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Carrimycin, a first in-class anti-cancer agent, targets selenoprotein H to induce nucleolar oxidative stress and inhibit ribosome biogenesis

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Abstract

Carrimycin is a synthetic macrolide antibiotic that has been shown to have anti-cancer activity; however, its exact mechanism of action and molecular target were previously unknown. It was recently elucidated that Isovalerylspiramycin I (ISP I), the active component of carrimycin, targets selenoprotein H (SelH), a nucleolar reactive oxygen species-scavenging enzyme in the selenoprotein family. ISP I treatment accelerates SelH degradation, resulting in oxidative stress, disrupted ribosomal biogenesis, and apoptosis in tumor cells. Specifically, ISP I disrupts the association between RNA polymerase I and ribosomal DNA in the nucleolus. This inhibits ribosomal RNA transcription and subsequent ribosomal assembly, which prevents cancer cells from sustaining elevated rates of protein synthesis and cellular proliferation that are necessary for tumor growth and malignancy. In this review, we (1) describe the historical categorization and evolution of anti-cancer agents, including macrolide antibiotics, (2) outline the discovery of SelH as a target of ISP I, and (3) summarize the ways in which carrimycin has been used both clinically and at the bench to date and propose additional potential therapeutic uses.

Graphical Abstract

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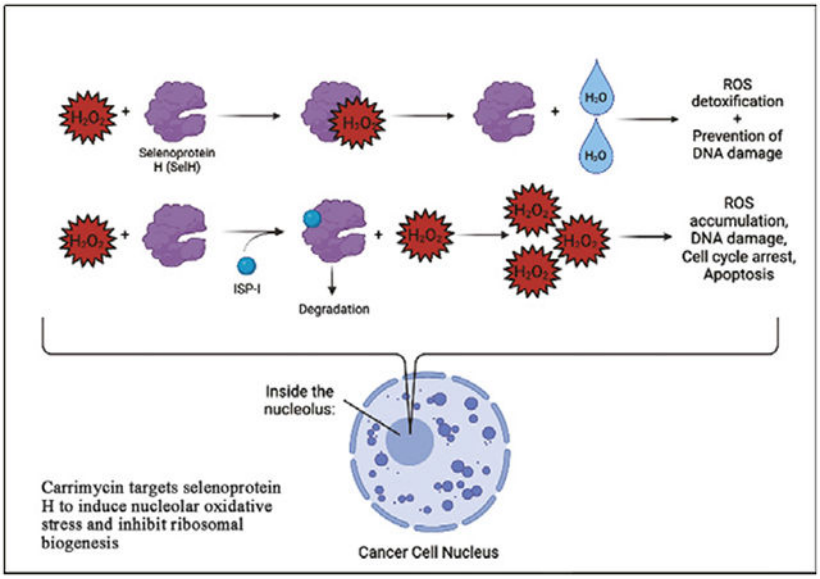
Conflict of interest

None.

Ethics statement

This work was performed in adherence to institutional ethics policies.



Keywords

Selenoprotein; Ribosome biogenesis; Macrolide; Cancer; Carrimycin

Introduction

Historically, anti-cancer agents have been categorized as alkylating agents, anti-metabolite agents, and anti-tumor antibiotics.[1,2] These therapeutic agents have been designed to target various hallmarks of cancer, such as resistance to cell death, evasion of growth suppressors, sustained proliferative signaling, replicative immortality, activation of invasion and metastasis, deregulation of cellular metabolism, and avoidance of immune destruction.[3-5] Additional anti-cancer strategies have recently emerged, including oncolytic viruses, immunotherapy, and immune checkpoint inhibitors. Some antibiotics double as anti-cancer agents, defying the conventional idea that anti-cancer drugs should specifically target eukaryotic tumor cells. Although antibiotics are typically used to fight bacterial infection, their anti-proliferative and pro-apoptotic capacities make them well-suited to combat cancer.[6]

Macrolides are a unique class of broad-spectrum antibiotics that act by directly binding to the nascent peptide exit side in bacterial 50S ribosomal subunits with high specificity, thereby interfering with protein synthesis.[7,8] Unrestrained proliferation that is characteristic of cancer cells relies heavily on sustained protein synthesis and, thereby, the ability of the cancer cell to aberrantly promote ribosome biogenesis.[9-11] Although several other chemotherapeutics also target protein synthesis at the level of ribosomal DNA (rDNA) transcription or ribosomal RNA (rRNA) processing, it is unclear to what extent these processes contribute to their cytotoxicity and overall efficacy. Macrolides have greater specificity than most chemotherapeutics and are thus associated with improved efficacy and reduced adverse events.[10] Further, macrolides have been shown to cluster within

leukocytes to utilize the adaptive immune response, which presents an exciting opportunity to study their anti-cancer effects in tumors that generate a systemic inflammatory response.[9] Since the discovery of erythromycin, the first macrolide antibiotic, in 1949, several new generations of macrolides have been developed, some of which may represent effective cancer therapeutics.[7,12]

Brief history of carrimycin development

Carrimycin, also known as shengjimycin, is a modified 16-component macrolide antibiotic that is produced from recombinant *Streptomyces* bacteria and contains several monomeric isovalerylspiramycins (ISPs) as its primary active component [Figure 1].[13] *In vivo* and *in vitro* experiments revealed that ISP I, a constituent of carrimycin, exhibits anti-cancer activity toward squamous cell carcinoma and hepatocellular carcinoma.[14,15] The carrimycin mechanism of action in bacterial cells involves its binding of the 50S ribosomal subunit, similar to the mechanisms of action of other macrolide antibiotics. As such, it was hypothesized that ISP I may bind to ribosomes in cancer cells, thereby inhibiting protein production and tumor cell proliferation. However, further studies unexpectedly revealed that ISP I acts by accelerating the degradation of a redox protein, selenoprotein H (SelH), in the nucleolus, thereby inducing nucleolar oxidative stress, inhibiting ribosomal biogenesis, and promoting tumor cell apoptosis.[13]

Anti-tumor effects of carrimycin

To date, carrimycin has been ascribed two unique anti-cancer properties: (1) inhibition of ribosome biogenesis as a macrolide antibiotic and (2) induction of cellular apoptosis through ISP I-mediated SelH inhibition. SelH is a 14 kDa (kDa) mammalian selenoprotein that plays a key role in maintaining redox homeostasis and modulating the cellular response to oxidative stress in eukaryotic nuclei.[16] Unlike most selenoproteins, SelH localizes to the nucleolus, the sub-nuclear compartment in eukaryotic cells, wherein rRNA transcription and ribosome biogenesis take place. In the nucleolus, SelH scavenges reactive oxygen species (ROS). Its distinct nucleolar localization and proximity to key ribosomal biosynthesis machinery distinguish SelH from other members of the selenoprotein family and render it a unique target for anti-cancer therapy.

Selenoproteins are a class of selenocysteine-containing proteins that are found in all three domains of life (i.e., Eukarya, Archaea, and Eubacteria). Approximately 25 functional human selenoproteins have been characterized, which are related only by the presence of a selenocysteine residue, and are replete with a vast array of active sites, protein conformations, and physiologic roles.[17] The overwhelming majority of human selenoproteins are involved in redox functions due to the molecular properties of their selenocysteine residue.[17] Selenocysteine is the 21st naturally occurring amino acid and is a selenium analog of cysteine, wherein the sulfur of the R group is replaced by a selenium atom [Figure 2].[18,19] The selenium atom gives selenocysteine a range of different properties compared to cysteine, such as a lower acid dissociation constant and enhanced nucleophilicity, making selenocysteine the quintessential amino acid for catalyzing redox reactions in the selenoproteome.[20]

Sequence, structural, and biochemical studies have revealed key features of SelH function. Structure and sequence analyses have identified a highly conserved CXXU redox motif (cysteine, followed by two other amino acid residues, followed by selenocysteine) in SelH that suggests a thioredoxin-like fold.[16] Biochemical redox assays revealed that SelH has glutathione peroxidase (GPx) activity, indicating that the antioxidant functions of SelH may protect against intracellular ROS accumulation.[16]

Increased ROS scavenging is a characteristic of cancer cells that arises from their increased metabolic rate and energy consumption and serves as one example of how cancer cells adapt to the stressors of increased proliferation. Sustained cell proliferation and reprogrammed cellular metabolism are hallmarks of cancer that lead to the buildup of ROS, such as hydrogen peroxide (H_2O_2) and superoxide (O_2•) free radicals.[5] In response to burgeoning ROS accumulation, tumor cells upregulate antioxidant response elements and ROS-scavenging enzymes, such as SelH, which decreases the intracellular ROS burden. Thus, inhibiting redox scavenging in cancer cells results in vulnerability to ROS-induced DNA damage in the nucleolus, cell cycle arrest, and apoptosis,[21-23] all of which appear to be involved in the ISP I mechanism of action.[24]

Nucleolus as a site for ribosome assembly and sensing oxidative stress

Nucleolar ribosome biogenesis is hyperactivated in cancer cells.[25] The process of ribosome biogenesis begins when tandemly repeated clusters of rDNA genes are transcribed into rRNA by RNA polymerase I (RNA POLI). Post-transcriptional modifications to the precursor 47S rRNA transcript create the mature 28S, 18S, and 5.8S rRNA subunits.[26] These subunits are then assembled with the necessary ribosomal proteins in the nucleolus before they are exported to the cytoplasm and rough endoplasmic reticulum.[26] Due to the rapid rate of ribosome biosynthesis in cancer cells, rDNA and rRNA components are especially sensitive to ROS-induced damage in the nucleolus.[27] Hence, SelH plays an indispensable role in scavenging ROS and maintaining efficient ribosome biogenesis in cancer cells.[28]

Rapid accumulation of ROS in the nucleolus leads to local structural and functional alterations that initiate downstream oxidative stress signaling.[29] Nucleolar stress has been associated with the translocation of nucleophosmin (NPM1) from the nucleolus to the nucleoplasm.[30] Under oxidative stress, NPM1 undergoes S-glutathionylation on cysteine 275, which triggers its nucleoplasmic translocation. This indicates that nucleolar stress signaling is an important mechanism for sensing redox homeostasis.[30] Increased oxidative stress has also been shown to activate c-Jun N-terminal kinase (JNK2) and inhibit RNA POLI transcription initiation factor IA (TIF-IA) in the nucleolus, resulting in subsequent downregulation of rRNA synthesis and induction of cell cycle arrest.[31] Nucleolar disruption further stabilizes p53, a key tumor suppressor gene that carries a loss-of-function mutation in 50% of human cancers, which leads to cell cycle arrest and induction of apoptosis.[32]

Thus, due to the nucleolar localization of its target (SelH), ISP I treatment leads to a significant accumulation of ROS in the nucleolar compartment. This further disrupts the process of ribosome biogenesis and inhibits protein synthesis. These effects, in turn, lead to an overall decrease in tumor growth and proliferation [Figure 3].[24]

Discovery of selenoprotein H as an isovalerylspiramycins I target

The anti-cancer effects of carrimycin were originally hypothesized to stem from its ability to hamper protein translation due to the critical role of ribosomal protein synthesis in highly proliferative cancer cells and the well-established mechanism of action of other macrolide antibiotics, which are known to bind and inhibit bacterial ribosomes.[33] However, while investigating the effects of ISP I on glioblastoma cells, it was found that ribosomes were not the direct target of ISP I. Drug affinity responsive target stability (DARTS) assays can be used to identify the target of small molecule inhibitors based on the principle that target protein interactions with the small molecule will create a stable conformation that protects the complex from proteolysis.[34] Using DARTS, researchers identified SelH as the most prevalent binding partner of ISP I.[24] This finding was confirmed with a cycloheximide (CHX) chase assay, wherein CHX is used to inhibit the elongation step of eukaryotic protein translation, preventing protein synthesis and allowing protein degradation rates to be observed.[35] Following the addition of CHX, ISP I significantly decreased the SelH half-life compared to dimethyl sulfoxide (DMSO)-treated controls. These experiments confirmed that ISP I binds to and promotes the degradation of SelH *in vitro* in tumor cell lines.

To verify that the anti-cancer effects of ISP I were dependent on SelH suppression, SelH-deficient cells were generated using short interfering RNA (siRNA) silencing and clustered regularly interspaced short palindromic repeats (CRISPR)-Cas9 to mimic the decrease in SelH protein levels caused by ISP I treatment.[24] The phenotypic similarity between ISP I-treated cells and SelH-deficient cancer cells in both *in vitro* and *in vivo* settings confirmed that ISP I acts through a SelH-dependent mechanism. Further, the authors showed that *in vivo* treatment of primary tumor models of glioblastoma with ISP I reduced primary tumor growth compared to that in mice treated with only DMSO.

Beyond their findings in primary tumor models, the authors revealed that ISP I prevents metastatic seeding by assessing the quantity of metastatic lung foci after tail vein injection of B16 melanoma cells *in vivo* in mice.[24] Combined, these *in vivo* models provide compelling evidence that ISP I exhibits anti-cancer activity toward primary tumor growth and metastatic tumor formation.

To assess the severity of ROS accumulation following ISP I-induced SelH suppression, the authors assessed hydrogen peroxide levels in glioblastoma cells and found them to be elevated after ISP I treatment.[24] In addition, there was a dose-dependent decrease in GPx with increasing concentrations of ISP I, which is consistent with previous literature describing the activity of SelH as an oxidoreductase.[16] Beyond defects in antioxidant enzymatic activity, transcriptional upregulation, specifically in genes implicated in the hydrogen peroxide response and antioxidant signaling pathways, were observed using RNA sequencing and gene set enrichment analysis.[24] Indications of the canonical nucleolar stress response were observed, including changes in the localization of nucleolar proteins such as NPM1, Fibrillarin, and RNA POLI.[29,30] Collectively, these studies suggest that ISP I treatment leads to significant ROS accumulation and activation of the nucleolar oxidative stress response.

The co-localization of SelH with vital components of the ribosome biogenesis machinery (i.e., rDNA in the nucleolus) prompted the authors to probe for DNA damage resulting from intracellular ROS accumulation. When assessing sensitive markers of DNA damage, such as the phosphorylated form of H2A histone family member X (γH2AX) with immunofluorescence imaging, the authors found increased levels of DNA damage in cells treated with ISP I compared to the levels in the controls.[24] ISP I-treated cells also exhibited higher levels of another indicator of genomic instability, RNA-DNA hybrid structures called R-loops. Finally, western blot and chromatin immunoprecipitation (ChIP) assays were used to investigate potential alterations in ribosome biogenesis caused by ISP I treatment. ISP I treatment increased phosphorylation of JNK2, which disrupts TIF-IA and DNA POLI interactions necessary for POLI transcription of rDNA, leading to overall disruptions in ribosome biogenesis.[31]

Insights and potential applications of carrimycin

As previously mentioned, rapidly proliferating cancer cells require heightened levels of protein synthesis and the translational machinery that sustains it.[3-5] Ribosome biogenesis is a dynamic nucleolar process that is often elevated in rapidly growing and dividing cells, such as oncogenic cells, virus-infected cells, and cytokine-producing cells, in order to sustain accelerated rates of protein synthesis and cellular proliferation.[11,36] In cancer cells, this increase is evidenced by the observation of hypertrophic nucleoli and represents an independent negative prognostic indicator in numerous tumor pathologies.[37]

SelH inhibition remains under investigation as an anti-tumor strategy, and our understanding of its mechanism of action is limited to the few studies mentioned in this review, including those evaluating the mechanism of ISP I in glioblastoma, squamous cell carcinoma, hepatocellular carcinoma, and metastatic melanoma animal models. Although the broader concept of selenoprotein inhibition as an anti-cancer strategy has led to an array of controversial conclusions regarding the role of selenium in tumorigenesis, it is important to note that selenoproteins represent a heterogenous class of molecules with varying physiological roles and paradoxical roles in promoting and preventing cancer.[38,39] The advantage of specifically inhibiting SelH, however, renders carrimycin a promising new avenue for anti-tumor therapy for several reasons. First, anti-cancer therapies that inherently induce cellular stress (i.e., alkylating agents) ultimately increase mutational burden through ROS accumulation. Drugs that are engineered to inhibit SelH prevent these inadvertent treatment-induced mutations by impairing ROS scavenging. Second, the downstream effects of SelH inhibition include inhibition of rRNA synthesis in the nucleolus, thereby concomitantly halting protein production. This is an added benefit of employing macrolide antibiotics as anti-cancer therapies.

To the best of our knowledge, SelH is the only selenoprotein that carrimycin inhibits.[24] This confers a novel use for carrimycin as compared to other macrolide antibiotics and other anti-cancer agents. However, carrimycin may still carry some of the side effects associated with other macrolide antibiotics (e.g., immunosuppression, myalgias, neuropathy, dysmotility), which warrants further study. By inhibiting SelH, carrimycin halts ribosome biogenesis and, therefore, protein production, which is similar to the effects of other macrolides,

including rapamycin, which was recently shown to inhibit rRNA synthesis.[40] In addition, carrimycin prevents radical scavenging in the nucleolus, which is critical for cancer cell proliferation. Further, carrimycin side effects are likely mitigated by its lack of binding to other selenoproteins that perform key cellular functions. The structures and functions of selenoproteins are highly variable, which makes them unique targets for anti-cancer molecules.

In addition to its anti-cancer effects, SelH has been ascribed antiviral functions. Abrogating nucleolar rRNA synthesis by suppressing SelH levels may also be effective at treating virus-infected cells burdened with high levels of viral protein synthesis. Yan et al demonstrated that carrimycin treatment significantly inhibited the synthesis of viral RNA and viral proteins in multiple cell types infected by human coronavirus 229E, OC43, and SARS-CoV-2.[41]

Another potential application for inhibitors of ribosome biogenesis is in the treatment of autoimmune or acute inflammatory disorders. In these disorders, cytokine-producing cells of the immune system, most notably cluster of differentiation 4 (CD4+) helper T-cells and macrophages, are inappropriately reactive toward the somatic cells of the body. Much like virus-infected cells, inflammatory immune cells are burdened by increased protein production, which renders them reliant on high levels of ribosome production and sensitive to the inhibition of nucleolar rRNA synthesis. Almeida et al demonstrated that linezolid, a ribosomal-targeting antibiotic (RAbo), strongly inhibited T-cell effector functions *in vitro* by inhibiting cytokine production and blocking mitochondrial protein synthesis.[42]

In conclusion, repurposing carrimycin, or specifically the active ISP I component of carrimycin, as an anti-cancer, antiviral, or anti-inflammatory drug is an exciting area of research. Preliminary preclinical studies have demonstrated promise for the use of carrimycin as an anti-cancer agent. In this review, we have summarized these insights and have highlighted a number of additional areas that require investigation.

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Data availability statement

Data sharing is not applicable as no datasets were generated or analyzed in the current study. The data that support the findings of this study are available within the original articles cited throughout the article.

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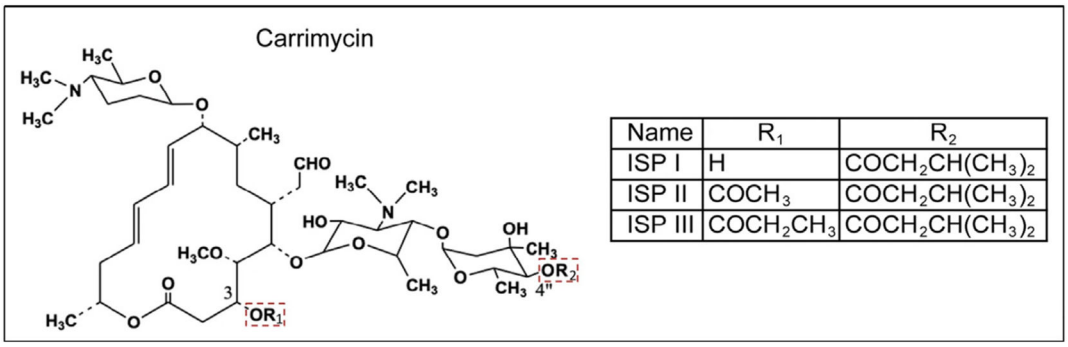
HIGHLIGHTS

- Carrimycin is a novel, first in-class anti-cancer agent.
- Carrimycin inhibits ribosomal biogenesis and radical scavenging.
- Carrimycin has been evaluated in preclinical cancer and clinical antiviral studies.



Name	R_1	R_2
ISP I	H	$COCH_2CH(CH_3)_2$
ISP II	$COCH_3$	$COCH_2CH(CH_3)_2$
ISP III	$COCH_2CH_3$	$COCH_2CH(CH_3)_2$

Figure 1.

Chemical structure of carrimycin and its main monomeric active components: isovalerylspiramycins (ISP) I, II, and III. Reprinted with permission.[24]

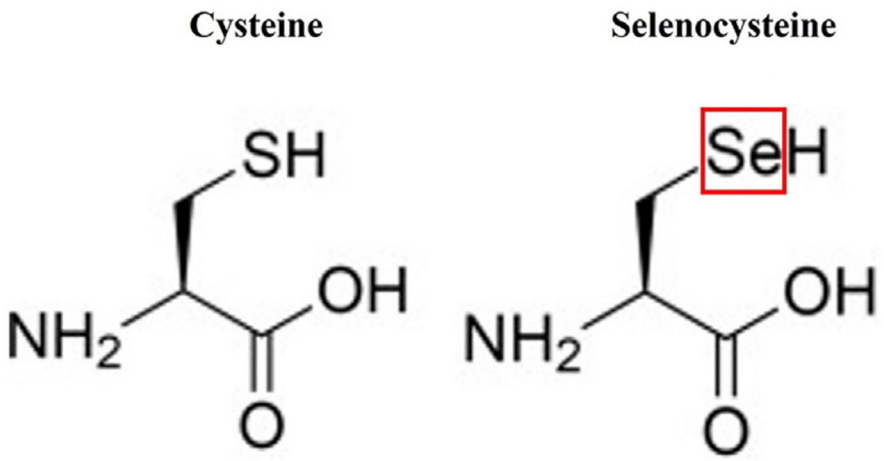


Figure 2.
Comparison of the cysteine and selenocysteine molecular structures. The replacement of sulfur by selenium is denoted by a red box.

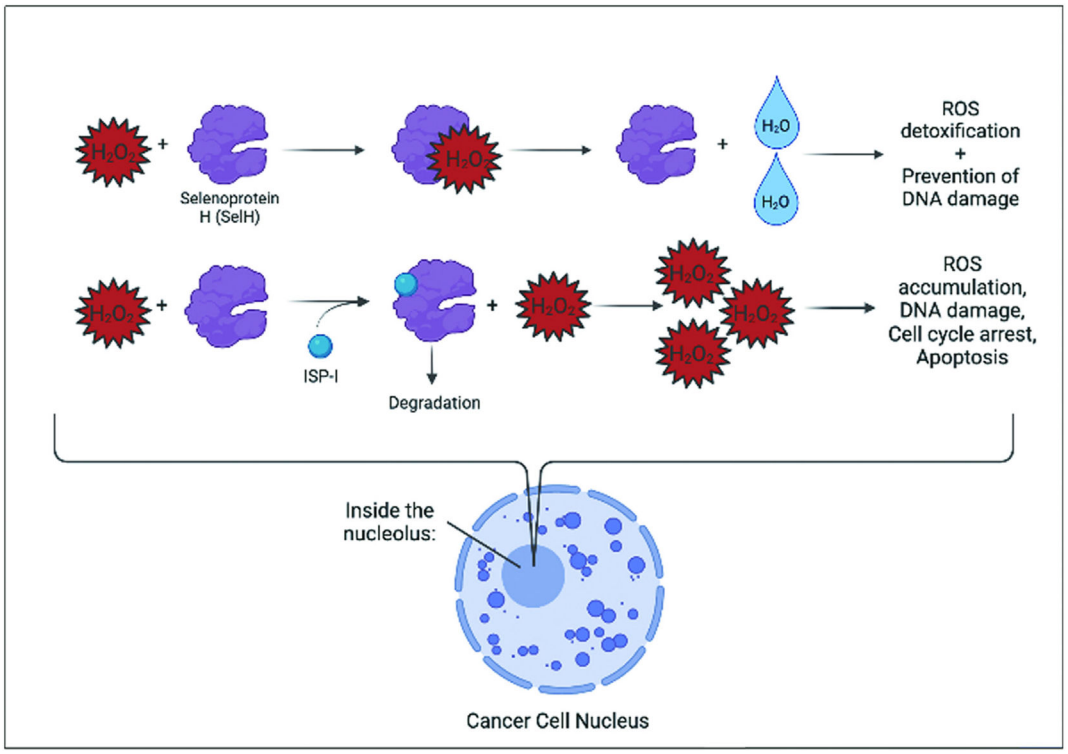


Figure 3.

Schematic depicting the oncogenic role of SelH as a ROS scavenger in the cancer cell nucleolus. SelH functions to prevent DNA damage (top row), and ROS accumulation due to ISP 1-mediated inhibition of SelH induces apoptosis (bottom row). ISP 1: Isovalerylspiramycins 1; SelH: Selenoprotein H; ROS: Reactive oxygen species.