Benha Journal of Applied Sciences (BJAS) **print: ISSN 2356–9751**
Vol. (8) Issue (2) (2023), (25-29) **online: ISSN 2356–976x**
http://bjas.journals.ekb.eg

R-Spondin-1 Level in Different Dermatoses: A Comprehensive Review

Amira.A.Esmail[(1)], Osama.H.Elkady[(1)], Hamasat.A.Abdel Khalik[(2)]and Shymaa.M.Rezk[(1)]
Dermatology, Venereology and Andrology Dept., Faculty of Medicine, Benha University[(1)]
Clinical and Chemical Pathology Dept., Faculty of Medicine, Benha University[(2)]
E-mail: amiraatia88@gmail.com

Abstract

Background: R-Spondin-1 is a protein involved in cellular signaling pathways that play crucial roles in skin homeostasis, development, and regeneration. Dysregulation of R-Spondin-1 levels has been observed in various dermatological conditions, including inflammatory disorders, skin cancers, and hair disorders. Understanding the role of R-Spondin-1 in these conditions may provide insights into their pathogenesis and potential therapeutic targets. **Objectives:** This article aims to demonstrate the role of R-Spondin-1 protein in different dermatosis conditions. It aims to examine its physiological function, explore its dysregulation mechanisms, review its diagnostic potential and also investigate therapeutic implications. **Conclusions:** R-Spondin-1 emerges as a promising molecule with multifaceted roles in dermatological conditions. Its altered expression levels and signaling pathways provide diagnostic and prognostic insights in skin disorders, such as psoriasis, atopic dermatitis, basal cell carcinoma, squamous cell carcinoma, and melanoma. Furthermore, targeting R-Spondin-1 signaling holds therapeutic potential for the development of novel interventions in these dermatoses.

Keywords: R-Spondin-1, dermatoses, inflammatory skin disorders, diagnostic biomarker, therapeutic target.

1. Introduction

R-Spondin-1 is a secreted protein that belongs to the R-Spondin family, which comprises four members (R-Spondin-1 to R-Spondin-4) [1]. These proteins have gained significant attention due to their essential roles in various cellular signaling pathways [2]. R-Spondins are known to interact with the Wnt signaling pathway, a crucial pathway involved in embryonic development, tissue homeostasis, and cell proliferation. Specifically, R-Spondin-1 has been extensively studied and shown to play diverse roles in several biological processes [3].

In recent years, there has been increasing interest in investigating the involvement of R-Spondin-1 in dermatological conditions. The skin, being the largest organ of the body, undergoes constant renewal and repair. Proper regulation of cellular signaling pathways, including those involving R-Spondin-1, is crucial for skin homeostasis and maintaining its barrier function. Alterations in R-Spondin-1 levels have been implicated in various dermatoses, suggesting its potential significance in the pathogenesis and management of skin disorders [4, 5].

The purpose of this review is to provide a comprehensive overview of the current knowledge regarding R-Spondin-1 levels in different dermatoses and to explore the implications of altered R-Spondin-1 expression in the context of diagnosis and therapeutic targeting. By summarizing the existing literature, this review aims to shed light on the role of R-Spondin-1 in dermatology and facilitate further research in this emerging field.

2. R-Spondin-1 and Skin Homeostasis

R-Spondin-1 regulates skin formation, maintenance, and regeneration, contributing to skin homeostasis. Its participation in several cellular signaling pathways is necessary for the skin's normal function [6].

1. Role of R-Spondin-1 in skin development, maintenance, and regeneration:

R-Spondin-1 is expressed in the developing skin throughout embryonic development and is involved in the production of the epidermis, hair follicles, and other skin appendages. It helps to the formation of the epidermal barrier by promoting the proliferation and survival of epidermal progenitor cells. Animal studies have demonstrated that R-Spondin-1 deficiency results in poor skin development, including a thinner epidermis and aberrant hair follicle formation [7].

R-Spondin-1 continues to serve an essential function in regulating tissue homeostasis in adult skin. It controls the proliferation and development of epidermal stem cells, the cells responsible for epidermal regeneration. R-Spondin-1 stimulates stem cell self-renewal and inhibits their differentiation, therefore preserving a pool of undifferentiated cells for tissue regeneration and repair. In addition, R-Spondin-1 increases the synthesis of critical growth factors and extracellular matrix components needed in wound healing and tissue regeneration [8].

2. Signaling pathways involved in R-Spondin-1-mediated skin homeostasis:

R-Spondin-1 exerts its effects through interacting with certain cell surface receptors, such as the leucine-rich repeat-containing G protein-coupled receptors (LGR4, LGR5, LGR6) and the Frizzled receptors (FZD). These interactions trigger signaling pathways that contribute to the homeostasis of the skin. R-Spondin-1 is mostly linked with the canonical Wnt/-catenin signaling pathway [9].

In the absence of R-Spondin-1, Wnt ligands bind to Frizzled receptors and the co-receptor

LRP5/6, leading in the stability and nuclear translocation of -catenin. R-Spondin-1 increases Wnt signaling by binding to LGR4/5/6 and enhancing the internalization of Frizzled receptors, hence increasing Wnt-Frizzed-LRP5/6 complex formation and -catenin activation. The result is the activation of target genes involved in cell proliferation, survival, and differentiation [10].

In addition, R-Spondin-1 signaling interacts with other pathways, including as the Notch, Hedgehog, and BMP/TGF- pathways, to control skin

Psoriasis:

Chronic inflammatory skin disease characterized by aberrant keratinocyte growth and immunological dysregulation. R-Spondin-1 appears to have a key role in the etiology of psoriasis, according to mounting data. In psoriatic skin lesions, notably in the hyperproliferative epidermis and inflammatory infiltrates, R-Spondin-1 expression is elevated [12].

R-Spondin-1 promotes epidermal proliferation by enhancing Wnt signaling and β-catenin activation, which contributes to the excessive growth and thickening of the epidermis observed in psoriasis. Furthermore, R-Spondin-1 induces the production of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), which are implicated in psoriasis pathogenesis [13].

Due to its role in psoriasis, R-Spondin-1 is a possible therapeutic target. Targeting R-Spondin-1 signaling pathways may assist to regulate epidermal proliferation and inflammation, hence providing a potential therapy strategy for psoriasis. To understand the particular processes through which R-Spondin-1 contributes to psoriasis development and to evaluate the efficacy and safety of targeting R-Spondin-1 in clinical settings, more research is required [12].

Atopic Dermatitis:

Eczema, or atopic dermatitis, is a chronic inflammatory skin disorder marked by extreme itching, dry skin, and eczematous lesions. R-Spondin-1 levels have been reported to be changed in atopic dermatitis. In individuals with atopic dermatitis, the expression of R-Spondin-1 is frequently lower in lesional skin than in non-lesional or healthy skin [14].

In atopic dermatitis, the loss of R-Spondin-1 may lead to reduced skin barrier function and disturbed skin homeostasis. R-Spondin-1 has been discovered to control the production of filaggrin, a critical protein in maintaining the integrity of the skin barrier. Reduced R-Spondin-1 levels may reduce filaggrin expression, resulting in impaired skin barrier function and heightened vulnerability to allergens and irritants [15].

Other Inflammatory Dermatoses:

R-Spondin-1 may also be involved in other inflammatory dermatoses besides psoriasis and homeostasis precisely. These interactions contribute to the equilibrium between cell proliferation, differentiation, and death, hence guaranteeing the integrity and function of the skin [11].

The specific processes by which R-Spondin-1 maintains the homeostasis of the skin are still the subject of ongoing research. R-Spondin-1-mediated effects on skin formation, maintenance, and regeneration require more investigation to understand the particular downstream targets and cross-talk with other signaling pathways [1].

atopic dermatitis. Exposure to allergens or irritants, for instance, can trigger inflammation and alter skin barrier function in contact dermatitis. In contact dermatitis, R-Spondin-1 may have a role in the control of epithelium repair and wound healing [15].

In autoimmune blistering illnesses, such as pemphigus and bullous pemphigoid, autoantibody-mediated destruction to the skin's adhesion molecules is characteristic. Studies indicate that R-Spondin-1 may affect the expression and function of adhesion molecules important in preserving the integrity of the skin, hence potentially influencing the development of autoimmune blistering diseases [16].

Emerging data shows that R-Spondin-1 regulates important processes, including inflammation, epidermal proliferation, and skin barrier function, but the precise functions of R-Spondin-1 in these inflammatory dermatoses are still being understood. To completely comprehend the processes behind R-Spondin-1 in various dermatoses and to investigate its potential as a therapeutic target, more study is required [17, 18].

R-Spondin-1 and Skin Appendage Disorders

Alopecia Areata:

Alopecia areata is an autoimmune condition that causes localized or widespread hair loss. R-Spondin-1 has attracted attention in the context of hair follicle regeneration and its possible role in alopecia areata. The activation, proliferation, and differentiation of latent hair follicle stem cells are essential for hair follicle regeneration. R-Spondin-1 has been discovered to stimulate hair follicle regeneration by activating the Wnt/beta-catenin signaling pathway, which plays a critical role in hair follicle growth and cycling. In animal models, R-Spondin-1 injection has been proven to increase hair follicle development and speed up the hair cycle, according to experiments. Understanding the relationship between R-Spondin-1 and hair follicle regeneration may provide novel treatment options for increasing hair regrowth in alopecia areata [19].

Hidradenitis Suppurativa:

Hidradenitis suppurativa is a chronic inflammatory skin condition that predominantly affects hair follicles and apocrine sweat glands. In the afflicted locations, recurring painful nodules, abscesses, and sinus tracts are present. Emerging data indicates that R-Spondin-1 may have a role in

the etiology of hidradenitis suppurativa. R-Spondin-1 expression was shown to be elevated in lesional skin of individuals with hidradenitis suppurativa. R-Spondin-1 may have a role in the aberrant proliferation and differentiation of epidermal cells, as well as the creation of sinus tracts and fibrosis, it is believed. In addition, R-interactions Spondin-1's with other signaling pathways may affect inflammatory responses. As a possible therapeutic option for hidradenitis suppurativa, targeting R-Spondin-1 or its downstream signaling pathways offers promise. To completely explain the function of R-Spondin-1 in hidradenitis suppurativa pathogenesis and evaluate its therapeutic potential, more study is required [20].

Nail Disorders:

There are several variables that impact the development, structure, and appearance of the nails. R-Spondin-1 has been linked to the control of nail formation and growth. R-Spondin-1 expression has been discovered in the nail matrix, the area responsible for nail plate development, in research concentrating on nail regeneration and nail matrix biology. By controlling the proliferation and differentiation of nail matrix cells, R-Spondin-1 may impact nail development and regeneration. Understanding the involvement of R-Spondin-1 in nail diseases might have implications for the development of medicines targeting nail regeneration and the treatment of ailments such as onychomycosis and nail dystrophy [21].

3. R-Spondin-1 and Skin Cancer

Basal Cell Carcinoma:

The most prevalent form of skin cancer, basal cell carcinoma (BCC) predominantly affects the basal cells of the epidermis. R-Spondin-1 has emerged as a promising marker for the diagnosis and prognosis of BCC. Studies have revealed that R-Spondin-1 is expressed differently in BCC tissues compared to normal skin. R-Spondin-1 expression has been found to be elevated in BCC tumors, indicating its potential as a diagnostic marker for differentiating BCC from normal skin or other skin diseases [22].

In addition, R-Spondin-1 expression levels have been linked to clinicopathological characteristics and aggressiveness of BCC tumors. High R-Spondin-1 expression has been linked with increased tumor size, invasion depth, and recurrence rates. This shows that R-Spondin-1 may also serve as a prognostic marker for BCC, predicting the behavior of tumors and patient outcomes [1].

It is hypothesized that R-Spondin-1 contributes to tumor development, invasion, and epithelial-mesenchymal transition in Basal Cell Carcinoma (BCC) pathogenesis, however this has to be determined (EMT). Understanding the specific processes underpinning R-Spondin-1 in BCC and exploring its potential as a therapeutic target requires more research [23].

Squamous Cell Carcinoma:

Squamous cell carcinoma (SCC) is an additional prevalent form of skin cancer that starts from squamous cells of the epidermis. The altered expression of R-Spondin-1 in SCC has been linked to the development of the tumor. R-Spondin-1 expression is commonly increased in SCC tissues compared to normal skin [24].

Studies reveal that elevated levels of R-Spondin-1 in SCC may contribute to tumor development and invasion. R-Spondin-1 increases cancer cell proliferation and may induce angiogenesis, resulting in the formation of a vascular supply for tumor growth. In addition, R-Spondin-1 has been linked to the control of EMT, which has been related with enhanced invasiveness and metastatic potential in SCC [25, 26].

Melanoma:

Melanoma is a very aggressive kind of skin cancer that arises from melanocytes, the pigment-producing skin cells. Emerging data shows R-possible Spondin-1's function in melanoma pathobiology, despite the fact that our understanding of R-role Spondin-1's in melanoma is still changing [27, 28].

Both increased and downregulated expression patterns have been identified in studies of melanoma R-Spondin-1 expression. R-Spondin-1 may affect several aspects of melanoma advancement, such as cell proliferation, migration, invasion, and metastasis. R-Spondin-1 may alter the behavior of melanoma cells by interacting with other signaling pathways, such as Wnt/beta-catenin and Notch [24].

4. Diagnostic and Therapeutic Perspectives

Diagnostic Perspectives:

R-Spondin-1 has diagnostic potential for a variety of dermatoses. Variations in R-Spondin-1 expression have been identified in a variety of skin illnesses, including inflammatory disorders, skin cancer, and hair problems. The identification and measurement of R-Spondin-1 expression in skin biopsies or using non-invasive procedures, such as blood tests or imaging techniques, may help in the diagnosis and distinction of certain dermatoses. For instance, higher R-Spondin-1 levels in psoriatic lesions or certain patterns of R-Spondin-1 expression in skin malignancies may aid in their precise identification. To create standardized techniques and demonstrate the clinical value of R-Spondin-1 as a diagnostic biomarker in dermatological disorders, however, more study is necessary [29].

Therapeutic Perspectives:

Targeting R-Spondin-1 signaling pathways is an exciting therapeutic strategy for dermatological disorders. Modifying R-Spondin-1 expression or its downstream signaling components may give

potential advantages in the treatment of a variety of skin conditions. In inflammatory dermatoses such as psoriasis and atopic dermatitis, for instance, targeting R-Spondin-1 may control aberrant signaling pathways, reduce inflammation, and restore skin homeostasis. Inhibiting R-Spondin-1-mediated stimulation of Wnt/beta-catenin signaling may reduce tumor development and spread in skin malignancies. In addition, altering R-Spondin-1 levels or activity might be investigated as a technique for promoting hair follicle regeneration in alopecia areata or facilitating wound healing in certain dermatoses. However, due to the intricacy of R-Spondin-1 signaling networks and the possibility of off-target consequences, further study is required to create accurate and safe treatment techniques [1].

Limitations and Future Directions:

Although the role of R-Spondin-1 in dermatological disorders is becoming increasingly apparent, various limits and obstacles remain. To begin with, the particular processes through which R-Spondin-1 exerts its effects in various skin conditions are not entirely understood. R-Spondin-1-mediated activities require more research to clarify their complicated signaling pathways and connections with other variables. In addition, the development of dependable and standardized methods for assessing R-Spondin-1 levels in clinical settings is necessary for its efficient use as a diagnostic biomarker [30].

5. Conclusion

R-Spondin-1 is a potential molecule with several functions in dermatological disorders. In skin illnesses such as psoriasis, atopic dermatitis, basal cell carcinoma, squamous cell carcinoma, and melanoma, its altered expression levels and signaling pathways give diagnostic and prognostic insights. In addition, targeting R-Spondin-1 signaling has therapeutic potential for the development of innovative treatments for various dermatoses. To untangle the complicated processes behind R-Spondin-1 participation and establish its clinical value as a diagnostic biomarker and therapeutic target, however, further study is required.

References

[1] K. Nagano. R-spondin signaling as a pivotal regulator of tissue development and homeostasis. Jpn Dent Sci Rev;55:80-7. 2019

[2] Y. Yuan, M. Guo, C. Gu, Y. Yang. The role of Wnt/β-catenin signaling pathway in the pathogenesis and treatment of multiple myeloma (review). Am J Transl Res;13:9932-49. 2021

[3] T. Napolitano, S. Silvano, C. Ayachi, M. Plaisant, A. Sousa-Da-Veiga, H. Fofo, et al. Wnt Pathway in Pancreatic Development and Pathophysiology. Cells;12. 2023

[4] L.F. Ng, P. Kaur, N. Bunnag, J. Suresh, I.C.H. Sung, Q.H. Tan, et al. WNT Signaling in Disease. Cells;8. 2019

[5] J. Gao, L. Fan, L. Zhao, Y. Su. The interaction of Notch and Wnt signaling pathways in vertebrate regeneration. Cell Regeneration;10:11. 2021

[6] E. Dellambra, S. Cordisco, F. Delle Monache, S. Bondanza, M. Teson, E.M. Nicodemi, et al. RSPO1-mutated keratinocytes from palmoplantar keratoderma display impaired differentiation, alteration of cell-cell adhesion, EMT-like phenotype and invasiveness properties: implications for squamous cell carcinoma susceptibility in patients with 46XX disorder of sexual development. Orphanet J Rare Dis;17:275. 2022

[7] M.S. Hu, M.R. Borrelli, W.X. Hong, S. Malhotra, A.T.M. Cheung, R.C. Ransom, et al. Embryonic skin development and repair. Organogenesis;14:46-63. 2018

[8] J. Schuijers, H. Clevers. Adult mammalian stem cells: the role of Wnt, Lgr5 and R-spondins. Embo j;31:2685-96. 2012

[9] A. Ordaz-Ramos, V.H. Rosales-Gallegos, J. Melendez-Zajgla, V. Maldonado, K. Vazquez-Santillan. The Role of LGR4 (GPR48) in Normal and Cancer Processes. International Journal of Molecular Sciences;22:4690. 2021

[10] D.M. Joiner, J. Ke, Z. Zhong, H.E. Xu, B.O. Williams. LRP5 and LRP6 in development and disease. Trends Endocrinol Metab;24:31-9. 2013

[11] J. Gao, L. Fan, L. Zhao, Y. Su. The interaction of Notch and Wnt signaling pathways in vertebrate regeneration. Cell Regen;10:11. 2021

[12] Y. Zhao, Y. Zhang, J. Li, N. Zhang, Q. Jin, Y. Qi, et al. Pathogenic sphingosine 1-phosphate pathway in psoriasis: a critical review of its pathogenic significance and potential as a therapeutic target. Lipids Health Dis;22:52. 2023

[13] M.E. Binnerts, K.A. Kim, J.M. Bright, S.M. Patel, K. Tran, M. Zhou, et al. R-Spondin1 regulates Wnt signaling by inhibiting internalization of LRP6. Proc Natl Acad Sci U S A;104:14700-5. 2007

[14] S.J. Brown. Atopic eczema. Clin Med (Lond);16:66-9. 2016

[15] M.C. Zaniboni, L.P. Samorano, R.L. Orfali, V. Aoki. Skin barrier in atopic dermatitis: beyond filaggrin. An Bras Dermatol;91:472-8. 2016

[16] A. Orsmond, L. Bereza-Malcolm, T. Lynch, L. March, M. Xue. Skin Barrier Dysregulation in Psoriasis. Int J Mol Sci;22. 2021

[17] G. Krönke, S. Uderhardt, K.A. Kim, M. Stock, C. Scholtysek, M.M. Zaiss, et al. R-spondin 1 protects against inflammatory bone damage during murine arthritis by modulating the Wnt pathway. Arthritis Rheum;62:2303-12. 2010

[18] V.P. Vidal, F. Jian-Motamedi, S. Rekima, E.P. Gregoire, E. Szenker-Ravi, M. Leushacke, et al. R-spondin signalling is essential for the maintenance and differentiation of mouse nephron progenitors. Elife;9. 2020
[19] M. Żeberkiewicz, L. Rudnicka, J. Malejczyk. Immunology of alopecia areata. Cent Eur J Immunol;45:325-33. 2020
[20] E.Y. Lee, R. Alhusayen, P. Lansang, N. Shear, J. Yeung. What is hidradenitis suppurativa? Can Fam Physician;63:114-20. 2017
[21] A. Subudhi, S. Jena, P. Mohanty, D.R. Panda. Study of Clinical and Dermoscopic Features in Nails of Papulosquamous Disorders and their Correlation with Disease Severity: A Cross-Sectional Study. Indian J Dermatol;67:488-94. 2022
[22] E. Niculet, M. Craescu, L. Rebegea, C. Bobeica, F. Nastase, G. Lupasteanu, et al. Basal cell carcinoma: Comprehensive clinical and histopathological aspects, novel imaging tools and therapeutic approaches (Review). Exp Ther Med;23:60. 2022
[23] L. Fania, D. Didona, R. Morese, I. Campana, V. Coco, F.R. Di Pietro, et al. Basal Cell Carcinoma: From Pathophysiology to Novel Therapeutic Approaches. Biomedicines;8. 2020
[24] L. Zhang, Y. Song, Z. Ling, Y. Li, X. Ren, J. Yang, et al. R-spondin 2-LGR4 system regulates growth, migration and invasion, epithelial-mesenchymal transition and stem-like properties of tongue squamous cell carcinoma via Wnt/β-catenin signaling. EBioMedicine;44:275-88. 2019
[25] W. Yan, Wistuba, II, M.R. Emmert-Buck, H.S. Erickson. Squamous Cell Carcinoma - Similarities and Differences among Anatomical Sites. Am J Cancer Res;1:275-300. 2011
[26] G. Pacella, B.C. Capell. Epigenetic and metabolic interplay in cutaneous squamous cell carcinoma. Experimental Dermatology;30:1115-25. 2021
[27] Y. Liu, M.S. Sheikh. Melanoma: Molecular Pathogenesis and Therapeutic Management. Mol Cell Pharmacol;6:228. 2014
[28] I. Yeh, B.C. Bastian. Melanoma pathology: new approaches and classification. Br J Dermatol;185:282-93. 2021
[29] P. Parma, O. Radi, V. Vidal, M.C. Chaboissier, E. Dellambra, S. Valentini, et al. R-spondin1 is essential in sex determination, skin differentiation and malignancy. Nat Genet;38:1304-9. 2006
[30] Y.E. Kang, J.M. Kim, H.S. Yi, K.H. Joung, J.H. Lee, H.J. Kim, et al. Serum R-Spondin 1 Is a New Surrogate Marker for Obesity and Insulin Resistance. Diabetes Metab J;43:368-76. 2019