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

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Abstract

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

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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 (TNF α), 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 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 Solenopsin S14 in mouse psoriasis model, which includes selenoprotein Gpx4.

2. Materials and methods

2.1. Retroactive psoriatic patient gene expression study

Data from gene expression data sets were analyzed from the Gene Expression Omnibus (GEO) database. For studies related to psoriasis, raw values from data GDS4602 (Ref GSE13355). (<https://www.ncbi.nlm.nih.gov/sites/GDSbrowser?acc=GDS4602>) [41] (shown) was analyzed and findings then validated on another data set GDS3539 (Ref GSE14905). The methods for collection of patient samples for human microarray data was previously described. Briefly, 58 psoriasis patients and 64 healthy control subjects recruited from Detroit, Michigan and surrounding areas. Patients were without systemic anti-psoriatic treatments for 2 weeks prior to biopsy, and without topical treatments 1 week prior to biopsy. In control subjects, biopsies were taken from the buttocks or upper thighs. Affymetrix Human Genome U133 Plus 2.0 Array,

The above data was validated against a second cohort from the Gene Expression Omnibus (GEO) database (Ref GSE14905) (<https://www.ncbi.nlm.nih.gov/sites/GDSbrowser?acc=GDS3539>) [42] (not shown). These data provided samples from healthy patient controls, as well as non-involved healthy skin and psoriatic lesions from the same patients. Using Affymetrix HGU133 Plus arrays, 54 total subjects donating skin biopsy samples from 21 healthy donors, 56 skin biopsy samples from 28 psoriasis patients who had match lesional and uninvolved tissue with 5 samples from psoriasis patients only providing lesional skin biopsies.

<https://www.ncbi.nlm.nih.gov/geo/info/disclaimer.html>

2.2. Retroactive $\text{INF}\gamma$ effect on psoriatic patient gene expression study

Data from gene expression data set GDS4607 (Ref GSE32407) (<https://www.ncbi.nlm.nih.gov/sites/GDSbrowser?acc=GDS4607>) [43] were analyzed from the Gene Expression Omnibus (GEO) database. Briefly, RNA isolation was performed on skin punch biopsies from healthy or non-lesional psoriasis patients at baseline or 24 h after placebo or $\text{INF}\gamma$ injection. For studies related to psoriasis, raw values from data. <https://www.ncbi.nlm.nih.gov/geo/info/disclaimer.html>

2.3. Statistical analysis

Statistical Analysis was performed using PRISM 6 GraphPad on raw values obtained from the Gene Expression Omnibus (GEO) database. Values were assessed for normal distribution. Normally distributed data were analyzed using one-way ANOVA, with graphs representing mean of individual patient gene expression values and error bars indicating $\pm$ SEM. Significance threshold was set to $p < 0.05$. Skewed data were analyzed using the non-parametric Kruskal-Wallis Test, with graphs representing the median individual patient gene expression values and error bars indicating $\pm$ interquartile range. Significance threshold was set to $p < 0.05$.

3. Results

3.1. Psoriatic skin lesions show reduced GPX4 gene expression

To assess for the possibility of ferroptosis, we first looked at GPX4 gene expression in the skin. A retroactive analysis of psoriasis patient samples indicated significant natural downregulation of GPX4 within psoriatic lesions when compared to non-involved skin or healthy patient controls (Fig. 2). These findings, which were validated in a second patient cohort, also showed what appears to be compensatory upregulation of other selenoproteins including, thioredoxin reductase1 (Txnrd1), and glutathione peroxidases 1, 2, 3, (GPX1, 2, 3), as well as, related proteins: thioredoxin (Trx1) and glutathione peroxidase 5 (GPX5) (Fig. 3). Interestingly, glutathione reductase (GSR) and glutathione peroxidase 8 (GPX8) were the only other proteins observed to be downregulated.

3.2. Upregulation of Nrf2 downstream targets observed in psoriatic skin lesions

Given that ferroptosis is defined as non-apoptotic cell death by lipid peroxidation. We then looked for signs of increased oxidative stress in the absences of apoptosis. We saw

significantly elevated expression of downstream targets of nuclear factor (erythroid-derived 2)-like 2 (Nrf2) such as heme oxygenase (decycling) 1 (HMO1), superoxide dismutase 2 (SOD2), sulfiredoxin-1 (SRXN1), NAD(P)H dehydrogenase quinone 1 (NQO1) and glutamate-cysteine ligase regulatory subunit (GCLM). While not conclusive, the increased antioxidant response through Nrf2 activation suggested oxidative stress possibly linked to low GPX4 expression (Fig. 4).

We also observed signs of double stranded DNA repair through significant upregulation of H2A histone family member X (H2AX), [44] and looked further to see if relevant apoptotic pathways were activated (Fig. 5). Consequently, upregulation of proapoptotic B-cell lymphoma 2 (Bcl-2) family proteins were noticed, included Bcl-2-like protein 4 (BAX), Bcl-2 homologous antagonist/killer (BAK), Bcl-2 ovarian killer (BOK) suggesting apoptosis [45]. However, significant downregulation of MIR24–2, an essential mediator of H2AX/Bcl-2 apoptotic pathway, was also observed. [46,47]

3.3. Gene expression in psoriatic skin lesions suggest an increased cellular import of iron

To investigate further if ferroptosis was plausible, we looked for indications linking the increased oxidative stress to intracellular iron levels. We looked at gene expressions of transferrins (TFRC or TFR1) and TFR2, which are known to import iron into the cell [48]. The data showed significant increases in expression of both genes, pointing to an innate effort to increase intracellular iron (Fig. 6).

We followed up in determining if increased transferrin expression led to an increase in intracellular iron by looking at genes inducible by elevated iron presence or inducible by iron deficiency. We saw significant increases in metal regulatory transcription factor 1 (MTF1) in agreement with elevated intracellular metal concentration, perhaps iron. [49,50] We also saw significant reduction in expression of specificity protein 1 (SP-1), which has been observed to increase in iron deficient conditions. [51] Interestingly glutaredoxin 3 (GRX3), known to be involved in intracellular iron sensing, [52] was also significantly upregulated. As expected, ceruloplasmin (CP), a ferroxidase and the human homologue to the yeast Fret3 downstream of GRX3, [53] was suppressed.

3.4. Psoriatic skin gene expression mirror erastm-induced ferroptosis, via Cystine/ Glutamate Antiporter-System X_C inhibition

Finally, we wanted to determine if events in psoriasis mirror known ferroptosis inducers with characterized mechanisms. We looked at previously described pharmacological mediators of ferroptosis, namely Erastin, RSL3, sorafenib, DPI, and FIN56 [54]. We found that psoriatic skin lesions displayed a gene expression pattern that mimicked erastin-induced inhibition of Cystine/Glutamate Antiporter-System X_C (System X_C) (Fig. 7). Similar to erastin treatment, we observed upregulation of System X_C subunits, namely SLC7A11 and SLC3A2, which has previously been attributed as a likely compensatory response to erastin. [55] Looking downstream of System X_C, we observed significant upregulation of Activating transcription factor 4 (ATF4) and ChaC Glutathione Specific Gamma-Glutamylcyclotransferase 1 (CHAC1) in agreement with an erastin-liked induced inhibition of System X_C. [55–57]

4. Discussion

The possibility of physiologic ferroptosis, or a protective iron armor of the skin hints at a refined physiological ability to regulate specific antioxidant expression. We point to a nuanced understanding of skin biology, where ferroptosis may be a way of resolving cutaneous inflammation and malignancy with some effective treatments acting in part by further suppressing gpx4 expression in the skin, as suggested by interferon gamma (INF γ) treatment (Fig. 8). We think that this hypothesis may explain several known phenomena in the skin, including: 1) Partial resolution of actinic keratosis and inflammatory conditions by emollients 2) Increased risk of cutaneous squamous cell carcinoma in transplant patients on cyclosporine A (CsA) 3) Presence of inactivating Notch mutations in cutaneous squamous cell carcinoma, and 4) Partial response of psoriasis to biologic therapies.

1) Partial resolution of inflammatory and premalignant conditions by emollients

It is well established that both premalignancy and inflammatory processes are associated with impaired barrier function. We have previously shown that cutaneous barrier disruption results in upregulation of vascular endothelial growth factor (VEGF), a common factor in both psoriasis and squamous cell carcinoma [11,58]. Barrier disruption can be caused by chemical removal of ceramides, which may occur through water and detergent exposure, xerosis of aging, which may be due to loss of ceramide synthesis or increased degradation, and immunological disruption of cutaneous architecture, resulting in an impaired barrier function. Emollients are beneficial in the treatment of psoriasis, although they rarely induce complete remission [22,24,33,59]. A previous study also showed that use of sunscreen caused regression of actinic keratosis [21]. Sunscreens have emollient properties, and it is highly likely that partial barrier restoration results in decreased vascular endothelial growth factor and other cytokines [60]. The rapid response to sunscreens suggests an emollient effect over sun protection, as actinic keratosis may take decades to develop, and the protection from a few months of sun is probably insufficient to reverse decades of mutagenesis. However, abnormalities persist in both chronically sun damaged skin without clinically evident actinic keratosis, just as they do with uninvolved skin in psoriasis patients. These clinically unaffected areas are primed to undergo inflammatory or premalignant transformation, and restoration of ceramide signaling may aid in doing so.

2) Increased risk of cutaneous squamous cell carcinoma in transplant patients on cyclosporine A (CsA)

Cyclosporine immunosuppression is associated with a high rate of cutaneous squamous cell carcinoma, at an incidence higher than immunosuppression with other agents such as sirolimus and tacrolimus [61,62]. Squamous cell carcinoma of the skin is a leading cause of death in transplant recipients. The increased rate of skin cancer has been attributed to decreased immunosurveillance, but other highly immunosuppressive agents do not have the same increased rate of squamous cell carcinoma. Thus, other factors must account for the high rate of

squamous cell carcinogenesis in patients with cyclosporine. CsA is a molecule with a dual function [36]. It inhibits NFAT mediated transcription, which is the basis of its anti-inflammatory properties. In addition, it binds and inhibits the function of mitochondrial cyclophilin D. CsA protects cells from mitochondrial stability and reactive oxygen stress, preventing apoptosis [63]. Therefore, physiologic ferroptosis, which involves destruction of aberrant mutated keratinocytes with physiologic reactive oxygen, is compromised by CsA, and thus directly antagonizes the beneficial effects of ceramides.

3) Presence of inactivating Notch mutations in cutaneous squamous cell carcinoma

We have previously discovered that Notch signaling is a major signaling pathway induced by reactive oxygen signaling. In fact, the gene that is most highly downregulated in our studies of NADPH oxidase inhibitors is Notch related Ankyrin related protein (Nrarp) [64]. Tumors that use reactive oxygen signaling invariably upregulate notch signaling as well. However, the most common mutation in cutaneous squamous cell carcinoma after p53 are missense mutations in Notch, which inactivate its function. Melanoma, which is predominantly wild type p53, and uses Notch and reactive oxygen signaling to avoid apoptosis, is far more resistant to oxidative stress [65]. These findings further confirm the role of physiologic ferroptosis in maintaining skin homeostasis.

4) Partial response of psoriasis to biologic therapies

Use of biologic therapies has revolutionized the treatment of severe psoriasis. Initially beginning with targeting TNF α , more recent therapies have targeted IL-17 and IL-23. However, some patients do not fully respond or relapse to these therapies. Aside from immunity to these exogenous proteins, it is likely that psoriasis changes signaling pathways in response to therapies. It is instructive to look at signaling in psoriasis and cutaneous neoplasia as a combination of two distinct signaling pathways with crosstalk. One is a NADPH-superoxide-canonical NF κ B signaling pathway, which can be activated by TNF α and other cytokines. The second is a ceramide-sphingosine-1 phosphate pathway resulting in activation of S1P receptors and stimulation of pro-inflammatory factors such as cyclooxygenase 2 (COX2). It is likely that the majority of pro-inflammatory factors credited to ceramides may result from conversion to pro-inflammatory S1P [66]. A potential candidate mediator of this crosstalk is I κ B ζ (NFKBIZ). The reasons for this is that first, I κ B ζ is overexpressed in psoriasis, and modulates NF κ B signaling [67,68]. Second, I κ B ζ regulates secretion of IL-22 and is required for IL-17 mediated psoriasis [69]. Finally, psoriasis exhibits some characteristics of the senescence associated secretory phenomenon (SASP) as result, in part, of prolonged TNF α presence [70], in which senescent cells are not eliminated, but are present and contribute to the inflammatory milieu. A recent study has shown that NFKBIZ is required for the maintenance of the SASP phenotype, which has significantly elevated levels in psoriatic lesions

(Fig. 9), and small molecules which downregulate NFKBIZ inhibit SASP [71,72].

There is likely feedback between these mechanisms, so when one is inhibited, the other is activated. Mechanistically, one could predict that selenium supplementation would lead to an increase in the selenoproteins involved in selenoprotein-mediated reductive activity, followed by an increase in glutathione levels [73], which would inhibit the reactive species produced as a result of TNF α stimulation. This would lead to decreased signaling through NF κ B, as reactive oxygen oxidizes I κ B [74], and blockade of I κ B oxidation would be predicted to result in decreased NF κ B signaling. Reactive oxygen also oxidizes tyrosine phosphatases which have free sulfhydryl groups that are susceptible to oxidation [75]. In our model, we predict that ceramides, normal components of the skin, may increase reactive oxygen without activating NF κ B, resulting in ferroptosis and therapeutic benefit. Psoriasis contains a balance of these two factors, with the proportion of signaling dependent on the genetic basis of the psoriasis as well as the current treatment. Since cutaneous squamous cell carcinoma is inhibited by reactive oxygen, it is likely to be ceramide-SIP predominant.

5. Conclusion

We provide data from the field of dermatology that selenium plays an important role on skin homeostasis, spurred by findings from our studies on stable ceramide analogs that propose a more nuanced view of selenium and anti-oxidants in the skin. Having found that these stable ceramide analogs cause a downregulation of selenoproteins in affected skin, and downregulation of GPX4 promotes a novel form of iron dependent death, called ferroptosis. We thus proposed that ferroptosis is a physiological mechanism that can be used to resolve both inflammatory and neoplastic disorders of the skin. We show that gene expression patterns in psoriatic skin lesions are in alignment with erastin mediated ferroptosis, via System X_C inhibition. Further studies are needed to validate these findings and improve our understanding on selenoprotein regulation in the skin. We now hypothesize that improving effective treatments for resolving cutaneous inflammation and malignancy may be achieved by promoting the skin's innate response toward ferroptosis.

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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
NQO1	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	I κ B ζ
SASP	Senescence associated secretory phenomenon

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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.

Fig. 2.

Lower GPX4 expression in Psoriatic Lesions.

Significantly reduced GPX4 expression in clinical samples suggesting physiologic ferroptosis. Data from GEO data set GDS4602 [41] comparing healthy patients (n = 64) to Psoriasis Patients with samples from nonlesional healthy skin (n = 58) and psoriatic skin (n = 58). Statistical Analysis: Normal distribution, ANOVA test with bars indicating mean raw values, $\pm$ SEM. **** and #### indicating $p < 0.0001$; and ns as $p > 0.05$.

Fig. 3.

Expression of Selenoproteins and related family proteins in Psoriatic Lesions.

Expression levels of major selenoproteins thioredoxin reductase1 (Txnrd1), and glutathione peroxidases 1, 2, 3, (GPX1, 2, 3), as well as, related proteins: thioredoxin (Trx1) and glutathione peroxidase 5 (GPX5) in healthy and psoriatic skin. Data from GEO data set GDS4602 comparing healthy patients (n = 64) to Psoriasis Patients with samples from nonlesional healthy skin (n = 58) and psoriatic skin (n = 58). Statistical Analysis: Normal distribution, ANOVA test with bars indicating mean raw values, $\pm$ SEM. **** and #### indicating $p < 0.0001$; *** or ### $p < 0.001$, * or # $p < 0.05$ and ns as $p > 0.05$.

Fig. 4.
Evidence of Nrf2 Activation and Elevated Expression of Downstream Targets in Psoriatic Lesions.

Significantly increased expression levels of downstream targets of Nrf2 suggesting oxidative stress in clinical samples from physiologic ferroptosis. Data from GEO data set GDS4602 comparing healthy patients (n = 64) to Psoriasis Patients with samples from nonlesional healthy skin (n = 58) and psoriatic skin (n = 58). Statistical Analysis: Normal distribution, ANOVA test with bars indicating mean raw values, $\pm$ SEM or nonparametric Kruskal-Wallis test with bars indicating median raw values, $\pm$ interquartile range. **** and ##### indicating $p < 0.0001$; *** or ### $p < 0.001$, * or # $p < 0.05$ and ns as $p > 0.05$.

Fig. 5.

Gene Expression Suggesting Halting of H2AX/Bcl-2 Apoptosis in Psoriatic Lesions.

Significant upregulation of H2A histone family member X (H2AX), proapoptotic B-cell lymphoma 2 (Bcl-2), Bcl-2-like protein 4 (BAX), Bcl-2 homologous antagonist/killer (BAK), and Bcl-2 ovarian killer (BOK) suggesting apoptosis likely halted by significant downregulation of MIR24-2, an essential mediator of H2AX/Bcl-2 apoptotic pathway. Data from GEO data set GDS4602 comparing healthy patients (n = 64) to Psoriasis Patients with samples from nonlesional healthy skin (n = 58) and psoriatic skin (n = 58). Statistical Analysis: nonparametric Kruskal-Wallis test with bars indicating median raw values, $\pm$ interquartile range. **** and ### indicating $p < 0.0001$; *** or ### $p < 0.001$, * or # $p < 0.05$ and ns as $p > 0.05$.

Fig. 6.

Gene Expression Suggesting Increase in Intracellular Iron in Psoriatic Lesions.

Significant changes in gene expression of transferrins (TFRC or TFR1) and TFR2, metal regulatory transcription factor 1 (MTF1), specificity protein 1 (SP-1), glutaredoxin 3 (GRX3), and ceruloplasmin (CP), involved cellular iron sensing suggest increases in intracellular iron in psoriatic skin. Data from GEO data set GDS4602 comparing healthy patients (n = 64) to Psoriasis Patients with samples from nonlesional healthy skin (n = 58) and psoriatic skin (n = 58). Statistical Analysis: Normal distribution, ANOVA test with bars indicating mean raw values, $\pm$ SEM. or nonparametric Kruskal-Wallis test with bars indicating median raw values, $\pm$ interquartile range. **** and ##### indicating $p < 0.0001$; *** or ### $p < 0.001$, * or # $p < 0.05$ and ns as $p > 0.05$.

Fig. 7.

Gene Expression in Psoriatic Skin lesions mirror Erastin-like System XC inhibition. Psoriatic lesions show gene expression pattern similar to erastin-like System XC inhibition. SLC7A11 and SLC3A2, were upregulated as compensatory response to similar erastin. Significant upregulation of Activating transcription factor 4 (ATF4), and ChaC Glutathione Specific Gamma-Glutamylcyclotransferase 1 (CHAC1) was also in agreement with an erastin-like induced inhibition of System XC, the mechanism of erastin-mediated ferroptosis. Data from GEO data set GDS4602 comparing healthy patients (n = 64) to Psoriasis Patients with samples from nonlesional healthy skin (n = 58) and psoriatic skin (n = 58). Statistical Analysis: nonparametric Kruskal-Wallis test with bars indicating median raw values, $\pm$ interquartile range. $\pm$ SEM. **** and ##### indicating $p < 0.0001$; *** or ### $p < 0.001$, * or # $p < 0.05$ and ns as $p > 0.05$.

Fig. 8.

INF γ suppresses GPX4 expression in Healthy skin and Psoriatic Lesions. Significantly reduced GPX4 expression in clinical samples from INF γ treated patients suggesting effective therapies such as cytokine-based therapies may act in part by physiologic ferroptosis. Data from GEO data set GDS4607 comparing healthy patients (n = 10) to Psoriasis Patients with samples from nonlesional healthy skin (n = 10) and psoriatic skin (n = 10). Statistical Analysis: non-parametric Kruskal-Wallis test with bars indicating median raw values, $\pm$ interquartile range. **** and ##### indicating $p < 0.0001$; *** or ### $p < 0.001$, * or # $p < 0.05$ and ns as $p > 0.05$.

Fig. 9.

Elevated NFKBIZ expression in Psoriatic Lesions.

Significantly elevated expression NFKBIZ, a modulator of NFKB, in clinical samples linking psoriasis with senescence associated secretory phenomenon (SASP). Data from GEO data set GDS4602 comparing healthy patients (n = 64) to Psoriasis Patients with samples from nonlesional healthy skin (n = 58) and psoriatic skin (n = 58). Statistical Analysis: Normal distribution, ANOVA test with bars indicating mean raw values, $\pm$ SEM. **** and #### indicating $p < 0.0001$; *** or ### $p < 0.001$, * or # $p < 0.05$ and ns as $p > 0.05$.

Table 1

Ceramide/Solenopsin analog S14 significantly affects gene expression in psoriasis mouse model.

Gene Symbol	gene_assignment	p-Value (S14 vs Control)	Fold-change (S1 4 vs Control)	Fold-change (S14 vs Control) (Description)
Gpx4	AK006441 // Gpx4 // glutathione peroxidase 4 // 10 C1110 39.72 cM // 625249 /// AK14577	0.0390953	-1.32133	S14 down vs Control
Txn2	AK002358 // Txn2 // thioredoxin 2 // 15 E1115 // 56551 /// AK010917 // Txn2 // thioredo	0.0467511	-1.23982	S14 down vs Control
Txndc17	AK004219 // Txndc17 // thioredoxin domain containing 17 // 11 B4111 43.92 cM // 52700 /	0.00314214	-1.26646	S14 down vs Control
Txndc15	AK009878 // Txndc15 // thioredoxin domain containing 15 // 13 B113 // 69672 /// AK2137	0.00931008	-1.31232	S14 down vs Control
Sod2	AK002428 // Sod2 // superoxide dismutase 2, mitochondrial // 17 A1117 8.75 cM // 20656	0.0150224	-1.33109	S14 down vs Control
Txndc12	AY548113 // Txndc12 // thioredoxin domain containing 12 (endoplasmic reticulum) // 4 C7	0.0307994	-1.34924	S14 down vs Control
Sod1	BC057074 // Sod1 // superoxide dismutase 1, soluble // 16 B5-C3116 51.56 cM // 20655 //	0.000836736	-1.42394	S14 down vs Control
Bvrb	AK153153 // Bvrb // biliverdin reductase B (flavin reductase (NADPH)) // 7 A317 // 233	0.0179024	-1.47698	S14 down vs Control
Gpx1	AK002245 // Gpx1 // glutathione peroxidase 1 // 9 F119 59.24 cM // 14775 /// AK010999 /	0.00951611	-1.60769	S14 down vs Control