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Review Article

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.

1. 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 [1,2]. 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.

2. 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

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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 perioperative 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 by-product of disease activity remains unclear. Decreased plasma Se levels and glutathione peroxidase (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 et al. 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].

3. 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 correlations observed by earlier researchers have been maintained. For example, patients with lower fasting plasma Se concentrations ($< 128\,\mu g/L$) display significantly greater likelihood and number of adenomatous intestinal polyps [46]. Likewise, low ($< 65\,\mu g/L$) and high ($> 153\,\mu g/L$) 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 ($< 70\,\mu g/L$) 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 et al., 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].