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Review Article

Caspase recruitment domain-containing proteins and dermatoses

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ABSTRACT

The caspase recruitment domain (CARD) is a protein interaction module that comes under the death domain superfamily. CARD mediates important cellular signaling events. Abnormalities in these cellular signaling events play a role in the pathogenesis of malignancies and immune disorders. The significance of CARD in dermatological diseases is less discussed. Mutations affecting CARD-containing proteins are reported to play a pathogenic role in certain patients with dermatoses such as psoriasis, pityriasis rubra pilaris, atopic dermatitis, and fungal infections. These underlying mutations are suggested to have therapeutic implications in various dermatoses, though more information is needed regarding this. This review discusses the association between dermatoses and mutations involving CARD-containing proteins.

Keywords: Caspase recruitment domain, Death domain superfamily, Psoriasis, Pityriasis rubra pilaris, Atopic dermatitis, Fungal infections, Mutation

INTRODUCTION

Caspase recruitment domain (CARD) is associated with important protein-protein interactions that occur in inflammation, apoptosis, and innate cell signaling.[1] CARD comes under the death domain superfamily.[1] Death domain superfamily mediates protein interactions which are essential for apoptosis and immune signaling pathways.[1] A pathogenic role for mutations affecting CARD-containing proteins is suggested in various dermatoses. The suggested mutations associated with dermatoses involve genes encoding caspase recruitment domain-containing protein 14 (CARD14), caspase recruitment domain-containing protein 11 (CARD11), and caspase recruitment domain-containing protein 9 (CARD9) and the dermatoses associated are psoriasis (CARD14), pityriasis rubra pilaris (CARD14), atopic eczema (CARD11 and CARD14), and fungal infections (CARD9).[2-6] We have attempted to provide a short review on dermatoses and mutations affecting CARD-containing proteins. Primary immunodeficiencies that manifest cutaneous lesions along with widespread involvement of other organs do not come within the purview of this article.

CARD14 and CARD11 are placed under the CARMA (caspase recruitment domain/membrane-associated guanylate kinase) family.[2] CARD14 and CARD11 are also designated as CARMA2 and CARMA1, respectively.[2] The other member of the CARMA family is CARD10 (CARMA3).[2] The CARMA family proteins show a similar domain structure characterized by a CARD domain at the N-terminus, a MAGUK (membrane-associated guanylate kinase) domain at the

C-terminus, and a coiled coil (CC) domain in between.[7] The members of CARMA family initiate NF-kB (nuclear factor of kappa light chain enhancer in B cells) and MAPK (mitogen activated protein kinase) signaling pathways by forming a complex (CBM complex) with BCL10 (B-cell lymphoma/leukemia 10) and MALT1 (mucosa-associated lymphoid tissue lymphoma translocation protein 1).[2] BCL10 and MALT1 proteins are ubiquitous in expression; hence, the specificity to the CBM complex is imparted by the CARD molecule.[2] Table 1 shows the tissue expression pattern of proteins of CARMA family which is cited as the reason for the variability observed in diseases caused by mutations involving different members of the family.[2]

PSORIASIS

The current knowledge suggests that psoriasis manifests when a genetically susceptible individual is exposed to environmental triggers such as drugs, extremes of climate, trauma, or infection.[2] Psoriasis itself shows varying clinical patterns ranging from plaque type psoriasis limited to a few body sites to extensive erythrodermic psoriasis, pustular psoriasis, and psoriasis with arthropathy. Genome-wide association studies identified more than 60 loci that could promote the development of psoriasis.[7]

In 1994, psoriasis susceptibility locus 2 (PSORS2) was mapped to the long arm of chromosome 17, in a large North European family with many members affected with psoriasis.[8] The members of the family with psoriasis manifested plaque-type disease. Among the affected, 30% also developed psoriatic arthropathy.[8,9] Seventeen years later, Jordan *et al*. identified a heterozygous gain-of-function mutation (c.349G>A [p.Gly117Ser]) in CARD14 gene that segregated with psoriasis in the same family.[9] The same group of researchers identified two other heterozygous gain-of-function mutations in CARD14. A family from Taiwan with many members affected with psoriasis and psoriatic arthritis showed a mutation in CARD14 gene (c.349+5G>A).[9] They also reported an infant with severe, early-onset generalized pustular psoriasis with no family history of psoriasis, who showed a *de novo* gain-of-function mutation (c.413A>C [p.Glu138Ala]) in CARD14.[9] The mutations were found to upregulate NF-kB activity. Keratinocytes from psoriatic individuals with the mutations showed increased transcription of genes that code for inflammatory mediators associated with the disease, such as interleukin (IL)-8, IL-36, and chemokine ligand 20 (CCL20).[9] Contrary to the normal skin, where CARD14 peptides are predominantly expressed in the basal layer of epidermis, psoriatic skin showed reduced CARD14 expression in the basal layer and increased expression throughout the upper layers of epidermis.[9] The authors concluded that keratinocytes showing CARD14 mutations activate NF-kB responsive genes and initiate an inflammatory process that leads to psoriasis. The pathomechanism underlying PSORS2 was identified as CARD14 mutation.[9]

Table 1: Tissue expression of members of CARMA family.

Member of CARMA family	Tissue localization
CARD11 (CARMA1)	Lymphoid cells and lymphoid tissue
CARD14 (CARMA2)	Skin and mucosa
CARD10 (CARMA3)	Epithelial tissue and endothelial tissue

CARMA: Caspase recruitment domain/membrane-associated guanylate kinase, CARD: Caspase recruitment domain

After further evaluation of thousands of cases and controls, Jordan *et al*. reported 15 rare missense variants in CARD14.[10] The rare variants were more frequent in cases in comparison to controls.[10] There was a clustering of many rare mutations in exon 4, which encodes part of the CC domain of CARD14.[10]

Berki *et al*., in an analysis of 416 patients with psoriasis, found no pathogenic variants in familial psoriasis vulgaris, acral pustular psoriasis, or erythrodermic psoriasis. However, they documented a CARD14 p.Asp176His variant that was associated with generalized pustular psoriasis in Japanese and Chinese populations.[11] Earlier, a similar observation was made by Sugiura *et al*., in a Japanese cohort.[12] They documented CARD14 c.526G>C (p.Asp176His) variant in about 21% (4/19) of patients with generalized pustular psoriasis with psoriasis vulgaris, but in none of the 11 patients with generalized pustular psoriasis without psoriasis vulgaris.[12]

A study in Chinese Han population by Qin *et al*. observed a significant association between rare CARD14 variants and generalized pustular psoriasis.[13]

In a study of larger sample size in Chinese Han population, Li *et al*. noted that CARD14 variants did not predispose to isolated generalized pustular psoriasis, but served as a predisposing factor for generalized pustular psoriasis with psoriasis vulgaris.[14] This finding was supportive of the existing knowledge that generalized pustular psoriasis could be an entity different from generalized pustular psoriasis that succeeded or accompanied psoriasis vulgaris (generalized pustular psoriasis with psoriasis vulgaris).[15] This is based on the association noted between mutations in IL36RN and generalized pustular psoriasis, and the rarity of the same in patients with generalized pustular psoriasis with psoriasis vulgaris.[15] However, Li *et al*. found no association between CARD14 p.Asp176His variant and generalized pustular psoriasis with psoriasis vulgaris.[14]

Signa *et al*. identified a novel CARD14 mutation (c.446 T > G, leading to the missense amino acid substitution p.L149R) in five members of a family with psoriasis, which included two children

(twins) with erythrodermic psoriasis. The children who showed poor response to retinoids and cyclosporine responded well to ustekinumab at a higher dose of 2 mg/kg every 8 weeks.[16]

Therapeutic implications

"CARD14-mediated psoriasis" and CARD14-associated generalized pustular psoriasis are reported to show better response to anti-tumor necrosis factor (TNF)-α treatment. Ustekinumab that targets the p40 subunit of IL-12/IL-23 was found beneficial in a few patients with "CARD14-mediated psoriasis."[2,16]

PRP

PRP, a papulosquamous disorder that shows morphological similarities with psoriasis, was broadly classified into five groups by Griffiths.[3,17] Later on, a sixth type (HIV-associated PRP) was added.[18] Familial PRP constitutes about 5% of all cases and comes under the atypical juvenile type (Type V) in Griffiths classification.[3] An early onset, a chronic course, and unsatisfactory response to treatment characterize the familial type PRP.[3] Researchers evaluated four families affected with autosomal dominant familial PRP and mapped the susceptibility to a region on the long arm of chromosome 17, which overlapped with PSORS2.[3] They identified three heterozygous CARD14 mutations in familial PRP that contributed to inflammation, by activation of NF-kB pathway.[3] It was proposed that the familial forms of PRP and psoriasis shared a common pathophysiology.[3]

Wu *et al*. identified a novel, heterozygous, and loss of function mutation: c.2263C>T, p.Q755* in a Chinese family with familial PRP.[19]

Danis *et al*. reported a patient with childhood-onset atypical PRP (Type V PRP), who had family members with psoriasis.[20] Four mutations in CARD14 gene were identified. Three of them were considered benign and the p.Arg682Trp missense variant was considered pathogenic. Immunofluorescence analysis of lesional and non-lesional skin of the patient with PRP, skin samples from healthy controls, and lesional and non-lesional skin of psoriasis patients showed that the nuclei of suprabasal epidermis of lesional skin of PRP patient alone stained positive for NF-κB p65 subunit. Further analysis showed higher NF-kB activity and elevated levels of cytokines in the keratinocytes (IL-1α and IL-1β) and peripheral blood mononuclear cells (IL-1α, IL-1β, IL-6, IL-8, and TNF-α) of PRP patient in comparison to healthy controls.[20] The authors proposed the possibility of unidentified mutations in other genes as the pathomechanism that led to the development of psoriasis in family members, though this could not be confirmed due to the reluctance of the members affected with psoriasis to undergo genetic screening.[20]

In a study of 22 patients with PRP, Takeichi *et al*. identified mutations {two novel mutations (c.380G>C, p.Cys127Ser and c.407A>T, p.Gln136Leu) and a mutation previously reported in psoriasis vulgaris/arthritis (c.349G>A, p.Gly117Ser)} near the known pathogenic domains in all three cases of PRP Type V.[21] Moreover, all the three PRP Type V patients manifested a patchy, macular, and brown hyperpigmentation. Whether the characteristic brown pigmentation is a diagnostic clue to PRP associated with mutations in CARD14 gene needs analysis in future studies.[21] In addition, one patient each with Type 1 and Type IV PRP in the series of Takeichi *et al*. manifested the variant p.Asp176His, which was reported earlier in association with generalized pustular psoriasis. The authors suggested that mutations involving CARD14 may be involved in other PRP types as well.[21]

Therapeutic implications

TNF-α antagonists may be of benefit in familial PRP with underlying CARD14 mutations, as they are known to target NF-kB signaling.[3] It is postulated that the activation of NF-kB signaling can increase production of IL-12/23, IL-17, and IL-22. It is suggested that IL-12/23 antagonists such as ustekinumab may serve as the first-line treatment in PRP patients with mutations involving CARD14.[22]

Although researchers have noted NF-κB activation in PRP and psoriasis, currently, there is no evidence to suggest that the level of activation correlates with either the disease severity or the phenotype of the disease.[10]

CARD14-ASSOCIATED PAPULOSQUAMOUS ERUPTION (CAPE)

Craiglow *et al*., in 2018 described CARD14 mutations in 15 families, which had members manifesting features of PRP and psoriasis.[23] Some showed predominant features of one of the two, while a few others showed features of both. The characteristic findings noted in the affected were "early age of onset, prominent involvement of the cheeks, chin (symmetric, well-demarcated pink-red patches, or thin plaques involving both the cheeks and chin with sparing of the infralabial region), and ears, family history of psoriasis or PRP, minimal response to conventional topical and systemic psoriasis therapies, and improvement with ustekinumab." This prompted the authors to suggest that the patients manifesting features of both PRP and psoriasis, especially those with a family history of any of the two and who show a lack of response to conventional anti-psoriatic treatment should be analyzed for CARD14 mutations.[23]

The authors noted a homozygous CARD14 mutation in one of the patients, whereas all other CARD14 mutations described till then for psoriasis and PRP were heterozygous. However, it was opined that the homozygosity does not predispose to a more severe phenotype.[23]

A comparative study on histopathology of CAPE, adult-onset plaque psoriasis, and adult-onset PRP by Ring *et al*. observed more histopathology similarity between CAPE and PRP, which included "comparable thickness of epidermis below the stratum corneum, follicular plugging, checkerboard parakeratosis and orthokeratosis, acanthosis, and lack of relative suprapapillary thinning."[24]

Therapeutic implications

Patients with PRP or psoriasis with CARD14 mutations were found to have increased NF-kB activity, which, in turn, favored recruitment of dendritic cells producing IL-23 and T-lymphocytes producing IL-17 and IL-22. Hence, ustekinumab that binds to the shared p40 subunit of both IL-12 and 23 was tried with good response in CAPE. Guselkumab (IL-23p19 inhibitor), secukinumab (IL-17A inhibitor), and ixekizumab (IL-17 inhibitor) are also suggested as potential treatment options in CAPE. Craiglow *et al*. treated one patient with ixekizumab and noted only a partial response.[23]

ATOPIC DERMATITIS

Peled *et al*. reported loss of function mutations involving CARD14 in three patients with severe atopic dermatitis. It was documented that the mutations led to reduced NF-kB activity and reduced secretion of antimicrobial peptides.[5]

BENTA (B-cell expansion with NF-kB and T-cell anergy) is a B-cell lymphoproliferative disorder, associated with germline, heterozygous gain-of-function mutations in the CARD11 gene. Desjardines *et al*. reported a four generation family with a germline, heterozygous mutation (c.701–713delinsT) in members who showed moderate B-cell lymphocytosis accompanied by atopic dermatitis or allergies. It was proposed that, though the mutation imparted increased NF-kB activity, the variant inhibited antigen receptor ligation-induced NF-kB activation by the wild variant.[25]

Ma *et al*. documented heterozygous mutations in CARD11 in eight patients (from four families) with severe atopic dermatitis. It was suggested that the mutations interfered with NF-kB and mammalian target of rapamycin complex 1 (mTORC1) activation leading to suppression of Th1 (T helper Type 1) differentiation and promotion of Th2 (T helper Type 2) response.[4]

Therapeutic implications

Ma *et al*., in their cohort of patients with severe atopic dermatitis and CARD11 mutations observed improvement of dermatitis following supplementation of glutamine (attributed to the CARD11-dependent transport of glutamine into T-cells).[4] The defective production of mTORC-1 and IFN-γ was partially corrected by supplementation of glutamine.[4]

FUNGAL INFECTIONS

CARD9 mutations are known to impair an individual's immunity against fungal infections.[26,27] It is noted that inactivation of both alleles is needed to impart susceptibility to fungal infection, leading to an autosomal recessive mode of inheritance.[27]

CARD9 shows similarity to members of CARMA family.[26] CARD9 has a N-terminal CARD region and a carboxy-terminal CC domain. Unlike the CARMA family members, CARD9 does not have a C-terminal MAGUK region.[27] CARD9 is expressed in myeloid cells.[26]

Knowledge gained from animal studies suggests that deficiency of dectin-1 (C-type lectin receptor) or CARD9 (which is essential for dectin-1 signaling) adversely affects immunity against fungal infections. Dectin-1 is a pattern recognition receptor for β-glucan component of the cell walls of fungi.[26] Mutations in CARD9 gene impart susceptibility to fungal infections by impairing the expression and function of CARD9 protein. CARD9-deficient individuals showed eosinophilic infiltration, but a defect in neutrophil accumulation in central nervous system (CNS).[27] It is well known that neutrophils (not eosinophils) play a major role in the fight against systemic infection by *Candida*.[27] This specific neutropenia affecting CNS places patients harboring mutations in CARD9 gene at a higher risk for fungal invasion of CNS.[27]

Vaezi *et al*. reported CARD9 mutation (*Q295* mutation) in a 26-year-old healthy female patient from Iran, who developed CNS involvement due to disseminated pheohyphomycosis and who succumbed to her illness, despite antifungal therapy.[28] The authors drew attention to the fact that there were more reports of CARD9-associated fungal infections from Iran, in comparison to other Asian countries.[28]

Glocker *et al*. studied a consanguineous, five generation, Iranian family with four members manifesting recurrent *Candida* infections.[29] Three other members of the same family had died in adolescence; the cause of death was candidal meningoencephalitis in two. The four family members with recurrent candidal infections showed a homozygous point mutation in CARD9 (Q295X), which affected the innate signaling from dectin-1. The affected members showed reduced number of Th17 cells (IL-17-producing helper T-cells).[29]

The various fungal infections reported in association with CARD9 deficiency were infections due to *Candida*, *Phialophora*, *Aspergillus,* and dark-walled molds.[27] There are occasional reports of patients with CARD9 mutations showing susceptibility to dermatophytes (such as *Trichophyton violaceum*,

Microsporum ferrugineum, and *Trichophyton rubrum*) or manifesting invasive infections with *Exophiala*, *Cryptococcus neoformans,* or *Histoplasma capsulatum*.[27,29,30] A CARD variant was associated with *Corynespora cassiicola* (a plant pathogen that rarely affects humans) infection in a Chinese patient.[31] Rosentul *et al*. did not observe any association between single nucleotide polymorphisms involving CARD9 (Ser12Asn, rs4077515) and susceptibility to recurrent vulvovaginal candidiasis.[32] However, the association between a specific CARD9 mutation and a particular fungal infection needs to be further elucidated.[27]

Vaezi *et al*., after reviewing published literature on fungal infections and CARD9 mutations opined that patients who manifest progressive fungal infection without any apparent reason should be evaluated for CARD9 mutations.[33]

Chronic granulomatous disease (a primary immunodeficiency disease) and mutations that involve and adversely affect the IL-12/IFN-γ pathway, can also increase susceptibility to fungi; however, unlike the above-mentioned immunodeficiencies, CARD9 mutations do not increase susceptibility to infections by microbes other than fungi.[6]

Therapeutic implications

Patients with CARD9 mutations who develop recurrences, despite receiving appropriate antifungal therapy, may be treated with an alternate antifungal or a combination of antifungals.[6] There is a scarcity of data on the efficacy of bone marrow transplant (or peripheral blood stem cell transplant) in the management of resistant fungal infections in individuals with CARD9 deficiency.[6] A surgical resection is advised for the major treatment-resistant lesion.[6] It is recognized that CARD9 deficiency reduces the ability to produce "granulocyte-monocyte colony-stimulating factor" (GM-CSF) by monocytes/macrophages in response to fungal infection.[6] GM-CSF and G-CSF ("granulocyte colony-stimulating factor") have been found useful in occasional patients with CARD9 deficiency, who manifested invasive candidal infection.[6,34]

BACTERIAL AND VIRAL INFECTIONS

It is postulated that CARD9 mutations can adversely affect immunity against intracellular bacteria, such as *Listeria monocytogenes* and *Mycobacterium tuberculosis* as well as immune response against viruses.[35] However, convincing evidence is lacking.[35]

OTHER DERMATOSES

Blau syndrome, which is considered as the early-onset, familial sarcoidosis, follows an autosomal dominant pattern of inheritance. The classical triad includes arthritis, uveitis, and skin manifestation characterized by eruptions of discrete papules.[36] Shaffer *et al*. documented granulomatous dermatitis as the early manifestation of the syndrome.[36] A mutation in CARD15 was reported in Blau syndrome and a therapeutic role was proposed for IL-1β antagonist.[37]

Watt *et al*. reported that CARD11 mutation-induced alteration in NF-kB signaling could be an early event in the pathogenesis of cutaneous squamous cell carcinoma.[38]

CONCLUSION

CARD mutations play a role in the pathogenesis, clinical manifestations, and treatment response observed in certain dermatoses. Further studies are needed to clearly understand the clinical and therapeutic implications of the associations reported between skin diseases such as psoriasis, PRP, fungal infections, and atopic dermatitis and CARD mutations.

Declaration of patient consent

Not required as there are no patients in this article.

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Conflicts of interest

Dr Fibin Thanveer is on the editorial board of the Journal.

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