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Selenium unmasks protective iron armor: A possible defense against cutaneous inflammation and cancer

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A B S T R A C T

Background: A link between selenium deficiency and inflammatory skin diseases have been noted by many, but this link is still not well understood. We have previously studied the efficacy of ceramide analogs, based on the fire ant venom Solenopsin A, against our psoriasis animal model. Treatment of animals with solenopsin analogs resulted in significantly improved skin as well as in a coordinate downregulation of selenoproteins, namely Glutathione Peroxidase 4 (GPX4). We thus hypothesize that ferroptosis may be a physiologic process that may protect the skin from both inflammatory and neoplastic processes.

Methods: We analyze and compare gene expression profiles in the GEO database from clinical skin samples taken from healthy patients and psoriasis patients (both involved and noninvolved skin lesions). We validated the gene expression results against a second, independent, cohort from the GEO database.

Results: Significant reduction in gene expression of GPX4, elevated expression of Nrf2 downstream targets, and expression profiles mirroring erastin-inhibition of Cystine/Glutamate Antiporter-System X_C activity in psoriatic skin lesions, compared to both noninvolved skin and healthy patient samples, suggest an innately inducible mechanism of ferroptosis.

Conclusions: We present data that may indicate selenoproteins, particularly GPX4, in resolving inflammation and skin cancer, including the novel hypothesis that the human organism may downregulate GPX4 and reactive oxygen (REDOX) regulating proteins in the skin as a way of resolving psoriasis and nonmelanoma skin cancer through increased reactive oxygen species. Further studies are needed to investigate ferroptosis as a possible physiologic mechanism for eliminating inflammatory and malignant tissues.

General significance: This study provides a fresh framework for understanding the seemingly contradictory effects of selenium supplementation. In addition, it offers a novel explanation of how physiologic upregulation of ferroptosis and downregulation of selenoprotein synthesis may mediate resolution of inflammation and carcinogenesis. This is of therapeutic significance.

1. Introduction

Psoriasis is a common inflammatory disorder that is specific to humans, and is associated with a number of systemic disorders, including coronary artery disease, obesity, nonalcoholic steatohepatitis, arthritis, and inflammatory bowel disease. Multiple cytokines have been implicated in the pathogenesis of psoriasis, including tumor necrosis factor alpha (TNFα), interleukins 17, 22, and 23, and vascular endothelial growth factor (VEGF). It is on the basis of these cytokines that cytokine-based therapies have been employed to treat psoriasis [1]. These novel drugs are often dramatically effective, but may lose efficacy over time, either due to formation of antibodies against these

Abbreviations: GPX4, Glutathione Peroxidase 4; System X_C, Cystine/Glutamate Antiporter-System X_C; TNFα, Tumor necrosis factor alpha; VEGF, Vascular endothelial growth factor; S1P, Sphingosine-1 phosphate; IL-22, Interleukin-22; Trx1, Thioredoxin; Txnrd1, Thioredoxin reductase1; GPX1, 2, 3, 5, Glutathione peroxidases 1, 2, 3, 5; GSR, Glutathione reductase; GPX8, Glutathione peroxidase 8; Nrf2, Nuclear factor (erythroid-derived 2-like 2; HMO1, Heme oxygenase (decycling 1); SOD2, Superoxide dismutase 2; SRXN1, Sulfiredoxin-1; NQ01, NAD(PH dehydrogenase quinone 1; GCLM, Glutamate-cysteine ligase regulatory subunit; H2AX, H2A histone family member X; Bcl-2, B-cell lymphoma 2; BAX, Bcl-2-like protein 4; BAK, Bcl-2 homologous antagonist/killer; BOK, Bcl-2 ovarian killer; TFRC or TFR1, Transferrin receptor 1; TFR2, Transferrin receptor 2; MTF1, Metal regulatory transcription factor 1; SP-1, Specificity protein 1; GRX3, Glutaredoxin 3; CP, Ceruloplasmin; ATF4, Activating transcription factor 4; CHAC1, ChaC Glutathione Specific Gamma-Glutamylcyclotransferase 1; INFγ, Interferon gamma; CsA, Cyclosporine A; Nrarp, Notch related Ankyrin related protein; COX2, Cyclooxygenase 2; NFKBIZ, IkBζ; SASP, Senescence associated secretory phenomenon

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reagents, or adaptation to different signaling pathways and cytokines [2,3]. Selenoproteins may play a role in resolving inflammation and skin cancer.

1.1. History of selenium in dermatology

Topical selenium sulfide was shown to have activity in psoriasis that was resistant to corticosteroids [4,5]. The form that was used, Selsun, was initially developed as a shampoo for Pityrosporum folliculitis, but appeared to be effective in selected cases of psoriasis. It is not known why this treatment is not widely used today, nor the metabolism of topical selenium sulfide. Unresolved questions include how much selenium penetrates the stratum corneum, and the metabolic fate of the topical selenium.

In an early study, levels of erythrocyte glutathione peroxidase, a selenoprotein, were found to be low in patients with psoriasis and other inflammatory conditions. The authors of the study administered tablets containing sodium selenite and tocopherol succinate, and noted a slow increase in glutathione peroxidase after 6 weeks. Some clinical benefit was noted. [6] Balneotherapy and oral ingestion of selenium-rich spa water (selenate 70/ig/l, and selenite 1/ig/l), resulted in a decreased PASI score of 47%. Plasma selenium levels were elevated as a result of selenium exposure, but levels of soluble CD25 did not change [7]. Defects in the absorption of selenomethionine from the gut of psoriatic and atopic dermatitis patients did not differ significantly from controls' [8]. Other studies showed no difference in selenium levels in patients with psoriasis compared with normal controls [9]. In short, the connection between selenium and psoriasis is unclear, with poor understanding of the absorption, handling of inorganic vs organic selenium, and transport of active selenium moieties to the skin. Perhaps additional methods of introducing selenium to the skin are warranted, and selenium has been conjugated to nucleosides, which may facilitate uptake [10].

Many known inflammatory and pre-neoplastic disorders are associated with impaired barrier function. [11–18] These include psoriasis, atopic dermatitis and actinic keratosis, the most common precursor to cutaneous squamous cell carcinoma [19,20]. Emollients are employed in the treatment of inflammatory disorders, and application of sunscreen has been shown to cause regression of actinic keratosis [21]. This likely involves barrier restoration in part, as protection of the elderly from sunlight is unlikely by itself to revert lesions that have taken decades to develop. It also proves that actinic keratosis formation is a reversible event, unlike typical cutaneous squamous cell carcinoma, which does not regress in the presence of emollients.

Ceramides are a family of lipids that are integral to cutaneous barrier function [22]. Once thought as inert fats, they have more recently been discovered to be biologically active molecules that have differing activities based upon the length of the fatty acid chains [4,23–25]. Ceramides are regulated both at the point of synthesis and degradation, and one of the major pathways of ceramide regulation is conversion to sphingosine-1 phosphate (S1P), a ligand that mediates pro-inflammatory and pro-neoplastic activities through a family of G protein based receptors [26]. Ceramide supplementation may correct ceramide deficiency, but can run the risk of being converted to S1P by enzymatic action. While impaired expression of barrier proteins such as filaggrin and claudins also play a major role in skin disorders, we would like to focus on deficiencies in ceramides [27–29], which have been found in human skin diseases [30] and murine knockouts of ceramide synthesis display cutaneous inflammation and alopecia [31,32]. We circumvented the problem of conversion of ceramide to S1P by the fortuitous discovery that solenopsin, the alkaloidal component of ant venom, acts biochemically similar to ceramide without being able to be converted to S1P [33]. Treatment of animals with solenopsin analogs resulted in a coordinate downregulation of selenoproteins and of the glutathione peroxidase family, and manganese superoxide dismutase, and especially downregulation of interleukin-22 (IL-22), a cytokine which is upregulated in both psoriasis and cutaneous squamous cell carcinoma [34–36]. The downregulation of these proteins are associated with ferroptosis (Fig. 1), with glutathione peroxidase 4 (GPX4) as an established master regulator. [37–40] Ceramides and solenopsin may act physiologically to coordinately reduce selenoproteins such as glutathione peroxidases and thus increase reactive oxygen (Table 1). We thus hypothesize that ferroptosis may be a physiologic process that may protect the skin from both inflammatory and neoplastic processes and looked toward clinical observations for clues.

A list of genes significantly downregulated by Solenospin S14 in mouse psoriasis model, which includes selenoprotein Gpx4.

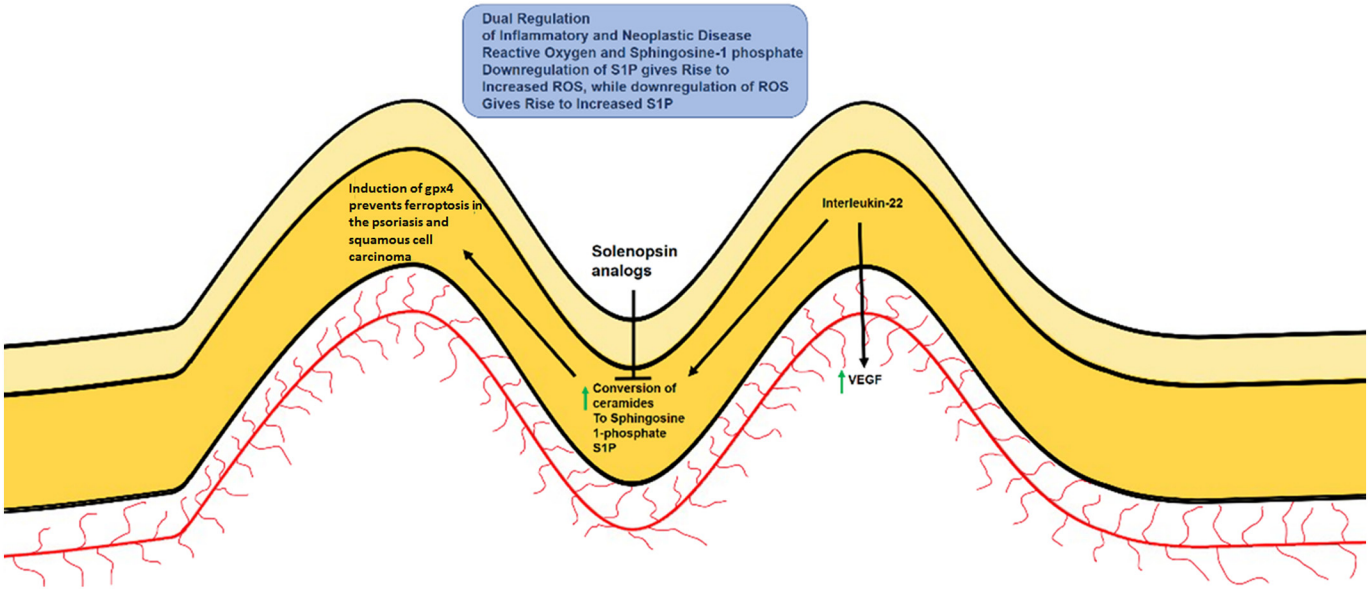

Fig. 1. Proposed Physiologic Ferroptosis in Psoriasis and SCC.
We hypothesize the concept of physiologic ferroptosis as a mechanistic target that may be induced by ceramide analogs, such as solenopsin derivatives, which suppress GPX4 expression is psoriatic lesions in mouse models. We believe that further suppression of GPX4 expression seen in clinical settings may play a role to resolving skin disorders.