathway and modulate production of inflammatory cytokines. Thus, these results indicate that context-specific knowledge may be key to understanding the exact mechanisms by which Se and SePs contribute to disease, and while the above studies lay a solid foundation, this is an area of great research need. For example, in the case of SELENOP, future studies analyzing SELENOP isoform expression, receptor-mediated signaling, and cell type-specific phenotypes will be of great interest.

Unfortunately, despite fairly consistent results demonstrating a protective effect of Se on CRC in pre-clinical models, the effect of Se on CRC risk in recent clinical trials is modest, at best. Instead, supranutritional Se supplementation was more closely associated with detrimental effects, such as T2D. Furthermore, not all effects attributed to SePs are tumor-suppressive, as GPx2 and SELENOP can both drive CRC cell proliferation and anchorage independent growth. However, these results suggest that context-specific knowledge of Se and SELENOP function may also represent a key unresolved factor in clinical trials that seek to determine the ultimate result of Se supplementation in intestinal diseases. For example, the majority of clinical trials have utilized participants from Se-replete populations, which may not benefit from Se supplementation as would patients with nutritional Se deficiencies. Patient cohorts with *SELENOP* SNPs that compromise its expression or function may represent another population where the benefits of Se supplementation would outweigh the potential risks. Thus, in the age of precision medicine, where individual patient biologies are factored into clinical regimens, it remains to be determined whether targeted supplementation in Se- or SELENOP-deficient populations represents an effective prevention and/or treatment strategy. It will be interesting to see what the future of SELENOP research holds, with more thorough study of its role in intestinal diseases and cancer.

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Figure 1. SELENOP's role in Se transport

SELENOP contains 10 Sec residues (U; white circles): one in an N-terminal redox domain (red outline) and 9 in a C-terminal Se transport domain (brown outlines). Extracellular SELENOP can bind to megalin or apoER2 receptors. After binding to apoER2, the receptor is endocytosed and SELENOP is lysosomally degraded. The freed Sec then undergoes a series of metabolism steps by selenocysteine lyase (SCLY) and selenophosphate synthetase (SPS2) to yield hydrogen selenide (HS; H_2Se) and monoselenophosphate (MSP; $\text{H}_2\text{O}_3\text{PSe}$). The monoselenophosphate then serves as the Se donor to convert a tRNA-associated serine into Sec for incorporation into nascent selenoproteins. Sec insertion is also mediated by a 3' SECIS sequence in SeP mRNA that recruits the Sec-tRNA and dedicated transcription factors such as the Sec-tRNA specific elongation factor (EFSec) and SECIS-binding protein 2 (SBP2).

Figure 2. Additional roles proposed for SELENOP

SELENOP can be synthesized by intestinal epithelial cells and has been found experimentally to inhibit WNT and TGF- β signaling pathways, as well as modify secretion of cytokines such as TNF- α . Secreted SELENOP can also serve as an extracellular antioxidant in the tissue microenvironment. However, much is unknown about SELENOP's expression patterns and functions in the intestine, such as whether SELENOP binds additional LRP receptors or modifies receptor-mediated signaling, which isoforms are expressed, and whether SELENOP has additional roles in intracellular signaling pathways.