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Role of TRIM Proteins in Inflammatory Skin Diseases

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ABSTRACT

Background: Despite the advance in treatment modalities of wide range inflammatory skin diseases, tripartite motif-containing (TRIM) proteins are expected to become a potential therapeutic target for prevention and treatment of dermatological disorders.
Objective: Studying the role of TRIM proteins in inflammatory skin diseases.
Material and Methods: We searched the PubMed and Google scholar databases for relevant studies that evaluated the expression of TRIM proteins in inflammatory skin diseases.
Study Selection: All the studies were independently assessed for inclusion. They were included if they fulfilled the following criteria: published in English language, published in peer-reviewed journals, focused on the role of TRIM proteins in inflammatory skin diseases. The initial search presented 30 articles of which 8 met the inclusion criteria. The articles studied the effect of role of TRIM proteins in inflammatory skin diseases.
Data Synthesis: Comparisons were made by structured review with the results tabulated.
Conclusion: We concluded that TRIM proteins play an important role in inflammatory skin diseases development, prognosis and treatment.
Keywords: Tripartite motif proteins, TRIM proteins, Inflammatory Skin diseases, Psoriasis, Atopic dermatitis.

INTRODUCTION

The skin is the largest organ of the human body and builds a barrier to protect from the harmful environment and from loss of water. Disturbed barrier allows the entry of substances into the skin that are immunologically reactive, which lead to inflammatory processes in the skin. In many common inflammatory skin diseases, a defect in the formation of the skin barrier is observed, and cytokine composition within the skin is different compared to normal human skin [(1)]. Inflammatory skin diseases are frequently chronic skin conditions affecting many people at all stages of life [(2)].

Due to their impact and complexity, they represent a major challenge of modern medicine. Dermatology textbooks describe more than 100 different inflammatory skin diseases based on clinical phenotype and histological architecture. Combining the enormous advances made in lymphocyte immunology and molecular genetics with clinical and histological phenotyping reveals six immune response patterns of the skin, which are the lichenoid pattern, the eczematous, the bullous pattern, the psoriatic pattern, fibrogenic pattern and the granulomatous pattern [(3)].

Multiple studies showed that TRIM family proteins play a significant role in a variety of cellular processes, including immunity, transcriptional regulation, inflammation, cell cycle progression, and apoptosis [(4)].

This study aimed to evaluate the role of TRIM proteins in inflammatory skin diseases.

Data Extraction:

If the studies did not fulfill the inclusion criteria, they were excluded such as studies on TRIM protiens in systemic diseases or skin diseases other than inflammatory, report without peer-review, not within national research program or letters/comments/editorials/news.
The analyzed publications were evaluated according to evidence-based medicine (EBM) criteria using the classification of the U.S. Preventive services Task Force & UK National Health Service protocol for EBM in addition to the Evidence Pyramid.

U.S. Preventive services Task Force:

- Level I: Evidence obtained from at least one properly designed randomized controlled trial.
- Level II-1: Evidence obtained from well-designed controlled trails without randomization.
- Level II-2: Evidence obtained from well-designed cohort or case-control analytic studies preferably from more than one center or research group.
- Level II-3: Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence.
- Level III: Opinions of respected authorities, based on clinical experiences, descriptive studies, or reports of expert committees.

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Study quality assessment included whether ethical approval was gained, eligibility criteria specified, appropriate controls, adequate information and defined assessment measures.

Quality Assessment

The quality of all the studies was assessed. Important factors included study design, attainment of ethical approval, evidence of a power calculation, specified eligibility criteria, appropriate controls, adequate information and specified assessment measures. It was expected that confounding factors would be reported and controlled for appropriate data analysis made in addition to an explanation of missing data.

Findings: In total 8 potentially relevant publications were included, there was an association between inflammatory skin diseases and TRIM proteins. This association was because TRIM proteins play role in inflammatory process of skin.

MATERIALS AND METHODS

This review was established using a prospective protocol. It was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [(5)].

Eligibility criteria:

We evaluated all studies that assessed expression of TRIM proteins in inflammatory skin diseases. We also included studies compared their expressions in association with the clinico-pathological features. We did not restrict the search by date or publication status. During December 2020, we searched PubMed and Google Scholar using the MeSH terms: Tripartite motif proteins, TRIM proteins, skin, inflammatory skin diseases, psoriasis and atopic dermatitis. We also browsed reference lists. Different methods of assessment were included, where we also browsed reference lists. Different methods of assessment were included, where Immunohistochemistry (IHC) was performed in some studies and quantitative real time-polymerase chain reaction (qRT-PCR) was reported in other studies. In addition, immunepercepition, immuneblotting, genotyping and cell culture from which data was obtained.

Search Strategy

We reviewed papers on the relation between TRIM proteins & inflammatory skin diseases from Medline databases, which are Pub Med, Medscape, and Science Direct. In addition, materials available in the internet from 2000 to 2020. We used inflammatory skin diseases, TRIM proteins, as searching terms.

Data Synthesis

A structured systematic review was performed with the results tabulated.

RESULTS

In total 30 potentially relevant publications were identified, 22 articles were excluded as they did not meet our inclusion criteria. A total of 8 studies were included in the review as they were deemed eligible by fulfilling the inclusion criteria.

These studies examined the role of TRIM proteins in inflammatory skin diseases. The studies were analyzed with respect to the study design using the classification of the U.S. Preventive Services Task Force & UK National Health Service protocol for EBM (evidence-based medicine).

The role of TRIM proteins in inflammatory skin diseases according to evidence base medicine was investigated in 8 studies (Tables 1 and 2).

Table (1): Studies investigating the role of TRIM proteins in inflammatory skin diseases

Study	Type	Level of EBM
Fiorentino *et al.* [(6)]	Systematic review and meta analysis	Level II -2
Fujimoto *et al.* [(7)]	Analytic study	Level II-3
Liu *et al.* [(8)]	Both experimental and case control study	Level II-3
Yucesoy *et al.* [(9)]	Case control prospective study	Level II-3
Yang *et al.* [(10)]	Analytic study	Level II-3
Tocchini & Ciosk [(11)]	Systematic review	Level II-2
Yang *et al.* [(12)]	Analytic study	Level II-3
Yang *et al.* [(13)]	Systematic review	Level II-2

Table (2): Studies investigating the role of TRIM proteins in inflammatory skin diseases

Study	Type	Technique	Result	Conclusions
Fujimoto *et al.* [6]	Systematic review and meta analysis	-		Anti-TIF1 autoantibodies are closely associated with juvenile dermatomyositis and adult cancer-associated dermatomyositis, both of which tend to present extensive inflammatory skin disease and relatively mild muscle disease Both in adults and children, patients with TIF1 autoantibodies have more extensive skin involvement.
Fiorentino *et al.* [7]	Analytic study	Immunoprecipitation /blot assay to detect anti–TIF-1γ antibodies in plasma	Patients with high TIF-1 autoantibodies were characterized by several significant cutaneous findings	Patients with TIF-1 autoantibodies had some characteristic findings including palmar hyperkeratotic papules, psoriasis-like lesions and a novel finding of hypopigmented and telangiectatic patches
Yucesoy *et al.* [9]	Case control prospective study	Genotyping and genomic DNA analysis	TRIM10 was expressed in patients with irritant contact dermatitis	TRIM10 associates with the major histocompatibility complex class I (MHCI) which is linked to skin irritation
Yang *et al.* [10]	Analytic study	PCR, immunoblotting, immunoprecipitation and immunofluorescence .	Knocking down Trim21 expression alleviated keratinocyte inflammation	(Trim21) is implicated in the inflammatory response, Its expression is upregulated in psoriatic skin
Tocchini & Ciosk [11]	Systematic review article			TRIM32 has been found at high levels in epidermal lesions caused by aberrant regulation of keratinocytes.
Liu *et al.* [8]	Both experimental and case control study	treatment with imquimod in mice compare expression of TRIM33 IN healthy control , psoriatic skin, atopic dermatitis skin	TRIM32 overexpression in psoriasis, TRIM32 levels were low in AD patients	TRIM32 protein expression is defective in Atopic Dermatitis lesional skin **and** over expressed in psoriatic skin
Yang *et al.* [12]	Analytic study	Cell culture, real time PCR, Immunoprecipitation and siRNA	A predominant control of IFN-g in Trim21 regulation in human keratinocytes.	Trim 21 is found to be upregulated in psoriatic epidermis
Yang *et al.* [13]	Review article			Trim 32 is found to be upregulated in psoriatic epidermis. Ubiquitination proteasome signaling pathway represents a promising target for the development of anti-psoriatic drugs

Tocchini and Ciosk [11] reported that in patients affected by psoriasis, TRIM32 has been found at high levels in epidermal lesions caused by aberrant regulation of keratinocytes. The detrimental effects of TRIM32 aberrations observed in the different diseases have been often explained by defects in the E3 ubiquitin ligase activity. **Yang and associates** [12] reported that Trim21 is implicated in the inflammatory response. Its expression is upregulated in psoriatic epidermis, which promotes keratinocyte inflammation. Hence, Trim21 represents a potential target for psoriasis treatment. **Fiorentino and associates** [6] indicated that patients with TIF-1 superfamily (TRIM33 and TRIM24) autoantibodies had some characteristic findings including palmar hyperkeratotic papules, psoriasis-like lesions and a novel finding of hypopigmented and telangiectatic patches.

Liu and associates [8] provided supporting findings, that TRIM32 protein expression is defective in Atopic Dermatitis lesional skin. **Yucesoy and associates** [9] reported that TRIM10 associates with the major histocompatibility complex class I (MHCI) which is linked to skin irritation and dermatitis. Moreover, **Fujimoto and associates** [7] discovered that Anti-TIF1 autoantibodies are closely associated with juvenile dermatomyositis and adult cancer-associated dermatomyositis. Both of which tend to present extensive inflammatory skin disease and relatively mild muscle disease both in adults and children. Patients with TIF1 autoantibodies have more extensive skin involvement.

DISCUSSION

Although many reviews have described skin inflammation and processes that lead to its clinical manifestations, great aware of reviews that have focused on immunologic activity occurring in the absence of any visual inflammatory cues [14]**.** In inflammatory skin diseases, deterioration of the skin barrier function was observed, and new information was obtained by analyzing changes in inflammatory markers in the blood and skin [15]**.** The detailed studies on the biological role of autoantibodies in inflammatory skin diseases are limited. This results in a few available tools for effective diagnosis and management of these diseases [16]**.**

Tripartite motif (TRIM) proteins are classified into 11 subfamilies, based on their C-terminal domains, which may mediate both substrates recognition and regulative protein–protein interactions [17]. TRIMs are also known to play important roles in a wide range of biological processes, including cell proliferation, differentiation, development, apoptosis, oncogenesis, innate immunity, neuropsychiatric disorders, cardiovascular diseases, chromosomal abnormalities, infectious diseases, cancer, immune and inflammatory diseases, and DNA repair [18]. To date, most of the available information about the role of TRIMs in inflammatory diseases has been obtained in context of innate immunity, where specific TRIMs contribute to modulate intensity and duration of inflammatory responses [19]. Large number of TRIMs have been found to enhance cytokine signaling pathways [20]**.** Tripartite motif (TRIM) contributes to the regulation of immune responses, including the production of type I interferon (IFNs) and pro-inflammatory cytokines. The idea that TRIMs contribute to the development of autoimmune and auto-inflammatory diseases is gathering momentum [21].TRIMs' biological effects are also reflected in their ability to interact directly with viral components, either alone or in combination with other cellular proteins, and to modulate signaling pathways that are triggered by the engagement of pattern recognition receptors (PRRs). This downstream regulation affects the expression of both type I and type II IFNs, cytokines that are involved in pro-inflammatory responses and in promoting different aspects of the adaptive immune response. Progress in this field may open new horizons for developing strategies to prevent or combat infectious diseases, inflammatory conditions and autoimmune disorders [22]**.**

Innate immunity is the first line of defense against environmental insults and is important for initiation of the adaptive immune response. Aberrant innate immunity has been implicated in many skin inflammatory diseases, including psoriasis and atopic dermatitis (AD). Enhanced innate immune response is associated with psoriasis, whereas defective innate immunity contributes to AD pathogenesis [23]**.** Trim32 is mainly involved in innate immunity. It regulates the signaling pathways triggered by innate immunity pattern recognition receptors [24]**.** Ubiquitination is an important post-translational modification that regulates a myriad of biological processes such as inflammation, immune response, cell differentiation and proliferation. During the last decade, progress in proteomics contributed to the identification of new E3 ligases and their substrates. Hence, deregulated ubiquitination events are involved in several inflammatory disorders, exemplifying by systemic lupus erythematosus (SLE), type 1 diabetes, rheumatoid arthritis (RA) and psoriasis. Trim32 belongs to the tripartite motif-containing (TRIM), Trim32 exerts its function as an E3 ligase. In general, Trim32 is found to be upregulated in psoriatic epidermis. Trim32 interacts with Piasy and directs its degradation through ubiquitination. Interestingly, in keratinocytes, Trim32 activates and Piasy inhibits the production of CCL20 through Piasy interaction with NF-kB p65 subunit. Given that Piasy acts as a negative

regulator of NF-kB, the degradation of Piasy mediated by Trim32 leads to activation of NF-kB, making Trim32 as a positive regulator of NF-kB in psoriasis [25].

Transcriptional intermediary factor (TIF)-1 belongs to the larger tripartite motif (TRIM) family of proteins that are implicated in a number of important biological processes, including cell proliferation, development, apoptosis, and innate immunity. Findings suggested that TRIM24 functions as a positive regulator to mediate the activation of immunity [26].

The major histocompatibility complex (MHC) encodes more than 180 highly polymorphic genes, many of which influence immune regulation and susceptibility to complex diseases. MHC class I molecules are important in the regulation of inflammatory responses. TRIM10 has association with MHC class I as single nucleotide polymorphisms (SNPs) [27].

Tripartite motif- containing protein 21 (TRIM21) is an E3 ligase composed of several domains. TRIM21 is involved in innate and acquired immunity via the ubiquitination of interferon regulatory factor. The dysregulation of TRIM21 in different cells and tissues contributes to the pathogenesis of autoimmune diseases, such as systemic lupus erythematosus, systemic sclerosis, psoriasis, cancer and inflammatory myopathies. This downregulation is associated with a proinflammatory cytokine response. These studies suggest that TRIM21 may act as an inflammatory promoter or inhibitor in different diseases, TRIM21 expression was significantly elevated in psoriatic epidermis [28].

Liu *et al.* [8] reported that mice treated with imquimod displayed many atopic dermatitis features including epidermal thickening, enhanced Th2 cytokine expression, infiltration of Th2, mast cells and eosinophils, reduced filaggrin expression and increased serum IgE level. Thus, they provide evidence that TRIM32 deficiency can result in a Th2 and AD type of skin disorder in response to toll-like receptor (TLR) activation. They compared patient-matched non-lesional skin and skin of healthy controls. TRIM32 protein levels were high in psoriasis and low in AD lesional skin. Taken together, their results suggest that TRIM32 is required for normal Th17 response, while Trim32 deficiency favors features of a Th2 atopic response. **Tocchini and Ciosk** [11] studied TRIM32 in patients affected by psoriasis, TRIM32 has been found at high levels in epidermal lesions caused by aberrant regulation of keratinocytes. The E3 ligase function of TRIM32 was shown to be important in the innate immune responses leading to its high expression.

Fiorentino *et al.* [6] reported that Anti-TIF1 autoantibodies are closely associated with juvenile dermatomyositis and adult cancer-associated dermatomyositis, both of which tend to present extensive inflammatory skin disease and relatively mild muscle disease. Also **Fujimoto *et al.*** [7] observed that patients with TIF-1 autoantibodies had some characteristic findings including palmar hyperkeratotic papules, psoriasis-like lesions and a novel finding of hypopigmented and telangiectatic patches.

Yucesoy *et al.* [9] using genotyping methods according to the standard protocol reported that TRIM10 genes were associated with skin irritation response. **Yang *et al.*** [10] demonstrated that TRIM21 promoted inflammation in keratinocytes by ubiquitinating the p65 subunit.

This is the first systematic review to specifically address the role of TRIM proteins in inflammatory skin diseases. Our results indicate that TRIM proteins have relationship with inflammatory skin diseases.

CONCLUSION

This review suggests that TRIM proteins play a role in patients with inflammatory skin diseases. However, further high quality and large-scale studies are required to confirm the results. This will help in establishing new therapeutic targets.

Conflict of interest: The authors declare no conflict of interest.

REFERENCES

1. **Hänel K, Cornelissen C, Lüscher B *et al.* (2013):** Cytokines and the skin barrier. International Journal of Molecular Sciences, 14 (4): 6720–6745.
2. **Thind C, Ormerod A (2008):** Recent advances in inflammatory skin diseases. Scottish Medical Journal, 53 (2): 30–66.
3. **Eyerich K, Eyerich S. (2018):** Immune response patterns in non-communicable inflammatory skin diseases. Journal of the European Academy of Dermatology and Venereology, 32 (5): 692–703.
4. **Zhang J, Li X, Hu W *et al.* (2020):** Emerging Role of TRIM Family Proteins in Cardiovascular Disease. Cardiology,145 (6): 390-400.
5. **Moher D, Shamseer L, Clarke M *et al.* (2015):** Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic Reviews, 4:1.
6. **Fiorentino D, Kuo K, Chung L *et al.* (2015):** Distinctive cutaneous and systemic features associated with antitranscriptional intermediary factor-1γ antibodies in adults with dermatomyositis. Journal of the American Academy of Dermatology, 72 (3): 449–455.
7. **Fujimoto M, Watanabe R, Ishitsuka Y *et al.* (2016):** Recent advances in dermatomyositis-specific autoantibodies. Curr Opin Rheumatol., 28 (6): 636-44.
8. **Liu Y, Wang Z, De La T *et al.* (2017):** Trim32 Deficiency Enhances Th2 Immunity and Predisposes to Features of Atopic Dermatitis. The Journal of Investigative Dermatology, 137 (2): 359–366.
9. **Yucesoy B, Talzhanov Y, Michael B *et al.* (2016):** Association of MHC region SNPs with irritant

susceptibility in healthcare workers. Journal of Immunotoxicology, 13 (5): 738–744.

10. **Yang L, Zhang T, Zhang C *et al.* (2020):** Upregulated E3 ligase tripartite motif-containing protein 21 in psoriatic epidermis ubiquitylates nuclear factor-κB p65 subunit and promotes inflammation in keratinocytes. The British Journal of Dermatology, 10: 1111.
11. **Tocchini C, Ciosk R (2015):** TRIM-NHL proteins in development and disease. Seminars in Cell & Developmental Biology, 48: 52–59.
12. **Yang L, Jin L, Ke Y *et al.* (2018):** E3 Ligase Trim21 Ubiquitylates and Stabilizes Keratin 17 to Induce STAT3 Activation in Psoriasis. Journal of Investigative Dermatology, 138: 2568-2577.
13. **Yang L, Guo W, Zhang S *et al.* (2018):** Ubiquitination-proteasome system: A new player in the pathogenesis of psoriasis and clinical implications. Journal of Dermatological Science, 89: 219–225
14. **Stamatas G, Morello A, Mays D (2013):** Early inflammatory processes in the skin. Current Molecular Medicine, 13 (8): 1250–1269.
15. **Ooi K (2019):** Protection of the Skin Barrier Function in Inflammatory Disease. Yakugaku Zasshi. Journal of the Pharmaceutical Society of Japan, 139 (12): 1553–1556.
16. **Khatri S, Torok K, Mirizio E *et al.* (2019):** Autoantibodies in Morphea: An Update. Frontiers in Immunology, 10: 1487-93.
17. **Van Gent M, Sparrer K, Gack M (2018):** TRIM Proteins and Their Roles in Antiviral Host Defenses. Annual Review of Virology, 5 (1): 385–405.
18. **Vunjak M, Versteeg G (2019):** TRIM proteins. Current Biology, 29 (2): 42–44.
19. **Di Rienzo M, Romagnoli A, Antonioli M *et al.* (2020):** TRIM proteins in autophagy: selective sensors in cell damage and innate immune responses. Cell Death and Differentiation, 27 (3): 887–902.
20. **Van Tol S, Hage A, Giraldo M *et al.* (2017):** The TRIMendous Role of TRIMs in Virus-Host Interactions. Vaccines, 5 (3): 23-28.
21. **Jefferies C, Wynne C, Higgs R. (2011):** Antiviral TRIMs: friend or foe in autoimmune and autoinflammatory disease?. Nature reviews. Immunology, 11 (9): 617–625.
22. **Ozato K, Shin D, Chang T *et al.* (2008):** TRIM family proteins and their emerging roles in innate immunity. Nature reviews. Immunology, 8 (11): 849–860.
23. **De Benedetto A, Agnihothri R, McGirt L *et al.* (2009):** Atopic dermatitis: a disease caused by innate immune defects?. The Journal of Investigative Dermatology, 129 (1): 14–30.
24. **Zhang J, Hu M, Wang Y *et al.* (2012):** TRIM32 protein modulates type I interferon induction and cellular antiviral response by targeting MITA/STING protein for K63-linked ubiquitination. The Journal of Biological Chemistry, 287 (34): 28646–28655.
25. **Liu Y, Lagowski J, Gao S *et al.* (2010):** Regulation of the psoriatic chemokine CCL20 by E3 ligases Trim32 and Piasy in keratinocytes. The Journal of investigative Dermatology, 130 (5): 1384–1390.
26. **Zhu Q, Yu T, Gan S *et al.* (2020):** TRIM24 facilitates antiviral immunity through mediating K63-linked TRAF3 ubiquitination. The Journal of experimental medicine, 217 (7): 2019-2083.
27. **Callahan A, Baron E, Fekedulegn D *et al.* (2013):** Winter season, frequent hand washing, and irritant patch test reactions to detergents are associated with hand dermatitis in health care workers. Dermatitis, 24 (4): 170–175.
28. **Zhou G, Wu W, Yu L *et al.* (2018):** Tripartite motif-containing (TRIM) 21 negatively regulates intestinal mucosal inflammation through inhibiting T_H1/T_H17 cell differentiation in patients with inflammatory bowel diseases. The Journal of Allergy and Clinical Immunology, 142 (4): 1218–1228.