International Journal of Chemical and Biochemical Sciences
(ISSN 2226-9614)

Journal Home page: www.iscientific.org/Journal.html

Plexins and psoriasis: New insights into pathogenesis and therapy

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Abstract

Psoriasis is a chronic autoimmune skin disorder affecting millions globally. Its complex pathophysiology involves interactions between keratinocytes, immune cells, and other skin cells. Recent research has highlighted disruptions in nerve fiber development (neuritogenesis) in psoriasis patients, suggesting possible neurological involvement. Semaphorin-Plexin signaling pathways, known for their roles in axon guidance and various biological processes, are now gaining attention in psoriasis research. Transcripts of semaphorins show differential expression in psoriasis samples, indicating their potential involvement in the disease. Plexins, acting as cell surface receptors in semaphorin axon guidance, are grouped into classes A, B, C, and D. They have diverse roles beyond axon guidance, impacting angiogenesis, immunological regulation, and development. Plexins possess a unique GAP domain, modulating GTPases like Ras and Rac1, vital for cellular functions. Plexins engage with over 20 interacting partners, contributing to various signaling pathways. Specific interactions vary among plexin classes and play roles in processes like dendrite growth and axonal repulsion. The study aims to explore the structural organization of plexins' cytoplasmic portion. Understanding plexin's intricate functions may shed light on its potential involvement in psoriasis pathogenesis, offering new avenues for research and therapeutic interventions. In conclusion, psoriasis is a complex skin disorder with potential neurological implications. Investigating semaphorin-Plexin signaling pathways, may provide valuable insights into psoriasis mechanisms and treatment strategies so on this review we try to give theories combining between psoriasis and plexins.

Keywords: Plexins; Psoriasis; Semaphorin; Signaling.

Full length article **Corresponding Author*, e-mail: betaalaa0@gmail.com

1. Introduction

, an enduring autoimmune dermatological disorder, poses a substantial worldwide health concern, impacting an estimated 125 million people globally and constituting 2-4% of the populace in Western nations [1]. In addition to its comparatively low fatality rate, psoriasis significantly affects the overall quality of life for individuals, imposing considerable psychological challenges. This pathological state is distinguished by the defining characteristics of excessive growth of the epidermis and the migration of immune cells into the dermal layers of the skin. The pathophysiology of psoriasis is complex, characterized by complicated interactions among keratinocytes, immune cells, and other resident skin cells [2]. Research conducted on individuals with psoriasis has shown disruptions in the process of neuritogenesis, which refers to the development of nerve fibers. These findings suggest the possibility of neurological implications in the development of psoriasis [3]. The involvement of Semaphorin-Plexin signaling pathways in several biological processes has been recognized subsequent to their first discovery in relation to neural projection development. These activities include functions related to the circulatory, immunological, and neurological systems. However, the precise role of semaphorins in the context of psoriasis remains an area that has not been well investigated, since there is a limited amount of information available about their contribution to the development of the illness. In addition, there exists a limited availability of evidence about the underlying processes of axon growth in the context of psoriasis, despite the recognized disruptions in neuritogenesis. Nevertheless, recent research has shown that there are transcripts of semaphorins that exhibit differential expression levels in samples obtained from persons diagnosed with psoriasis, therefore implying their possible involvement in the pathogenesis of this condition [4]. The intricate interaction

between semaphorins and their receptors, with a specific focus on Plexins, offers a promising avenue for further investigation in understanding the underlying mechanisms of psoriasis pathogenesis [5]. While the exact mechanisms of their involvement remain incompletely elucidated, the recognition of their presence in psoriatic skin underscores the complex character of the condition and offers potential for novel therapeutic strategies targeting these cellular pathways. A new study has shed light on the likely role of semaphorin-Plexin signaling pathways, which have traditionally been related with axon guidance, in the complicated mechanisms that contribute to the development of psoriasis. Psoriasis is characterized by a wide spectrum of clinical symptoms, and this new study has shed light on this topic. The expansion of our understanding of this phenomena paves the way for novel lines of inquiry in academic research as well as novel therapeutic interventions in the field of psoriasis treatment.

2. Plexins

In the process of semaphorin axon guidance protein function, plexins may be thought of as a type of cell surface receptor that is of assistance. On the basis of the degree to which their sequences are conserved, the varied collection of semaphorins, which consists of more than 20 members, may be separated into eight distinct groups. The enhancement of axon development and projection within the nervous system is the most noteworthy biological activity that these proteins have a role in [6, 7]. These proteins are involved in a range of other biological processes as well. In the context of the human species, plexins are separated into four distinct classes that are denoted by the letters A, B, C, and D respectively. It is important to keep in mind that in order to establish functional receptor complexes, certain Class A members require the presence of co-receptors that are referred to as neuropilins. According to Janssen et al. [8], the astonishing diversity of plexins and their interactions with co-receptors is emphasized as a key factor in the regulation of a wide variety of developmental and physiological processes. Beyond their well-established role in guiding axons, plexins have emerged as substantial contributors to several physiological processes, including angiogenesis, immunological regulation, and bone homeostasis. Genetic knockout experiments revealing the disruption of plexin function have demonstrated embryonic mortality and significant developmental abnormalities, particularly within the neurological and cardiovascular systems [9, 10]. Recent investigations into the structural aspects of plexin signaling have yielded critical insights. According to Wang et al. [11], plexins are distinguished by the presence of a unique GAP (GTPase Activating Protein) domain in their cytoplasmic region, enabling them to directly modulate the activity of small GTPases like Ras and Rac1. GTPases are central regulators of crucial biological processes, such as cell proliferation and cytoskeletal dynamics. Plexins stand out among cell surface receptors due to their possession of a GTPase-activating protein (GAP) domain, which sets them apart in their role in governing cellular morphology and motility [12]. In addition to the GAP domain, the cytoplasmic region of plexins harbors other functional segments. A RhoGTPase Binding Domain (RBD) interacts with Rho family small GTPases like Rac1, RND1, and RhoD, further fine-tuning plexin signaling. Moreover, a juxtamembrane segment at the N-terminus of the plexin cytoplasmic region serves as a critical regulatory element [13]. Plexins engage in a wide range of protein interactions, with more than 20 known interacting partners. These interactions contribute to a diverse array of signaling pathways, and certain plexin family members 7possess unique protein interaction sites that mediate specific signaling processes. For instance, Class B plexins interact with PDZeRhoGEF and LARG, while Class A plexins engage FARP1 and FARP2. These interactions play roles in processes such as dendrite growth and axonal repulsion, expanding our comprehension of the multifaceted functions of plexins in various cellular contexts [14, 15]. In summary, the intricate structural and functional attributes of plexins in orchestrating diverse signaling pathways position them as central players in a wide spectrum of physiological and developmental processes. Further research is imperative to unravel the full extent of their roles and the intricate mechanisms governing plexin signaling [14, 15]. The plexin family consists of nine identified members, classified into four subfamilies: plexin A1 to A4, plexin B1 to B3, plexin C1, and plexin D1 [16]. From the previous insights different plexins may have an association with psoriasis (Figure 1).

2.1. Plexin-A

Plexin-A proteins are primarily known for their roles in axon guidance and neuronal development, and their involvement in the pathogenesis of psoriasis, which is an autoimmune skin disorder, had not been a prominent focus of research up to that point **[17].**

2.1a. PLXNA1 (Plexin A1)

The protein known as PLXNA1, or Plexin A1, is a plasma membrane protein that exhibits a high degree of conservation. It has a molecular weight of around 208.6 kilodaltons (kDa). The protein under consideration is characterized by the presence of a single Sema (semaphorin), two PSI (domain present in plexins, semaphorins, and integrins), and three IPT (Ig-like, plexins, transcription factors) domains. According to McKown et al. [18], Aceview has made predictions about the presence of seven splice variants of PLXNA1. The etiology of psoriasis is primarily affected by immunological dysregulation, namely the activation of T cells and the creation of inflammatory cytokines inside the dermis. Psoriasis is characterized by complex interactions between immune cells, signaling pathways, and genetic factors, all of which contribute to its molecular processes. There is presently no direct evidence relating Plexin-A proteins to psoriasis [19].
According to O'Connor and Ting, 2008 [20], the cell surface signaling receptor PLXNA1 interacts with ligands such as Sema6D. Sema6D has been demonstrated to increase the production of interleukin-12 (IL-12) by targeting dendritic cells. According to Inaba and Inaba [21], dendritic cells that express PLXNA1 have a lower effectiveness in activating T-cells. Psoriasis is characterized by immune dysregulation, including the activation of T cells and increased production of inflammatory cytokines [22]. Therefore, it is possible that altered PLXNA1 signaling in dendritic cells could affect their function in psoriasis-related immune responses, potentially contributing to the disease's pathogenesis However there is no direct association between psoriasis and PLXNA1 was observed or noted in the literatures.

2.1b. Plexin A2 (PLXNA2)

Plexin A2 (PLXNA2) functions as a co-receptor for semaphorin 3A (SEMA3A) and semaphorin 6A (SEMA6A), hence playing a crucial role in facilitating the signaling pathways begun by SEMA6A and other class 3 semaphorins. This ultimately leads to the reorganization of the cytoskeleton. The functional role of this phenomenon spans a range of key functions, including axon guidance, invasive growth, and cell migration. In the context of class 3 semaphorin signaling, semaphorins have been seen to form complexes with neuropilin proteins and plexins. The inclusion of plexin A2 in this assemblage affects the binding strength of the assemblage towards certain semaphorins. Significantly, the intracellular region of plexin A2 plays a crucial role in initiating subsequent signaling cascades inside the cytoplasm of the cell [23, 24]. While there is no direct evidence establishing a connection between Plexin A2 (PLXNA2) and psoriasis, the role of PLXNA2 in mediating signaling initiated by semaphorins, particularly SEMA3A and SEMA6A, suggests a hypothetical mechanism that may associate the two. Psoriasis is characterized by immune dysregulation, involving T cell activation and inflammatory cytokine production [25]. PLXNA2's involvement in cell migration and cytoskeletal remodeling, as well as its role as a coreceptor for semaphorins [23], implies potential relevance to immune cell behavior in psoriasis-affected skin. SEMA3A and SEMA6A signaling could impact immune cell responses, and the formation of complexes with neuropilins and plexins, including PLXNA2, might influence the binding affinity for specific semaphorins [26, 27]. Nevertheless, concrete associations between PLXNA2 and psoriasis require further investigation beyond the provided information.

2.1c. PLXNA3 (Plexin A3)

PLXNA3 (Plexin A3) is a gene encoding a protein [28]. PLXNA3 is implicated in various biological pathways, notably those involving Semaphorin interactions and the development of the nervous system. Gene Ontology (GO) annotations pertaining to PLXNA3 underscore its role as a signaling receptor, particularly in the context of semaphorin signaling [29]. PLXNA3 shares structural and functional similarities with another gene, PLXNA1, which is considered an important paralog of PLXNA3 [30]. PLXNA3, an annotated signaling receptor with involvement in semaphorin interactions [31], raises the intriguing possibility of a connection to psoriasis, a condition characterized by immune dysregulation. Semaphorins, having roles in immune regulation alongside functions in nervous system development [32], may potentially intersect with immune cell behavior in psoriasis-affected skin via PLXNA3.

2.1d. PLXNA4 (Plexin A4)

Plexin-A4, a member of the plexin-A subfamily, plays a role in the assembly of a receptor complex with neuropilins, enabling the transmission of signals initiated by sema3A in immune cells. The presence of Plexin-A4 mRNA has been detected in several immune cell populations, such as T cells, dendritic cells (DCs), and macrophages, suggesting its possible role in their respective developmental mechanisms [33]. This raises the possibility that PLXNA4 could influence immune cell behavior, particularly in T cells and DCs, which play crucial roles in the immune dysregulation observed in psoriasis. As psoriasis is characterized by alterations in immune cell behavior and cytokine production, further research is needed to explore the direct associations between PLXNA4 and psoriasis pathogenesis [33].

2.2. Plexin-B

Plexins serve as neural receptors for Semaphorins, which are molecules involved in the repulsive guiding of axons. Plexin B (PlexB) exhibits direct binding affinity towards the activated state of the Rac GTPase, specifically when it is in its GTP-bound conformation. The binding of RacGTP requires a specific seven amino acid sequence inside PlexB. The need of the interaction between PlexB and RacGTP has been shown for the process of Plexin-mediated axon guidance in vivo [34].

2.2a. PLXNB1, 3 (Plexin B1,3)

PLXNB1 and PLXNB3 are genes categorized as Protein Coding, plays a significant role in various biological pathways, notably those associated with Semaphorin interactions and Signaling by Rho GTPases. Gene Ontology (GO) annotations related to PLXNB1,3 highlight its functions, including serving as a signaling receptor and binding to GTPase activating proteins [35]. Semaphorins, which interact with PLXNB1 and also PLXNB3, have emerging roles in immune regulation, angiogenesis, and organ development. Therefore, PLXNB1,3 involvement in these pathways suggests a potential link to immune cell behavior and cytokine production, central to psoriasis [36].

2.2b. PLXNB2 (Plexin B2)

PLXNB2 (Plexin B2), is a transmembrane receptor protein primarily found in the nervous system. It plays a crucial role in processes like axonal guidance, neuronal migration, angiogenesis, immune response modulation, and tumor progression. As a receptor for semaphorins, PLXNB2 regulates the growth cone dynamics and helps guide the axons during embryonic development [37]. In Hemida et al., [38], Plexin-B2 expression: Controls (66), Perilesional (116), Lesional (159.7) skin. Lesional dermal cells (153.67) vs. Control (25.71). Lesional and perilesional > Controls. No difference between lesional and perilesional. Plexin-B2 H-score correlated with PASI scores: Lesional epidermis ($r=0.593$, $p<0.001$), Dermal inflammatory cells ($r=0.406$, $p<0.026$). Correlation between epidermis and dermal cells ($p<0.032$). The presence of elevated levels of Plexin-B2 in the affected epidermis has been shown to be associated with the occurrence of parakeratosis ($p<0.016$). Furthermore, an association has been observed between dermal cells and the presence of acanthosis ($p=0.006$) as well as hyperkeratosis ($p<0.001$). The investigation carried out by Hemida et al. [38], included the comparison of Plexin-B2 expression levels across various skin diseases. The control group had an expression level of 66, but both the perilesional and lesional skin displayed elevated levels of 116 and 159.7, respectively. Moreover, the dermal cells in the lesional group exhibited an expression level of 153.67, whereas the control group had a level of 25.71.

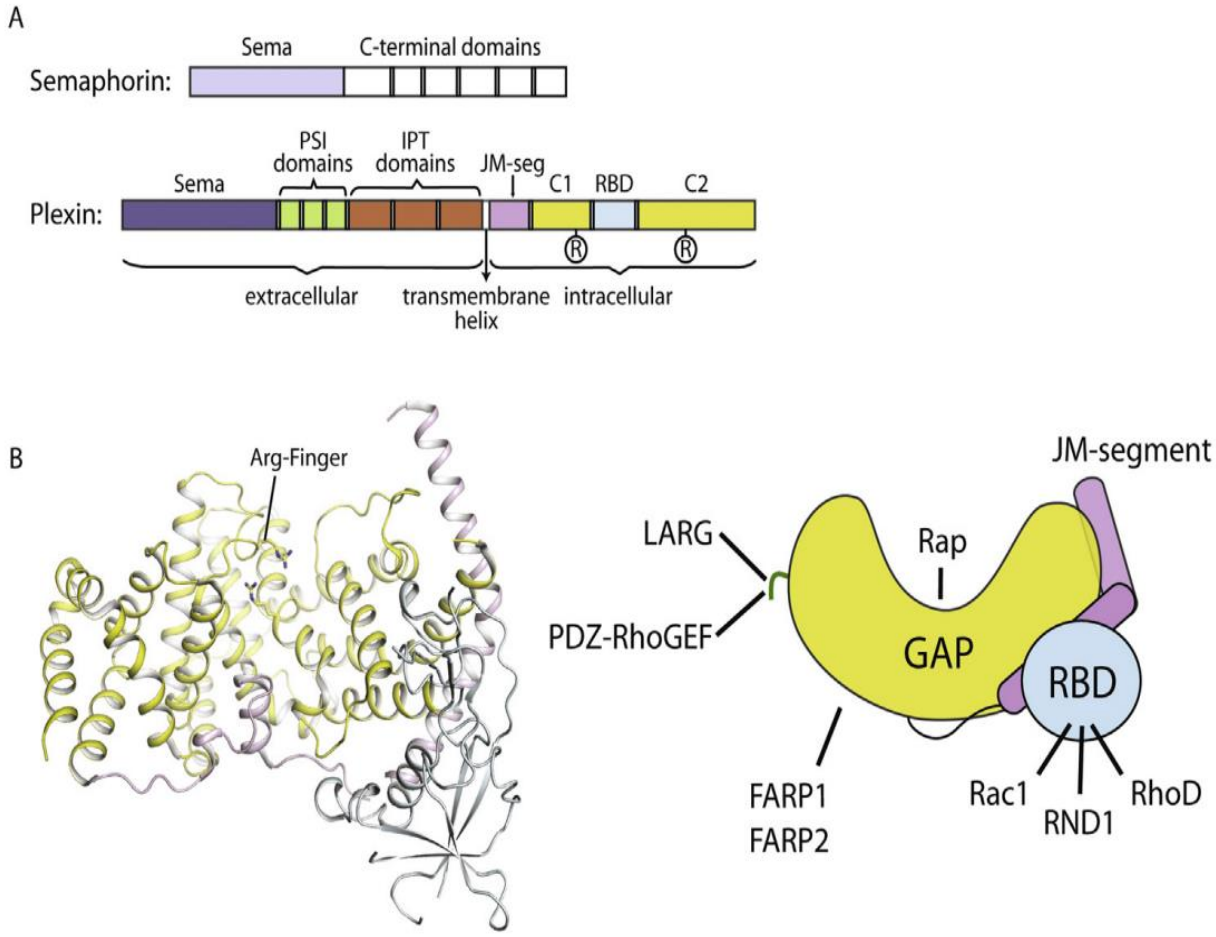

Figure 1: The present study aims to elucidate the comprehensive organization of the cytoplasmic portion of plexins. The domain structures of semaphorin and plexin are being discussed. The cartoons provide an overview of the structural characteristics of plexin and semaphorin, excluding any divergences seen among individual members within their respective families. The cytoplasmic portion of plexin has a distinct structural organization. The structure of mouse PlexinA3, as represented by PDB ID: 3IG3, is shown. The schematic of the building is seen in the right panel. The color palette used in (A) remains consistent. The C-terminal tail in class B plexins is shown by the green line and is responsible for interacting with LARG and PDZeRhoGEF. The GAP domain in (A) is comprised of two homology regions, C1 and C2, which undergo folding to merge into a single entity. The GAP domain is characterized by the presence of two conserved arginine residues, which are prominently emphasized. The residue known as the catalytic arginine finger is often referred to as "Arg-Finger". The juxtamembrane segment is a region located next to the cell membrane **[14].**

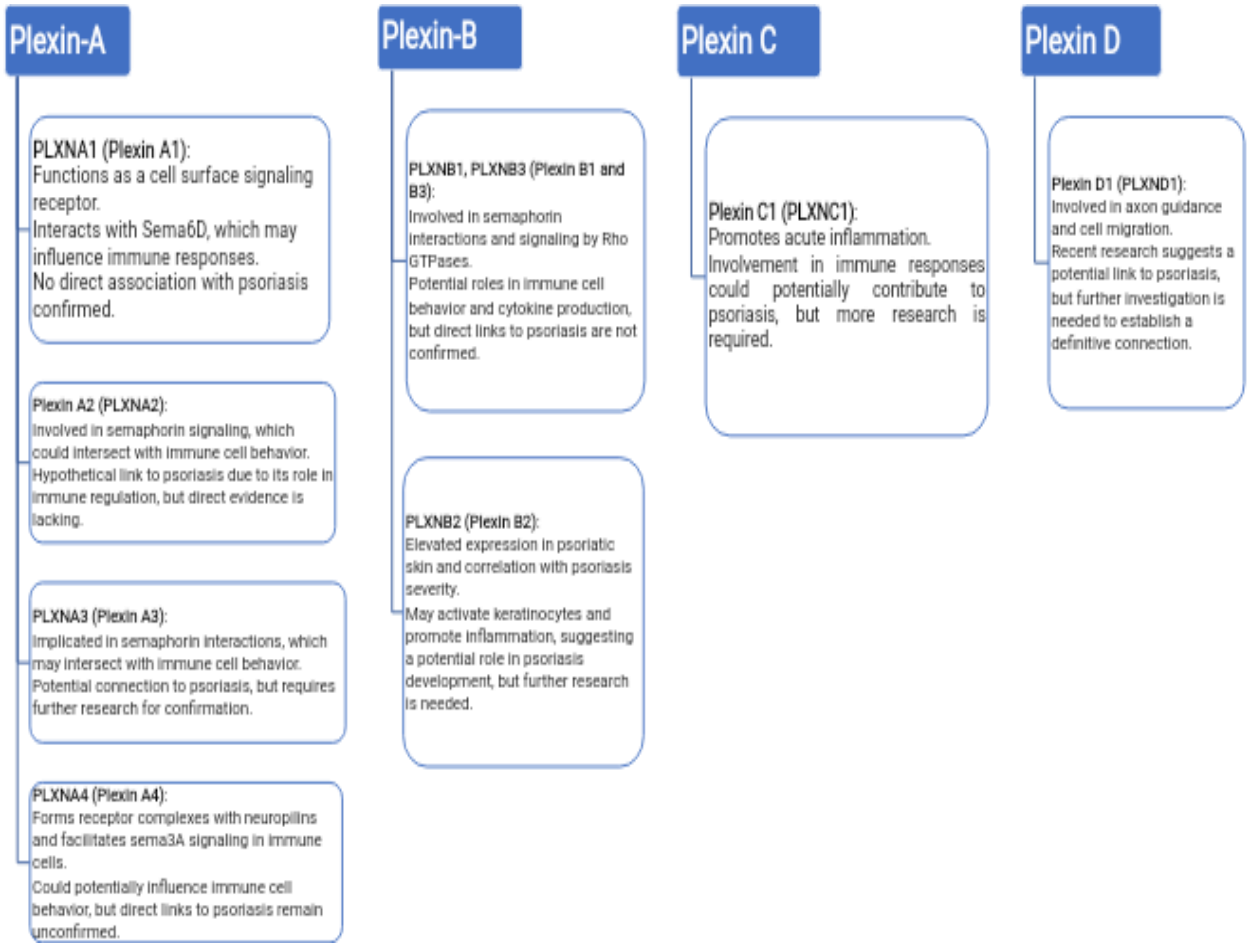

Figure 2: Illustrations of plexins and theoretical mechanisms may be involved in causing psoriasis.

The H-score mean values of both lesional and perilesional skin were found to be considerably greater compared to the control group, suggesting an elevated expression of Plexin-B2. Despite this, there was no statistically significant difference between the skin at the lesion site and the surrounding skin. Plexin-B2 H-scores were shown to have a significant and positive correlation with the severity of psoriasis, as determined by the Psoriasis Area and Severity Index (PASI) score. These findings were gleaned from the findings of a research study. Lesional epidermis (r = 0.593, p 0.001) was shown to have a substantial association with dermal inflammatory cells (r = 0.406, p 0.026), as indicated by the data. In addition, a correlation between the scores of epidermal and dermal cells was found that was statistically significant (p=0.032). Plexin-B2 expression levels in the afflicted epidermis were shown to be strongly linked with the prevalence of parakeratosis (p=0.016). Similarly, higher expression of Plexin-B2 in dermal inflammatory cells was observed to be associated with acanthosis (p=0.006) and hyperkeratosis (p=0.001). The findings of this research support the idea that perilesional psoriatic skin contains activated keratinocytes and is prone to the production of psoriasis lesions. This finding may aid in understanding the fundamental process of Koebnerization. In contrast, Zhang et al. [39], discovered equal amounts of Plexin-B2 expression in the normal skin of both psoriasis patients and healthy people. Furthermore, Hemida et al. [38], discovered a significant positive relationship between the expression of Plexin-B2 in the lesional epidermis and dermal inflammatory cells with the severity and progression of psoriasis. This discovery suggests that Plexin-B2 may play an important role in the etiology and progression of psoriasis, maybe by activating keratinocytes and promoting the inflammatory response. Worzfeld and Offermanns, [40], further highlighted Plexin-B2's potential as a promising target for pharmaceutical therapies in disorders such as psoriasis. Plexin-B2 has been found to have an important role in the stimulation of skin inflammation and keratinocyte proliferation in psoriasis vulgaris. As a result, it seems to be a potential choice for focused therapeutic interventions in the treatment of psoriasis. The proteins Plexin-B2 (PlxnB2) and its receptor, CD100 (Semaphorin 4D), have been implicated in the regulation of axon guidance over the course of brain development. Nevertheless, further studies have revealed that the interplay between CD100 and Plexin is implicated in a diverse range of immunological responses. When comparing atopic dermatitis with psoriatic lesional skin, it was shown that the latter had a much higher level of PlxnB2 expression on keratinocytes. The aforementioned discovery was reported by Zhang et al., [39]. The study demonstrated that the concentrations of soluble CD100 (sCD100) and

membrane CD100 (mCD100) were elevated in the serum of individuals with psoriasis and in the keratinocytes of their affected skin. The interaction between soluble CD100 (sCD100) and PlxnB2 resulted in the activation of the NLRP3 inflammasome, leading to an enhanced production of CXCL-1, CCL-20, IL-1, and IL-18 by keratinocytes. According to Zhang et al., [39] and, Shahi et al. [41], the CD100-PlxnB2 complex aids keratinocytes in activating the NF-B signaling pathway. RhoA and Rac1 activation causes this stimulation. Zhang et al., [39], discovered that the interaction of CD100 and PlxnB2 exacerbated keratinocyte inflammation. The activation of the NF-B and NLRP3 inflammasomes induced these effects. Psoriasis has also been connected to this interaction. CD100/PlxnB2 might be a potential target for psoriasis therapy.

2.3. PLXNC1 (Plexin C1)

Ultraviolet (UV) radiation increases the activity of the semaphorin 7-binding plexin C1 (PLXNC1) receptor, according to previous research. found that PLXNC1 increases acute peritonitis inflammation [42]. The PLXNC1 receptor causes chronic inflammatory skin disease psoriasis and boosts acute inflammation and immunological responses. Psoriasis causes erythematous, desquamating lesions in several places. Erythematous scaled lesions define psoriasis. Erythematous skin lesions with silver scales can occur anywhere on the body in psoriasis [42].

2.4. PLXND1 (Plexin D1)

Semaphorin is plexin D1 receptor. Receptor protein is transverse to cell membrane. Tissue development, axon guidance, and cell migration require this protein. This molecule binds mostly to semaphorins. Semaphorins are membrane-bound or soluble signaling proteins. Plexin D1 improves axonal guidance and cellular migration in embryonic and adult brain systems**.** Plexin D1 binds to semaphorins and other co-receptors in this interaction. This technique is critical for brain growth [43]. An extensive review of publicly available RNA-sequencing data reveals a relationship between psoriasis and the gene PLXND1, also known as Plexin D1. The dermatological disorder psoriasis has revealed novel gene-pathogenesis ideas. According to study, psoriasis sufferers exhibit neuritogenesis anomalies. The Semaphorin-Plexin signaling pathways are known to influence several phases of neuronal projection development. Semaphorins, signaling proteins, have been revealed in recent studies to govern neuronal growth and axon guidance. Recent study indicates that these components may have a role in the evolution of psoriasis, however their specific significance in its genesis is unknown. Differently expressed transcripts show that semaphorins like as SemaB and SemaF are involved in axon attraction and repulsion. Depending on the presence of its co-receptor NRP1, the interaction between Sema3E and its receptor PLXND1 may reverse axon development. Semaphorins and their receptors, notably PLXND1, may impair neurogenesis and contribute to the pathogenesis of psoriasis. More study is needed to understand the processes of this connection [44].

3. Conclusions

In summary, while direct links between specific Plexin proteins and psoriasis are unclear, their roles in axon guidance and immune regulation suggest potential relevance to the disease complex pathogenesis, requiring further research for concrete associations and therapeutic possibilities.

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