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Selenoproteins and oxidative stress-induced inflammatory tumorigenesis in the gut

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Abstract

Selenium is an essential micronutrient that is incorporated into at least 25 selenoproteins encoded by the human genome, many of which serve antioxidant functions. Because patients with inflammatory bowel disease (IBD) demonstrate nutritional deficiencies and are at increased risk for colon cancer due to heightened inflammation and oxidative stress, selenoprotein dysfunction may contribute to disease progression. Over the years, numerous studies have analyzed the effects of selenoprotein loss and shown that they are important mediators of intestinal inflammation and carcinogenesis. In particular, recent work has focused on the role of selenoprotein P (SEPP1), a major selenium transport protein which also has endogenous antioxidant function. These experiments determined SEPP1 loss altered immune and epithelial cellular function in a murine model of colitis-associated carcinoma. Here, we discuss the current knowledge of SEPP1 and selenoprotein function in the setting of IBD, colitis, and inflammatory tumorigenesis.

Keywords

Enteroids; stem cells; Glutathione Peroxidase; Selenoprotein P; inflammation; interferon-γ; antioxidant

Introduction

Inflammatory bowel disease (IBD) is estimated to affect over 1 million Americans and 2.5 million Europeans [1]. IBD is primarily comprised of two types of chronic inflammatory disorders of the intestine, Crohn's disease (CD) and ulcerative colitis (UC) [2]. IBD etiology is incompletely understood, but evidence to-date suggests a complex interplay between microbes, other undefined environmental exposures, genetic susceptibility, and

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inappropriately sustained and severe autoimmune inflammatory responses, which ultimately results in repetitive injury to the GI tract [3, 4]. Longstanding colonic IBD also predisposes patients to colorectal cancer (CRC). In this situation, sustained inflammation results in a protumorigenic microenvironment in which reactive oxygen species (ROS) induce protein and DNA damage, stimulate immune cell recruitment and polarization, and accelerate epithelial cell proliferation [5].

As greater disease activity is associated with increased cancer risk, understanding the molecular pathogenesis of IBD and identifying modifiable factors affecting disease severity are of paramount importance. Toward that goal, recent studies have implicated the essential micronutrient selenium (Se) as well as specific selenium containing proteins (selenoproteins, SePs), such as selenoprotein P (SEPP1) and members of the glutathione peroxidase (GPx) family, in modifying inflammation and tumorigenesis. The aim of this article is to review the literature on Se and SePs in colitis and colitis-associated carcinoma and pose the argument that Se and SePs are valid targets for therapeutic intervention in IBD.

Selenium and Selenoprotein Function

Se was discovered by J.J. Berzelius in 1817 and initially recognized to be a toxin when ingested in large amounts [6]. However, Se was later determined to be an essential micronutrient and indispensable for the production of SePs, where it is incorporated as the 21st amino acid selenocysteine (Sec). Functionally, SePs are known to be potent antioxidants, and the majority of characterized SePs catalyze oxidation-reduction reactions using the Sec as an active site [7]. SePs are particularly effective antioxidants owing to the selenol group in Sec, which is more fully ionized than the thiol of cysteine (Cys) at physiological pH. Additionally, Sec has a lower pKa (~5.2) and reduction potential than Cys. This makes Sec more reactive than Cys, which is present within the active site of many non-selenoprotein enzymes [8]. Aside from the normal antioxidant activity contributed by the Sec, SEPS and SEP15 can process and remove misfolded proteins [9, 10] and MsrB1 is capable of regulating antioxidant protein repair through protein disulfide shuffling [11].

Expression of SePs is tightly controlled by the Sec translational process which is highly dependent on the presence of Se (for reviews on translational regulation of selenoprotein synthesis see [12–14]). Se deficiency reduces the intracellular amounts of mature tRNA Sec, a special transfer RNA charged with Sec, which in turn results in decreased SeP production. In the setting of limiting Sec tRNA levels, SePs may still be translated; however, there is a “hierarchy” of SeP expression. This hierarchy reflects the relative importance of the selenoproteins in cellular homeostasis. For example, depending on the particular tissue GPx4 > SEPP1 > thioredoxin reductase 1 > type I deiodinase > GPx1 [15, 16]. Selenoprotein synthesis is also considered to be modulated by differential expression of two Sec tRNA isoforms which are distinguished by the presence of 2′-*O*-methylribose at position 34 (Um34). The Um34 modification is also dependent on Se availability, with mice maintained on a high Se diet having increased percentages of mcm^{5}Um-containing Sec tRNA [17]. These two Sec tRNA isoforms are differentially associated with production of distinct classes of SePs. The SePs most responsive to the modified mcm^{5}Um-containing Sec tRNA are stress-related SePs, such as GPx1 and GPx3, whereas housekeeping SePs,

essential for survival, are not dependent on the Um34 modification allowing higher expression in the context of decreased Se availability [18]. While originally described in mouse models, mutation of the Sec tRNA gene (*TRSP*) which interferes with the Um34 modification has recently been described in a human subject, where authors note decreased expression of stress-related SePs while expression of housekeeping SePs was largely preserved [19].

Selenium in Human Disease

Se and SePs contribute greatly to human health and their functions are most often linked to antioxidant ability. Indeed, Se deficiency, due to Se-poor soil, is correlated with the congestive cardiomyopathy known as Keshan disease [20] and the deforming osteochondropathy, Kashin-Beck disease [21]. Keshan disease incidence has been reduced by administration of Se-fortified table salt [22], implicating Se deficiency as the etiologic precipitant in this disorder. Fulvic acid supplementation and selenium deficiency in mice recapitulated many of the symptoms of Kashin-Beck disease [23], suggesting that Se supplementation may prevent this disorder. However, a double-blind, randomized control trial of Se supplementation did not affect the clinical course of patients with Kashin-Beck disease [24]. Additionally, patients with genetically impaired selenoprotein biosynthesis present with multisystem disorders. For example, mutation of SBP2 (*SECISBP2*) is characterized by failure of spermatogenesis, impaired T lymphocyte proliferation, abnormal mononuclear cytokine secretion, telomere shortening, increased cutaneous ROS, and susceptibility to ultraviolet radiation-induced oxidative damage [25]. Impaired oxidative defenses, muscle defects, and thyroid dysfunction were also observed in the setting of Sec tRNA (*TRSP*) mutation [19]. Together, these studies underscore the importance of Se and SePs in the maintenance of human health.

Epidemiological studies of patients with below average Se levels have further suggested important biological functions for SePs. Observational studies associate lower serum Se levels with epilepsy [26], age-associated neurological disorders [27], and decreased survival following HIV infection [28]. It should be noted that, as these are observational studies, the causative roles of Se in these diseases have not been proven, but suggests that Se might be protective. Further research on the benefit of Se supplementation in these diseases is essential.

As Se may confer protection against disease by reducing chronic oxidative stress and inflammation, it was hypothesized that Se supplementation would protect against cancer development. Indeed, animal models have demonstrated that Se supplementation can reduce the incidence and severity of liver [29], esophageal [30], pancreatic [31], prostatic [32], colon [33], and mammary carcinogenesis [34]. Unfortunately, large clinical trials have yielded mixed results, some suggesting that Se supplementation and/or higher Se status may reduce cancer risk [35–37] and others failing to correlate serum Se levels with cancer risk [38–40]. Thus, the impact of Se supplementation on cancer is a more complex issue than has been heretofore recognized.

Selenium and IBD

Interestingly, the benefit of Se supplementation might be best realized in populations with low baseline Se and high inflammatory burden, such as patients with IBD. IBD patients can have defects in intestinal absorption, leading to nutritional deficiencies which are important to recognize and treat in disease management. Se deficiency and decreased SeP activity have been described in both CD and UC patients, often correlating with disease severity [41–47]. Similar findings have been observed in the dextran sulfate sodium (DSS) mouse model of colitis where decreased plasma Se levels and GPx activity were observed [48]. However, these studies do not indicate a causal role for Se in IBD development. Nevertheless, experiments analyzing Se deficiency in the context of colitis observed exacerbated disease severity, with higher mortality, decreased body weight, increased diarrhea, more pronounced inflammatory injury, and increased activation of pro-tumorigenic pathways, such as EGF and TGFβ [48]. Increased tumorigenesis and disease progression have also been observed in Se-deficient mice placed on a colitis-associated carcinoma (CAC) protocol, using azoxymethane (AOM) to initiate genetic mutations followed by repeated cycles of DSS-based epithelial injury [48]. Together, these studies suggest a direct role for Se in mediating IBD severity and its associated cancer risk.

Investigating selenoproteins through SEC tRNA mutations

While Se is primarily incorporated into SePs, it was still unclear whether the effects observed with Se were due to the loss of Se-containing proteins or low-molecular weight Se compounds. To broadly investigate the role of SePs, mouse models were developed with modified expression of Sec tRNA which interferes with selenoprotein biosynthesis [49]. Collectively, these models have indicated that SePs exert the bulk of Se's influence in regulating oxidative stress and tumorigenesis in the gut.

The first developed Sec tRNA mouse model [(i^6A^-) $tRNA^{[Ser]Sec}$] relied on transgenic expression of mutated Sec tRNA specifically interfering with synthesis of mcm^5Um-containing Sec tRNA. Global transgene expression decreased levels of stress-related SePs [49]. In the gut, Sec tRNA transgenic mice were observed to have increased numbers of aberrant crypt foci (ACF), a type of preneoplastic colonic lesion, after exposure to AOM [50]. Interestingly, these were the first data to show that SeP expression could directly modify the development of colorectal tumorigenesis. To date, this mouse model has also been used to show that decreased SeP expression augments development of prostatic intraepithelial neoplasia, hepatocarcinoma, and inflammatory pyogranulomas, indicating a broad role for stress-related SePs in tumorigenesis across organ systems [51, 52].

As global loss of the mammalian Sec tRNA gene (*Trsp*) is embryonic lethal, studies to analyze the effect of complete Sec tRNA and selenoprotein loss have relied on a conditional knockout (KO) model to determine tissue-specific effects [53, 54]. However, the effects of tissue-specific Sec tRNA loss were often severe, with SeP expression in many tissues, such as the endothelium, cardiac muscle, liver, and skin, required for survival [55–57]. Nevertheless, Se has long been known to contribute to immune cell function (reviewed in [58]), and this model has provided useful insight into the function of SePs in different

immune cell populations, and particularly how they may contribute to inflammatory tumorigenesis in the gut. *Trsp* knockout in myeloid lineages through a *LysM-Cre* driver led to increased oxidative stress, upregulated transcription of antioxidant enzymes, accumulation of reactive oxygen species, altered expression of extracellular matrix-related genes, and diminished migration through matrix [56, 59]. Furthermore, placing these mice on an acute DSS-induced colitis protocol resulted in worse colitis characterized by pronounced inflammation, neutrophil infiltration, edema, weight loss, shorter colon length, and expression of pro-inflammatory cytokines relative to WT mice treated with DSS [60]. While intestine epithelial-specific *Trsp* KO has not yet been described, these data suggest selenoprotein expression in myeloid-derived immune cells are potent suppressors of inflammation in the gut and likely contribute to inflammatory tumorigenesis.

Glutathione peroxidases

In addition to global SeP loss through modulation of Sec tRNA expression, other studies have analyzed contributions of individual selenoproteins. While several SePs have been examined in the context of colitis and CAC, some of the best studied are those of the glutathione peroxidase (GPx) family. As these proteins are characterized by their ability to metabolize hydrogen peroxide (H_2O_2) and other peroxides, they are considered to be some of the most potent mediators of Se's effects in oxidative stress and inflammation. In colitis, extracellular GPx levels increase dramatically following DSS treatment, suggesting these enzymes are upregulated in response to oxidative injury [61]. Specifically, *GPx2*, a recently described target of STAT family transcription factors, was determined by gene expression profiling to be one of only seven genes upregulated in three separate models of colitis: DSS, transfer of $CD4^+$ $CD45RB^{high}$ T cell populations, and 2,4,6-trinitrobenzene sulphonic acid (TNBS) treatment [62, 63]. *GPx2* upregulation was further observed in tissues from both CD and UC patients, as well as colorectal adenomas [63]. Interestingly, GPx1 and GPx2 were also the SePs most affected by expression of the (i^6A^-) $tRNA^{[Ser]Sec}$ Sec tRNA transgene in the colon, suggesting that reduced GPx expression is a contributing factor to the augmented DSS-induced colitis observed in this model.

Determining the precise role of the GPx's in colitis and inflammatory tumorigenesis has been further aided by the development of individual knockout mouse models. While there are eight GPx family members, GPx's 5–8 are not SePs in the rodent as the Sec is substituted for cysteine. Of the remaining GPx family members, global loss of *Gpx4* is embryonic lethal, perhaps not surprising given its place at the top of the selenium hierarchy noted above [64]. On the other hand, mice lacking *Gpx1*, *Gpx2*, and *Gpx3* all develop normally, with no overt baseline phenotypes. However, mice deficient for both *Gpx1* and *Gpx2* developed spontaneous ileocolitis [65] linked to excess NADPH oxidase-generated ROS [66]. Individual knockout of *Gpx1* or *Gpx2* also rendered mice more susceptible to salmonella-induced colitis [67], while *Gpx2* and *Gpx3* knockout mice each have increased inflammation and CAC in AOM/DSS models [68, 69]. Together, these studies suggest a broad role for GPx family selenoproteins in mediating oxidative stress in the context of intestinal inflammation and downstream tumorigenesis.

Selenoprotein P and cancer

In addition to GPx family SePs, selenoprotein P (SEPP1) has also been implicated in mediating Se's effect on inflammatory tumorigenesis. Unlike the majority of SePs which are best characterized by their enzymatic activity, SEPP1 is better known as the predominant Se transport protein. SEPP1 is primarily expressed in the liver where the majority of Se metabolism takes place, incorporating Se in 10 Sec residues within its primary structure (in comparison, most SePs only have 1 Sec). The majority of these Sec's exist within SEPP1's Se-rich C-terminal domain, which is necessary for the delivery of Se to distant tissues via the plasma, where it can be taken up and degraded to free Se for synthesis of other SePs. SEPP1 currently has two known receptors which are differentially expressed based on tissue type. In tissues such as the brain and testes, SEPP1 is taken up by apoER2-mediated endocytosis, although in other tissues such as the kidney, the primary SEPP1 receptor is megalin, a lipoprotein receptor localized to the proximal tubule epithelium within the kidney [70–72]. To illustrate the effect of SEPP1 in Se transport, hepatocyte specific *Sepp1* knock out resulted in a 90% reduction in plasma Se levels greatly reducing whole body and tissue Se [73]. However, it is important to note that SEPP1 can also function as an antioxidant through a single N-terminal Sec, which exists within a UXXC motif that catalyzes the oxidation of glutathione (GSH) by a hydrogen peroxide or phosphatidylcholine hydroperoxide [74, 75]. Thus, both N- and C-terminal domains contribute to the overall function of SEPP1, making it vital for the production of other selenoproteins within target organs and giving it the ability to serve in an antioxidant function.

SEPP1 levels and activity are significantly decreased in colon tumors, human prostate tumors, mouse tumors, and in prostate cancer cell lines [76, 77]. Furthermore, several SNPs have been identified in *SEPP1* that may contribute to decreased expression in colorectal adenomas and have been associated with cancer risk [78–80]. Indeed, *SEPP1* transcript levels are decreased as early as the adenoma stage in CRC [81, 82]. Collectively, these data suggest that SEPP1 regulates intestinal homeostasis and protects from colitis and CAC.

SEPP1 modifies CAC

Recently, a global *Sepp1* knockout mouse model was used to investigate the contribution of SEPP1 to intestinal injury and development of CAC. In this study, *Sepp1* wild type (WT, $Sepp1^{+/+}$), heterozygous ($Sepp1^{+/-}$) and null ($Sepp1^{-/-}$) mice were subjected to the AOM/DSS initiation-promotion protocol to model inflammatory tumorigenesis. These studies suggest that SEPP1 functions as a haploinsufficient tumor suppressor, with $Sepp1^{+/-}$ mice displaying increased tumor multiplicity, a higher degree of dysplasia, increased intratumoral proliferation, and a greater extent of oxidative DNA lesions relative to both $Sepp1^{+/+}$ and $Sepp1^{-/-}$ mice. Thus, reducing, but not eliminating, SEPP1 results in significantly increased tumor burden. Contrary to expectations, complete *Sepp1* deficiency ($Sepp1^{-/-}$) resulted in decreased tumorigenesis concomitant with increased apoptosis, decreased proliferation, and high genomic instability [82]. Thus, it is postulated that this observation is due to the "double-edged-sword" of oxidative stress where instead of promotion of malignancy with increased ROS production, critically high levels of oxidative injury lead to the clearance of initiated $Sepp1^{-/-}$ cells. This is supported by the observation

that when *Sepp1*$^{-/-}$ mice are treated with either AOM or DSS as single modalities tumor multiplicity is increased [82].

Specific assessment of the role of SEPP1 in tumorigenesis is confounded by the fact that SEPP1 participates in Se transport and contributes to the production of other SePs which may influence colitis. To test whether SEPP1's Se transport capacity contributes to CAC development, mice with truncated Se-rich C-terminal domain [70] were subjected to AOM/DSS treatment. These mice show increased tumor number and dysplasia, although not to the extent of *Sepp1* heterozygous mice [82], indicating that at least some of the phenotype observed in SEPP1 deficiency was due to loss of this domain. However, a contribution of the Sec redox active was also observed in mice containing an enzymatically dead serine in place of Sec [75] also had increased tumor number and size with associated increased proliferation and DNA damage. Thus, both the Se transport and enzymatic functions of SEPP1 contribute to protect against intestinal injury and CAC. As complete knockout of SEPP1 resulted in a phenotype that differed significantly from that seen with loss of either component alone, other impacts of SEPP1 loss cannot be ruled out.

Cell-type specific roles for SEPP1

SEPP1 is expressed in the intestinal epithelium and immune cells, and in the context of global SEPP1 loss it remained unclear which cell type was mediating the observed phenotypes. Macrophages contribute to the pathogenesis of colitis and tumor development and loss of SeP synthesis within macrophages increases inflammatory injury in DSS-based colitis models [60]. Interestingly, SEPP1 is also the most upregulated gene in pro-inflammatory tumor conditioned macrophages [83] suggesting an important role for SEPP1 in macrophage function. It is likely that multiple selenoproteins contribute to the inflammatory microenvironment and a loss of balance within the macrophage selenoproteome alters immune cell activity. Moreover, SEPP1 expression and/or secretion is decreased by the cytokines TGF-β_1, interleukin 1β, tumor necrosis factor α, and interferon γ (IFN-γ) [84, 85], further complicating the role of SEPP1 in immune cell activity. Experimentally, an increase in total and M2 macrophages was observed in tumors from AOM/DSS treated *Sepp1*$^{+/-}$ mice. The increase in M2 macrophages was determined to be due to skewed polarization as opposed to recruitment, as direct stimulation with either IFN-γ and LPS or IL-13 led to decreased M1 polarization and increased M2 polarization, respectively, in SEPP1 heterozygous naïve macrophages. This only occurred in heterozygous macrophages and was not seen in full knockout macrophages, indicating that tight regulation of SEPP1 levels is required for proper macrophage function. Thus, SEPP1 may protect against inflammatory tumorigenesis through its attenuation of proinflammatory immune cell polarization, though the roles of SEPP1 in the immune environment are complex.

On the other hand, *Sepp1*$^{-/-}$ mice demonstrated increased DNA damage and significantly altered apoptosis and proliferation within the epithelial compartment, suggesting this cell population may be differentially affected by SEPP1 loss. To determine whether SEPP1 mediates epithelial tissue-autonomous effects, small intestinal organoids (enteroids) [86] were generated from WT and *Sepp1*$^{-/-}$ mice. These studies demonstrated increased plating

efficiency, branching, and stem spheroids (Figure 1) in enteroids from *Sepp1*$^{-/-}$ mice, all indicators of increased stem cell function [87–89]. These data suggest that loss of SEPP1 in epithelial cells drives them to a more stem cell-like and potentially pro-tumorigenic phenotype. Moreover, assessment of tumor tissue isolated from *Sepp1*$^{-/-}$ mice revealed increased expression of genes regulated by the Wnt signaling pathway, a pathway heavily implicated in maintaining stem cell populations as well as being a key driver in intestinal tumorigenesis [90]. Together, these functional alterations in *Sepp1*$^{-/-}$ enteroids highlight changes that are likely occurring within the intestinal epithelial cells which may independently contribute to cell transformation and tumor promotion.

Conclusions

Pre-clinical studies strongly indicate that antioxidants, such as many of the SePs which are produced depending on local Se concentration, should be chemopreventative agents in malignancy, but human trials have proven a disappointment. The US case-control study testing the efficacy of Se and vitamin E supplementation in cancer (SELECT) did not demonstrate a protective effect of Se supplementation on risk of CRC [91], and an intervention trial meta-analysis determined that oral administration of Se was not effective in preventing colorectal neoplasia [40]. However, research on SePs in inflammatory cancer suggests that patient selection will play a significant role in the success of Se supplementation studies in humans. Thus, targeted supplementation in Se-deficient populations may be an effective prevention strategy. Indeed, some patients with IBD are Se deficient, with SEPP1 expression decreased as much as 50% in patients compared to healthy controls [92, 93]. As SEPP1 haploinsufficiency leads to increased tumorigenesis in rodent CAC models, the degree of SEPP1 reduction observed in IBD patients is to a level that, in animals, promotes tumorigenesis. In further support of a protective role for Se supplementation, a significant survival benefit was demonstrated in mouse cohorts fed a high Se diet (1.0 PPM) as opposed to a Se sufficient diet (0.25 PPM) when subjected to the AOM/DSS protocol [82]. As selenoprotein expression should be optimized at 0.25 PPM, it may be that the protective effect of the high Se diet occurs due to reduced Se uptake in mice subjected to the inflammatory carcinogenesis protocol.

Se supplementation may additionally benefit populations with decreased *SEPP1* expression due to genetic polymorphisms affecting its expression. Case control studies of incident prostate cancer cases and matched controls indicated increased prostate cancer risk in patients harboring *SEPP1* SNPs, possibly influenced by decreased plasma SEPP1 [78, 94]. Four *SEPP1* variants are significantly associated with advanced colorectal adenoma risk [79] and genetic instability has been observed in the *SEPP1* promoter $(T)_{17}$ repeat motif in CRC in the context of the MSI-CRC mutator phenotype [80]. Though these polymorphisms are incompletely understood, they tend to be linked with increased cancer risk and modulate either expression or isoform proportion of SEPP1. Genotyping of *SEPP1* in patients with CAC may predict increased responsiveness to Se supplementation.

In conclusion, this review presents a broad role for SePs in protection against inflammatory carcinogenesis. Studies relying on mutation of selenocysteine tRNA indicate a protective role of SePs in inflammatory tumorigenesis, but do not identify the SePs responsible. It is

likely that multiple SePs can contribute to this phenotype. For example, loss of both GPx1 and GPx2 worsens colitis, indicating these two SePs are important in mitigating intestinal inflammation. Furthermore, decreases in SEPP1 contribute to inflammatory tumorigenesis by reducing redox capacity, enhancing stem cell characteristics and proliferation of epithelial cells, and modulating immune cell polarization toward a pro-tumorigenic phenotype. Loss of GPx3, in a similar model, results in increased tumorigenesis and dysplasia concomitant with increased proliferation, hyperactive WNT signaling, and increased DNA damage. It is likely that, with more thorough study of SePs in inflammatory tumorigenesis, we will see a common trend amongst SePs which will further promote Se and SePs as *bona fide* therapeutic targets in the prevention of inflammatory tumorigenesis.

Non-standard abbreviations

SEPP1	Selenoprotein P
CAC	Colitis-associated cancer
IBD	Inflammatory bowel disease
CD	Crohn’s disease
UC	Ulcerative colitis
SeP	Selenoprotein
GPx	Glutathione Peroxidase
ROS	Reactive oxygen species
Se	Selenium
CRC	Colorectal cancer
AOM	Azoxymethane
DSS	Dextran sulfate sodium
Sec	Selenocysteine
SECIS	Selenocysteine insertion sequence
Cys	Cysteine
GSH	Glutathione
ACF	Aberrant crypt foci
TNBS	2,4,6-trinitrobenzene sulphonic acid
IFN-γ	Interferon-γ

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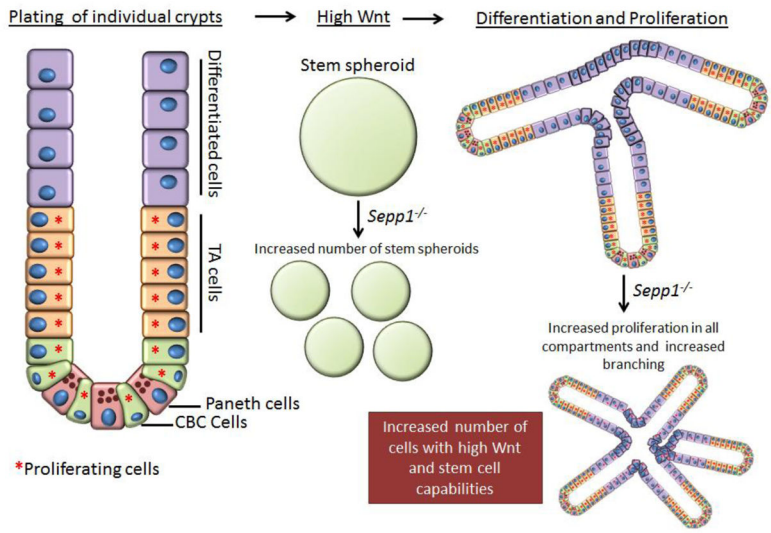

Figure 1. *Sepp1*$^{-/-}$ enteroids demonstrate increased stem cell characteristics

This schematic shows normal growth characteristics upon plating single intestinal crypts. Proliferating cells (red asterisk) include stem cells (crypt-based columnar cells, CBCs) and transient amplifying (TA) cells. Upon differentiation, cells no longer proliferate but complete the crypt structure. When WNT is added to the Matrigel matrix, an increased propensity to form stem spheroids occurs. Once WNT has been expended, enteroids proliferate and component cells differentiate. In the case of *Sepp1* knockout, enteroids form more stem spheroids, indicative of increased WNT-tone. *Sepp1*$^{-/-}$ enteroids also demonstrate increased branching, which suggests a higher percentage of stem cells within the population, and higher proliferation even in regions where cells should be differentiated and quiescent. All of these characteristics indicate that loss of SEPP1 contributes to increased tumorigenic properties in epithelial cells.